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Advances in Telemedicine

Applications in Various Medical Disciplines and Geographical Regions

Edited by Georgi Graschew and Theo A. Roelofs

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http://dx.doi.org/10.5772/1863
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Notice

First published in Croatia, 2011 by INTECH d.o.o.
eBook (PDF) Published by IN TECH d.o.o.
Place and year of publication of eBook (PDF): Rijeka, 2019.
IntechOpen is the global imprint of IN TECH d.o.o.
Printed in Croatia

Legal deposit, Croatia: National and University Library in Zagreb

Additional hard and PDF copies can be obtained from orders@intechopen.com

Advances in Telemedicine: Applications in Various Medical Disciplines and Geographical Regions
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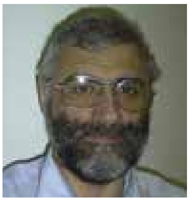
p. cm.

ISBN 978-953-307-161-9

eBook (PDF) ISBN 978-953-51-6425-8

Meet the editors



Dr. Georgi Graschew has been Scientific Coordinator of the Surgical Research Unit OP 2000 at the Max-Delbrück-Center for Molecular Medicine and the Experimental and Clinical Research Center of Charité – University Medicine Berlin (Germany) since 1993. Following his research studies at the Department for Mathematics and Natural Sciences of the Technical University Dresden (Germany) he gained his Ph.D. there in 1974. After research appointments at various international sites he became in 1987 co-founder of the Research Unit OP 2000 at the German Cancer Research Center DKFZ in Heidelberg (Germany), where he acted as its Scientific Coordinator until its transfer to Berlin. He made major contribution to numerous leading national and international telemedicine projects: SICONET, PANORAMA, GALENOS, DELTASS, MEDASHIP, EMISPHER. He has co-authored more than 360 scientific publications and presentations and holds 18 patents in Germany, the European Union, Japan and USA.

Dr. Theo A. Roelofs has been working since 1999 as Research Associate & Project Manager at the Surgical Research Unit OP 2000 of the Max-Delbrück-Center for Molecular Medicine and the Experimental and Clinical Research Center of Charité – University Medicine Berlin (Germany). He also contributed to various international Telemedicine projects (GALENOS, DELTASS, MEDASHIP) and acted as manager of the EMISPHER project. Following his studies in Molecular Sciences at the Wageningen University (Netherlands) and his Ph.D. in Biophysics (Max-Planck-Institute for Radiation Chemistry, Germany, and Free University at Amsterdam, Netherlands) he was a visiting research associate at the Chemical Biodynamics Department of the Lawrence Berkeley National Laboratory (USA, 1992-1994) and a research & education associate at the Physics Department of the Free University at Berlin (DE, 1994-1999). He has co-authored more than 140 scientific publications.

Contents

Preface

Innovative developments in information and communication technologies (ICT) irrevocably change our lives and enable new possibilities for society. One of the fields that strongly profits from this trend is Telemedicine, which can be defined as novel ICT-enabled medical services that help to overcome classical barriers in space and time. Through Telemedicine patients can access medical expertise that may not be available at the patient's site. The use of specifically designed communication networks with sophisticated quality-of-service for Telemedicine (distributed medical intelligence) contributes not only to the continuous improvement of patient care, but also to reducing the regional disparity in access to high-level healthcare. Telemedicine services can range from simply sending a fax message to a colleague to the use of broadband networks with multimodal video- and data streaming for second opinioning as well as medical telepresence. Depending on the specific medical service requirements, a range of classes-of-services is used, each requiring its own technological quality-of-service.

Originally started as *interdisciplinary* efforts of engineers and medical experts, Telemedicine is more and more evolving into a *multidisciplinary* approach. Consequently, compiling a book on recent "Advances in Telemedicine" will have to cover a correspondingly wide range of topics. In addition, if each topic shall be treated in sufficient depth to allow the reader to get a comprehensive understanding of both the developmental state-of-the-art as well as the broad spectrum of issues relevant to Telemedicine, one might easily end up with a huge tome, too big to be practical in handling. Therefore, this book "Advances in Telemedicine" has been split into two volumes, each covering specific themes: Volume 1: Technologies, Enabling Factors and Scenarios; Volume 2: Applications in Various Medical Disciplines and Geographical Regions. The Chapters of each volume are clustered into four thematic sections.

The current Volume 2 "Advances in Telemedicine: Applications in Various Medical Disciplines and Geographical Regions" contains 15 Chapters clustered into the following thematic sections:

- Cardiovascular Applications (Chapters 1-3),
- Applications for Diabetes, Pregnancy and Prenatal Medicine (Chapters 4-7),
- Further Selected Medical Applications (Chapters 8-12),
- Regional Applications (Chapters 13-15).

The section on ***Cardiovascular Applications*** begins with an overview of the use of **Telemedicine in Stroke (1)**. A detailed description of the use of Telemedicine in various stroke care settings is followed by a discussion of requirements for successful implementation in terms of technology, networks and organisational models. Existing barriers seem to be related to technology, costs and reimbursement schemes, as well as to legal and ethical issues. Recommendations are made for further improvements. The next chapter puts **Telestroke Network Design (2)** further into focus. Starting with a description of three leading telestroke network concepts (drip-and-ship, specialists on call, TEMPiS) a new systematic taxonomy of network concepts is presented, based on the central protagonist roles involved (patient, primary care hospital and expert consultant). As a result a hierarchical decision algorithm is proposed that specifies which questions to answer along the road to a functioning implementation of telestroke. This book section ends with a valuable collection of practical hands-on information on the **Operation of Telemedicine for Arterial Hypertension (3)**. The chapter addresses various methods of blood pressure measurements (office-, ambulatory-, self- and telemetric measurements) and describes techniques, problems and advantages of the use of telemetry in these cases. A guide is presented on its application in daily practice during the various stages: diagnosis, start and change of therapy, long-term observation.

The section on ***Applications for Diabetes, Pregnancy and Prenatal Medicine*** starts with an overview of **Telemedicine Applications in the Follow-up of Diabetic Patients (4)**. An extensive review of the literature on the usefulness of telemedicine systems in these cases underlines the need for *well-designed clinical trials*. The results of a prospective randomised interventional study with two parallel groups of patients with gestational diabetes mellitus (GDM) to evaluate a telemedicine system based on Internet and SMS indicate that such a system can be a useful tool if complemented by conventional face-to-face monitoring. Another study, presented in the next chapter on **Telemedicine in Pregnancy Complicated by Diabetes (5)** also shows that telemedicine can be a practical way to provide specialist care. The use of a simple telephone-based telemedicine system that is easy to use and does not require computer literacy has been shown to have a positive impact on quality of life, to reduce the number of visits to the diabetes clinic and to support better metabolic control. The next chapter presents **Advances in Fetal Monitoring by Prenatal Telemedicine (6)**. Besides describing communication networks of various levels of sophistications the authors also give an overview of the various techniques available for investigating the fetal heart and the uterine activity. Special emphasis is put on algorithms for signal processing methods to extract the fetal ECG and the uterine activity from abdominal signals. The last contribution in this section presents a **New Telemedicine System for Telecardiotocography and Tele-Ultrasonography in Prenatal Medicine (7)**. It describes the organisation and operation of the first and unique prenatal telemedicine network in Italy that is based on the TOCOMAT system. The study gives a comprehensive treatment of the various relevant aspects, such as network design and components, operation, clinical and scientific results, satisfaction of both operators and patients, efficiency and costs study, legal and ethical aspects, as well as future potential of the system in resource-limited settings (e.g. Africa).

The section on ***Further Selected Medical Applications*** begins with the presentation of a powerful **Computer-Aided Diagnosis System for Glandular Tumours (8)** to be used for internet-based telemedicine. It allows classifying glandular tumours into cancers and adenoma, based on various morphological shape and texture features of the cytoplasm and the nucleus of glands. These features are extracted by numerical conversion and binarisation methods of red and green colour components, yielding correct classification results in 88%-94% of the cases. The next chapter presents the **Development and Introduction of a Telemedical System into the Blood Transfusions Practice (9)** in Slovenia. The system allows for the remote readout and interpretation of the results of pre-transfusion agglutination tests performed on gel-cards. A special device (Gelscope) was developed for reliable readout of gel-card images. The overall system, conceived as a server/client set-up, follows a high level of security, user identification and data protection requirements, thus providing medically reliable readout, interpretation and diagnosis in form of legally valid electronic documents. The following chapter treats the use of **Telemedicine as an Aid to Clinical Practice, Research and Education in Plastic Surgery (10)**. Due to its strong reliance on both static and dynamic images, plastic surgery can strongly profit from telemedicine and at the same time it acts as a model for research and development in telemedicine. Convincing case studies on triage and management of problem wounds, relevant technical considerations, users' perception (both of patients and physicians), usage as educational tool, as well as on outcome assessment are presented. The following chapter makes a strong case for **Teledentistry: Telemedicine in Dentistry (11)**. Combined use of the Internet as ubiquitous communication channel and computerisation for capture, analysis and processing of medical images and patient data unlocks potentials in various dentistrial sub-disciplines. Telemedicine applications and corresponding benefits are described for oral and maxillofacial surgery, orthodontics, endodontics, pediatric and preventive dentistry, oral medicine and dental prosthetics. These applications support the establishment of evidence-based dentistry. This section is completed by a systematic literature review that documents and critically analyses recent **Advances in Teleophtalmology (12)**. This study includes 107 original papers, following multi-criteria selection from three databases. The majority of the papers describe store-and-forward telemedicine scenarios; only eight of them describe the use of real-time telemedicine. General eye care, premature retinopathy and diabetic retinopathy were the main areas of research interest. Over 90% of the studies conclude positive views on the use of teleophtalmology. However, as only a very small minority of the studies employed Randomised Controlled Trial design (two studies) or even control groups (four studies), it seems obvious that the evidence provided is inadequate to draw an informed conclusion.

The last section of this book is dedicated to ***Regional Applications*** and starts off with a contribution on **Telemedicine for the Management of Hepatitis C** exemplified by the **California Telehealth Network (13)**. In particular for hepatitis C virus infected patients who live in rural and underserved areas the use of telemedicine allows to close the gap of access to the required speciality care. Real-time telemedicine consultations and video conferencing between the patient, specialist and primary care provider lead to an increased quality of patient care and at the same time contributes to continuous education of the primary care providers. The statewide California Telehealth network has been set up as a dedicated tool to improve equal access to these and similar high-quality collaborative health services. The next chapter describes in much detail the **AVERA eCARE® Telemedicine Program for the Rural North Central Region of the USA (14)**. A variety of services has been implemented (eConsult, eICU, eEmergency, eStroke, ePharmacy, eUrgent Care, eNursery) and objective documented improve of various outcomes is presented (including mortality, length of stay, air transport saving). The system has thus leveraged health care expertise in the health system in this region because it overcomes barriers related to the geographic separation of many sparsely populated town and cities in the upper Midwest. The last chapter of this book presents **Recent Advances in Telepathology in the Developing World (15)**. The causes for poor laboratories services in developing countries can be summarised as pervasive weakness of laboratories facilities in terms of budget, staff, training, infrastructure, regulations and continuous education. Following a presentation of selected projects, the chapter focuses on existing barriers for further improvements: socio-cultural aspects, inadequate lab infrastructure, archaic telecom facilities, funding and sustainability, personnel shortage, poor technical quality of slides and unresolved legal issues.

This book has been conceived to provide valuable reference and learning material to other researchers, scientists and postgraduate students in the field. The references at the end of each chapter serve as valuable entry points to further reading on the various topics discussed and should provide guidance to those interested in moving forward in the field of Telemedicine.

We sincerely acknowledge all contributing authors for their time and effort in preparing the various chapters; without their dedication this book would not have been possible. Also we would like to thank Katarina Lovrecic from InTech Open Access Publisher for her excellent technical support during the realisation process of this book.

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Part 1

Cardiovascular Applications

1

Telemedicine in Stroke: Potentials, Limitations and Ongoing Issues

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1. Introduction

1.1 The burden of the disease

Stroke is a high frequency neurological disorder and the most common cause of complex disability in adults (Adamson et al. 2004). It is the second and third most common cause of mortality in the developing and developed worlds respectively (Lyons & Rudd 2007). In the United States, 780,000 people per year experience either a new or a recurrent stroke. In 2004, stroke mortality was estimated to be in excess of 150,000 and the prevalence of stroke in people over the age of 20 was 5.8 million in 2005. About 30% of stroke survivors are permanently disabled and about 20% require institutional placement at three months (Rosamond et al. 2008). Stroke is an example of a largely preventable disease that presents acutely, with a short time window for amelioration. It is associated with a high mortality rate, a significant risk for residual disability, and has a large impact on society, the patients and their families (Demaerschalk et al. 2010). Stroke recurrence can lead to a stepwise decline into dependency, resulting in a financial burden on society. According to Rosamond et al (2008), the indirect and direct costs of stroke in the United States were calculated at $65.5 billion in 2008. The majority of strokes are due to cerebral infarction (87%) and as such are amenable to a variety of pre-stroke risk factor modification strategies, as well as thrombolysis or intravascular clot retrieval strategies during the acute phase (Hachinski 2002; Yusuf 2002; Rosamond et al. 2008). The remaining subtype of stroke, i.e. intracerebral haemorrhage, is largely preventable by pre-stroke blood pressure control (Hachinski al. 2010).

1.2 The rural challenge

Globally, the majority of strokes occur in rural areas where there is often a lack of stroke services. In these areas, stroke care is often fragmented and does not adhere to recommended guidelines (Hess et al. 2005; Joubert et al. 2008). This, together with the world-wide focus on provision of health services, the geographical barriers that are associated with a general attenuation of access to healthcare resources and the paucity of stroke experts results in an inequitable distribution of resources, which frequently limits access to evidence–based care (Park & Schwamm 2008). Service delivery is frequently variable even within developed countries, but even more so in developing countries. In rural Australia, for example, over 90% of hospitals have 24-hour access to CT scanning, but residents have to travel, on average, about 100km. A study carried out in Montana and Northern Wyoming by Okon et al (2006) revealed that only 39% of hospitals had 24-hour CT capabilities. A study in China by Liu et al (2007) showed the use of CT in rural areas to be "low" compared to urban areas, but exact data are not available. In India, there are no reliable data on rural Indian CT services. In a study of stroke services in 21 rural hospitals in Idaho by Gebhardt et al (2006), 77.8% reported patient delays and 66.7% reported transport delays. There were equipment delays in 22.2% and ancillary service delays in 61.1%. Only 33.3% of hospitals were involved in quality improvement programmes, thrombolytic therapy was available for stroke in only 55.6% and no hospital had a designated stroke team. In Scotland, although it was revealed that the admission rate for symptomatic carotid disease was significantly higher in deprived rural populations, less carotid endarterectomies were performed in the rural compared to the urban areas. An assessment by Read et al (2005) of the differences in stroke care practices between regional and metropolitan hospitals in Australia showed that rural patients were less likely than their urban counterparts to receive CT of the head within 24 hours of admission, swallowing assessment, echocardiography, carotid imaging, lipid or glucose estimations or services from allied health professionals. Furthermore, no rural hospital in New South Wales had a stroke-specific clinical nurse compared with 21 stroke nurse case manager positions in metropolitan New South Wales, and only one third of the rural hospitals had access to a neurologist .

1.3 Telemedicine/Telestroke

Telemedicine has been defined as the delivery of healthcare services to the underserved, employing telecommunication (Misra et al. 2005). A more extensive definition is "the process by which electronic, visual and audio communications (including the telephone) are used to provide diagnostic and consultation support to practitioners at distant sites, assist in or directly deliver medical care to patients at distant sites, and enhance the skills and knowledge of distant medical care providers (Deshpande et al. 2008).

"Telestroke" refers to the application of telemedicine to stroke care. It is a new application of existing technology in the care of stroke patients (Sato & Ohta 1993). Demonstration projects have proven the feasibility of telestroke (Goldstein & Rothwell 2007) and suggested its potential to facilitate access to specialist stroke expertise in hospitals without access to specialist clinicians. Importantly, use of this technology may promote implementation of best-practice management of vascular risk factors in the stroke survivor after discharge (Bouffard 1997; Susman 1997; Park & Schwamm 2008). The main drivers have been technological advances, such as the digitisation and compression of data permitting the rapid transfer of images (Levine & Gorman 1999).

2. Current and potential uses of telestroke

Telemedicine, as a distant communication tool, was first attempted in radiology 50 years ago (Jutras 1959) and subsequently in psychiatry (Wittson et al. 1961). Since 1999 there has been a gradual increase in telemedicine programmes and, more recently, a growing interest in its use in stroke, mainly in facilitating thrombolysis, (Wang 2003; Audebert 2006; Park &

Schwamm 2008), but also in establishing diagnoses and guiding treatment options (Wiborg & Widder 2003).

Telestroke has the potential to improve the care of the stroke patient in the acute phase, the subacute phase, the rehabilitation phase and in the long term for the prevention of recurrence of cerebrovascular or cardiovascular events. Attention at all these levels can substantially lower the net cost of the condition to society by reduction of lost productivity, nursing home costs and rehabilitation (Hachinski et al. 2010). So, although in the past telemedicine has mainly focused on the area of thrombolysis in the acute stage of the disease, it has now been acknowledged to have the potential to also bring substantial benefits to the remaining stages of the stroke victim's journey.

2.1 Telestroke for acute stroke management

Thrombolysis of acute ischaemic stroke

The Recommendations for the Establishment of Stroke Systems of Care by the American Stroke Association (ASA) task force state that:

> *"A stroke system should make certain that clinical pathways are used consistently to ensure the organized application of interventions to prevent or limit stroke progression or secondary complications" (Schwamm et al. 2005).*

The current and most common use of telestroke is to provide specialist expertise to distant sites in the administration of recombinant tissue plasminogen activator (rt-PA). The importance of this treatment is that the majority of strokes are ischaemic (87%) and if the cause for the ischaemia can be removed within a three hour time-window (and possibly longer) there is a significant reduction in the amount of damage to brain tissue compared to cases where ischaemia is left unresolved for many hours or days. In this context, as has been often stated, "Time is brain". Since 1996, rt-PA has been approved by the US Food and Drug Administration as the only treatment for ischaemic stroke with the express goal of reducing neurological damage, improving recovery and reducing disability (Demaerschalk et al. 2010). In the landmark study of the National Institute of Neurological Disorders and Stroke (NINDS), a randomised, double-blind trial where 624 stroke patients were either administered placebo or rt-PA within 3 hours of the onset of stroke symptoms, significantly more patients in the rt-PA group had a favourable outcome compared to those in the placebo arm of the study (odds ratio, 1.7; 95% confidence interval, 1.2-2.6). Thus at three months after the stroke, 31% to 50% of those who were administered rt-PA had minimal or no disability compared to 20% to 38% of the placebo group. There was an increase in intracerebral haemorrhage in those treated with rt-PA (6.4 % vs. 0.6%) but at three months, there was no difference in mortality rates between the two groups (17% for rt-PA group and 21% for the placebo group) (Demaerschalk et al. 2010).

Despite the recommendations from the American Heart Association (AHA)/ASA for the use of rt-PA in acute stroke subject to stringent guidelines, because of the constraints imposed by the time-window, as well as apprehension from treating physicians of the complication of haemorrhage, only a minority (2%-3%) of stroke victims receive this form of therapy (Alberts et al. 2000). This may change with attempts to widen the time-window to 4.5 hours, following the results of the European Cooperative Acute Stroke Study (ECASS III) (Hacke et al. 2008).

As a result of the limitations described above, the Joint Commission commenced the certification of hospitals as Primary Stroke Centres (PSCs) in 2004, and by 2006, 200 such centres had been certified in the United States (Demaerschalk et al. 2010). Since the AHA/ASA guidelines were determined, such PSCs have used telestroke in areas which, due to geographical or other reasons, require distant support in the evaluation of patients who could benefit from thrombolysis. Meyer et al (2008) reported that a telemedicine network in Southern California has treated 28% of ischaemic stroke patients with rt-PA in this way. Similarly, an evaluation by Lattimore et al (2003) of 8 PSCs in Phoenix, Arizona demonstrated that 18% of patients with cerebral infarction were treated with rt-PA and in Bethesda, Maryland, a PSC reported an increase of use of rt-PA in acute stroke from 1.5% to 10.5%.These data indicate that medical services that normally would avoid using thrombolytic therapy for a variety of reasons, when supported by stroke centres, usually by a telestroke link-up, will offer acute stroke victims the opportunity to receive this evidence-based treatment accepted by the Food and Drug Administration for the treatment of acute ischaemic stroke.

In a recent systematic review by Johansson and Wild (2010), of the fifteen studies using telestroke reviewed, all reported that implementation of a telestroke-guided distance treatment with rt-Pa was not only feasible, but acceptable. In one of the earliest telestroke networks, the TEMPiS network in Bavaria, Audebert et al (2006) reported improved health outcomes and a reduction of mortality at three months post stroke. A variety of telestroke modalities was used including telephone support and two-way real-time videoconferencing. The review has raised the need for further studies to counter the lack of standardized reporting of outcomes and the use of facilities and resources as well as economic studies addressing the use of telestroke.

Pre-hospital diagnosis and evaluation of suitability for thrombolysis

Urban situations are more likely to have readily accessible rapid response transport, e.g. MICA ambulance, for the acute stroke patient. In more isolated or rural settings, these options may not be as readily available, and a degree of screening may therefore be useful. Pilot studies have been carried out which have employed telestroke technology as a method of screening eligible patients and, in particular, assessing stroke severity (LaMonte et al. 2004). This is obviously a useful employment in remote areas, such as the Australian Outback, particularly for clinic nurses when vast distances are involved. However, the cost-effectiveness and reliability of this method still need to be tested in a controlled trial situation.

Virtual neurological assessment and identification of stroke "mimics"

An important feature of telestroke consultations is that with real-time videoconferencing, geographically distant sites can benefit from visual confirmation of the stroke diagnosis. There are several mimics of an acute stroke including hypoglycaemia, epilepsy, hysteria and movement disorders (Pfrieger 2009). Many of these can be quickly identified by experienced physicians, and so avoid unnecessary transport and promote the correct treatment. In a study comparing the initial diagnosis, before imaging, between emergency physicians, primary care doctors and stroke experts, the rate of misdiagnosis by non-stroke doctors was 30%. This area of real-time video consultation by experienced neurologists has significant implications both in terms of cost-saving as well as patient welfare (Hachinski et al. 2010).

Neurological advice in complex cases

Small hospitals at a distance from PSCs often have the ability to implement suggestions that would save a patient being transported at cost to the PSC. Complex problems such as diabetic control, management of dissection or timing of interventions (such as anticoagulation after a stroke) can all be the subject of videoconferencing, with great benefit to the distant hospital and improvement in patient care. In addition, expert advice can be given regarding management of raised intracranial pressure, appropriateness of transfer for decompressive surgery and treatment of post-stroke seizures (Schwamm et al. 2009).

Screening and facilitation of management of suspected Transient Ischaemic Attacks (TIAs)

TIAs are often neglected or misdiagnosed by non-neurologists. Expedited evaluation and prompt management by stroke experts has demonstrated a lower than predicted subsequent stroke rate, but in rural or geographically isolated areas, the delay between TIA and evaluation is often protracted. This can have serious consequences since certain TIA subsets are associated with very high risk of future stroke. Patients with an ABCD2 (Age, Blood Pressure, Clinical Features, Duration and Diabetes) score of 4 or higher have a particularly high subsequent stroke risk (Uchiyama 2009). Prompt evaluation and immediate treatment is important in TIA patients since the longer the wait after the TIA, the higher the risk of stroke (Lavallee et al. 2007). The ASA has suggested that telestroke has the potential to provide the needed specialist input (Schwamm et al. 2009) but this model has yet to be evaluated. Telestroke screening by experienced clinicians will allow for identification of TIA mimics as well as true TIAs, especially those posing the greatest threat, and facilitate effective triage and management.

2.2 Telestroke for Subacute Stroke Management & Rehabilitation

Augmentation of existing facilities in subacute care scenarios

The Recommendations for the Establishment of Stroke Systems of Care by the ASA task force state that:

> *"A stroke system should use organized approaches (e.g., stroke teams, stroke units, and written protocols) to ensure that all patients receive appropriate subacute care" (Schwamm et al. 2005).*

Govan et al (2008) have unequivocally demonstrated that the care of stroke patients in dedicated stroke units reduces institutionalisation, lowers stroke-related mortality and enhances functional outcome. About one third of all stroke patients deteriorate within the first 48 hours after a stroke (Castillo 1999) and the increased mortality and morbidity during the in-hospital phase is directly related to this deterioration. Common causes are conditions such as urinary tract infections, development of aspiration and hypostatic pneumonia and fluctuations of blood pressure. The elements of care that are needed are not complex; they consist of simple guidelines such as assessment of swallowing and avoidance of hyperthermia (Adams et al. 2007). These considerations, often not part of the general ward routine, can be transmitted by experienced stroke teams by telestroke contact and education. Thus, the expertise from stroke specialists in the subacute phase can be made available to smaller centres which do not deal with these issues on a daily basis. With a widespread lack of direct contact with stroke specialist teams (Trimble et al. 2007), telestroke can augment a rudimentary clinical situation so that the required guidelines are followed. The clinical approach to symptomatic carotid stenosis is different to that required in embolic stroke secondary to atrial fibrillation. Guidance in this stage where stroke subtype differentiation informs treatment can be furnished by telestroke contact. Intimation of the effect of telestroke in this regard has emerged from studies in Germany. In the Bavarian TEMPis project by Audebert et al (2006), part of the telestroke initiative consisted of providing protocols for management, ongoing medical education and a comprehensive quality management programme. Of the 3122 patients enrolled in the programme, 37% were admitted to 5 control regional hospitals without telestroke support, while 63% were admitted to 5 regional hospitals where telestroke support was available. In those hospitals supported by the telestroke system, more patients received rt-PA, and appropriate investigations were more commonly performed. Thus, rapid brain imaging (74% versus 32%), carotid Doppler studies (83% versus 32%) and swallowing evaluation (73% versus 48%) all indicated more appropriate early management of stroke patients. At three months after the stroke, fewer patients were disabled, placed in institutions or dead in the telestroke-supported distant hospitals. In fact multivariate analysis demonstrated a lower probability of poor outcome in these hospitals (OR 0.062, 95% CI 0.52 to 0.74). The TEMPiS study clearly demonstrated that not only for guidance in thrombolysis, but also at the subacute stage, telestroke support provided an augmentation of services at a distance, which was significant not only in terms of process but also outcomes.

The TESS (Telemedicine in Stroke in Swabia) programme supported the above findings; post-hoc evaluation indicated that in more than 75% of cases, useful advice was obtained regarding radiological evaluation, stroke diagnosis and management via telestroke contact (Wiborg & Widder 2003). Telestroke systems are therefore in a position to provide expert advice from stroke specialists to community and other hospitals in the subacute management of patients who have been admitted with a stroke. In particular, this advice and support will help prevent complications in the immediate post-stroke period as well as encourage the initiation of the correct therapies such as anticoagulation at appropriate times and management of blood pressure discrepancies. It can also help to encourage application of the recommendations of the ASA task force (Schwamm et al. 2005).

Rehabilitation in subacute stroke

The Recommendations for the Establishment of Stroke Systems of Care by the ASA task force state that:

> *"Stroke patients should be referred to an inpatient facility, an outpatient facility, or a home care service that provides for their medical and functional needs" (Schwamm et al. 2005).*

Many stroke sufferers lack access to rehabilitation services (physio-, speech and occupational therapy). There are many reasons for this including overload of services, financial constraints for the victim or family and geographic limitations (Frankel et al. 2007). Moreover, although stroke rehabilitation is effective, often neither the time nor the intensity is available from stretched resources (Hachinski et al. 2010). If this is so in the urban setting, it is manifestly more so in the rural areas of the world. Simple educational teleconferencing adapted to local circumstances can, even if only partially, bridge the gap between need and delivery. Show-and-tell educational programmes can involve and make use of family members and friends in the implementation of evidence-based rehabilitation strategies. This is particularly applicable in the developing world. Telecommunication has the potential to bring expertise from multidisciplinary teams to a vast number of stroke survivors at very low cost, but the effect of telecommunication in providing such education in stroke survivors has not yet been adequately evaluated.

The challenge is to be able to evaluate the relative value of each rehabilitation activity in terms of return per unit of investment of time, resources or both (Hachinski 2001). Apart from traditional methods, the AHA/ASA has endorsed the development of novel technology-assisted rehabilitation modalities (Hachinski et al. 2010). Electronic communication between stroke survivors anywhere in the world and stroke experts has tremendous potential to promote self-management. Creativity will be the key, and telecommunication, in particular videoconferencing, should provide the vehicle of communication. A telemedicine programme can therefore be of use not only in a community hospital setting, but also in the organisation of home rehabilitation, thereby allowing the recommendations of the ASA task force to be followed in all settings.

Psychiatric evaluation and intervention

Telemedicine in the form of videoconferencing was, from a very early stage in its history, used for long-distance psychiatric evaluation and treatment, and was found to be effective (Doze et al. 1999; Matsuura et al. 2000; Simpson et al. 2001). A systematic review by Hackett et al (2005) of all published non experimental studies of depressive symptoms after stroke reported that one third of all people experience significant depressive symptoms at some time after the onset of stroke. The authors acknowledge, however, that this is probably a conservative estimate due to potential under-reporting or under-recognition of altered mood, and the difficulties typically associated with mood assessment of stroke patients, particularly when there are communication problems caused by dysphasia and/or dementia. The effect of this is to delay rehabilitation, to limit compliance with secondary prevention measures as well as to increase the long-term morbidity. Therefore, identification of post-stroke depression (PSD) is vitally important. Telestroke is a technology which would be ideal for periodic screening for depression as well as delivery of appropriate treatment. Again, as a member of the multidisciplinary stroke team, the psychiatrist can add a valuable segment to the armamentarium required to maintain the stroke chain of recovery. The effect of this form of surveillance and appropriate intervention requires evaluation in the future.

Social evaluation and intervention of patients, family and proxy

The social burden placed on stroke victims and their families is often enormous. Ongoing evaluation of the impact of stroke, particularly on the carers and families is seldom performed. The evaluation of social situations often requires skilled interviewing. This is another area in which a telestroke model has potential. As a member of the multidisciplinary stroke team, an experienced social worker can contribute vastly in bringing to light financial and other social problems, and providing expert advice either directly or via a proxy such as a district nurse.

2.3 Telestroke for secondary prevention after discharge from hospital

Importance of preventive strategies

The most effective way to reduce the burden of recurrent cerebrovascular disease on society is by prevention (Gorelick 1997). Long-term effective risk factor management presents a positive challenge to stroke management as the risk for recurrent stroke can be reduced by around 70-80% if simple best-practice recommendations are implemented (Hachinski 2002; Yusuf 2002). Unfortunately, secondary prevention measures are all too frequently sub-optimally implemented in stroke survivors (Jencks et al. 2000; Touze et al. 2008). In a recent landmark paper, Hachinski et al (2010) point out that despite the fact that stroke is increasing on a world-wide scale as the result of several well-known risk factors, these factors are frequently not well managed and are in fact neglected. There is a considerable degree of “therapeutic inertia” at primary care level and a high rate of medication discontinuation in stroke survivors after discharge (Dergalust et al. 2003).

For example, a large Swedish population-based cohort study of 28,449 participants by Li et al (2008) showed that in people with a history of previous stroke, 7.5 years after enrolment there was a high rate of hypertension (79.4%), only half were on anti-hypertensive medication and only 11.5% achieved a blood pressure < 140/90 mm Hg. In addition, the majority of stroke survivors with hypercholesterolaemia were not treated with lipid lowering medication, and antithrombotics were used in only 38%. One third was still smoking and two thirds were obese. The calculated stroke risk was significantly higher in stroke survivors than in people without stroke. The evidence from Canada suggests that although many hospitals have directed their attention to acute service provision, ongoing patient support related to secondary prevention has not been adequately addressed (Deshpande et al. 2008). A review of hospital-based stroke services over 5 years in North Carolina showed that during that period there had been almost no change in hospital programmes related to stroke prevention (Camilo & Goldstein 2003). Further, in the Netherlands, a study by Boter (2004) showed that the quality of life deteriorated significantly in the post-discharge period and that about 50% of stroke survivors were dissatisfied with the care provided after discharge.

There have been 21 studies (one being an RCT) describing the application of telestroke in rehabilitation. Most of the studies have described the use of technology solutions, principally to support rehabilitation activities (Hersh et al. 2006).

Joubert et al (2006; 2008a; 2008b) examined the effect of a telemedicine intervention on risk factor management and depressive symptoms in the ICARUSS study. Despite the published importance of implementation of best-practice management principles, this is the only telestroke study that has addressed risk factor management directly and shown results in an RCT. The intervention in the trial was telephone contact with patients and carers, and bi-directional information sharing between coordinator, patient and general practitioner using telephone and facsimile, coupled with data management, surveillance and response through a web-based EDC. Telephone contact between stroke specialist and primary care physician was maintained by telephone. The target populations were patients, carers and general practitioners. In this study, there was a significant improvement in a variety of measures such as risk factors, BMI, physical activity, and disability as measured by modified Rankin score (mRS) in patients exposed to the telestroke intervention compared to usual care. Moreover, depressive symptoms were significantly reduced in the telestroke group.

Support for caregivers and stroke survivors

About 80% of stroke survivors are reliant on family caregivers for emotional and physical support, ranging from assisting with activities of daily living, to arranging and escorting to medical appointments. These caregivers are often elderly, some infirm. Caregiver failure or collapse is more a cause for stroke survivor institutionalisation than is commonly realised. If the carer can be "enrolled" and supported in the role of a member of the team there is an increased likelihood that the stroke survivor will remain in the community (Grant et al. 2002).

The Internet-based support study by Pierce et al (2004) highlights caregivers' need for emotional and social support, and the general acceptance of a telestroke support system. Pilot work had indicated that a major issue identified by caregivers was the need to increase their level of knowledge about stroke in general, which the Internet-based study attempted to rectify.

Important issues of acceptance by stroke survivors' caregivers was emphasised in the study by Buckley et al (2004) who found that to some, new technology presented an extra burden.

Some caregivers only wanted simple telephone support. In this study, it was evident that the nurse's support was paramount.

Assessment of the caregiver appears to be an important measure. An evaluation of their level of technical competence, their fear of intrusion into their privacy and their desire for inclusion into a telestroke system should be carried out. Often overlooked issues include the functional ability of the caregiver, the amount of time able to be provided by the caregiver, the number of individuals sharing the burden, and involvement of the caregiver in management planning prior to discharge (Grant et al. 2002). These studies emphasise the fact that there is an unmet need in caregivers, but that the solution is probably not simple, and that telestroke support to this important group needs further study.

Coaching the Primary Care physician

In the study by Boter et al (2004), patients and carers were advised to seek help from primary care physicians if the situation warranted this. The contact and coordination with primary care physicians was more directed and active in the study by Mayo et al (2008) but neither provided and supported the general practitioner in risk factor management. In the Australian ICARUSS model, there is bi-directional information sharing regarding risk factor status of stroke survivors between the coordinator, specialist stroke services and primary care physician (Joubert, Joubert et al. 2008). Reaction to persistently abnormal values is an integral part of the EDC. The telephone support from the specialist physician to the primary care physician is part of the "shared care" component of ICARUSS. In this model, screening for symptoms of depression is done on a three-monthly basis and the results faxed to the primary care physician.

Highlighting specialist stroke services and the coordinator's role

ICARUSS also provides an example of a telestroke model that maintains specialist involvement throughout. The immediate, real time potential specialist support to the primary care physician provides the "contemporaneous sharing of responsibility" between primary care physicians and specialist, which is the element of shared care. The coordinator plays a key role in all the telestroke models for stroke survivors described below in section 3. In some, the role is passive (Camilo & Goldstein 2003) while in others (Grant et al. 2002; Joubert et al. 2008a) the interaction is more active. The coordinator plays a role in problem solving, education, surveillance and reaction as well as psychological and social support. In ICARUSS, the coordinator is the link between patient, caregiver, primary care physician and the specialist stroke services. Interestingly, the results of the latter models were significantly more positive compared to the former studies.

2.4 Telestroke for overall stroke management and education (patients and professionals)

The Recommendations for the Establishment of Stroke Systems of Care by the ASA task force state that:

> *"A stroke system should develop support tools to assist the population as a whole, patients and providers in long-term adherence to primordial and primary preventive treatment regimens" (Schwamm et al. 2005).*

Indeed, stroke programmes have a vital role to play in educating the public and primary physicians about risk factors, symptom management, and stroke prevention (Moulin & Hommel 2005). Telemedicine can be particularly useful in applying this recommendation to populations or communities in rural or under-serviced areas. Appropriately timed educational videoconferencing by stroke experts may be useful not only in forums open to the general public, but also for patients, carers, nursing and allied health staff as well as medical personnel. Topics that can be covered are signs and symptoms of cerebrovascular disease, acute treatment options, in-hospital management and implementation of preventive strategies. Virtual contact with the opportunity for discussion as a supplement to written guidelines may be particularly valuable and should be the subject of future research. This is separate from the educational aspects of the virtual neurological telestroke conferencing described above.

Awareness of signs of stroke is variable, particularly in rural areas. In Montana, a telephone survey of 800 rural residents revealed that 70% were able to identify 2 or more warning signs, although only 38% recognised that speech difficulty was a sign of a stroke. In West Virginia, only 20% of residents were able to identify all stroke warning signs, most were unaware of the importance of loss of vision and severe headache as indications of stroke. The results of a survey in northeast Bulgaria by Dokova et al (2005) were similarly disappointing and a study in rural Georgia, USA, also revealed a low level of awareness of stroke warning signs. Although 48% of respondents had experienced a stroke in the family, and 95% considered stroke an emergency, only 39% of 602 adults could name 1 or more stroke warning signs in response to unaided questions. A component of the current web-based support tool for rural caregivers in rural Ohio and Michigan is raising the awareness of features of stroke in caregivers. Stroke signs were readily identified by Tsongan and Mozambican populations, but the reaction was to consult traditional healers (Hundt et al. 2004).

Awareness of risk factors for stroke is equally as patchy, and again, particularly in rural areas. In a rural Mennonite community study by Michel et al (1993) only 8% of the study population had ever been screened for serum cholesterol, despite the fact that one-third of those over the age of 55 years had either had a stroke or a myocardial infarction. Cooper et al (2005) reported that in sub-Saharan Africa hypertension awareness rates were as low as 20%, and in a Montana-based study by Blades et al (2005), only 44% of the participants were able to identify hypertension as a risk factor for stroke. A rural-urban study by Hu et al (2000) in a population of 35 years and older in China showed that awareness of hypertension was 2.6% in rural populations compared to 4.4% in urban ones.

Risk factors for vascular disease including stroke are on the increase. Examples of this are the obesity epidemic, the increase in diabetes and prevalence of raised blood pressure, particularly evident in the developed world, but also strongly predicted in the developing world (Beaglehole et al. 2007; Thompson & Hakim 2009).

Telemedicine opens the possibility for primordial prevention in communities. Individuals at risk, as identified in clinics or by primary care physicians or nurses, family members of stroke victims and other members of the general public, could all be targeted for teleconferencing from stroke centres. This aspect of the prevention of stroke has been sorely neglected. Telemedicine as a modality of education in stroke prevention clinics has not been studied and deserves evaluation as to whether it is equal to or an improvement on current modalities of education, and in fact whether it can be used as an adjunct to these modalities (Hachinski et al. 2010).

3. Telestroke requirements

3.1 Technology options for telestroke

A range of generic and personalised technology options have been used in different studies, including telephone, facsimile, email, videoconferencing, and internet-based communication.

Use of telephone

Simple telephone contact has been shown to be useful in different situations, such as giving practical problem-solving advice to caregivers. Moreover, the contact was useful in reducing stress in a study by Grant et al (2002). Telephone interviews have been shown to be reliable in the application of a variety of assessment and measuring tools, such as the Stroke Impact Scale (SIS) (Kwon et al. 2006), and proved reliable for evaluation of function, disability and cognitive function in community outpatients (Meschia et al. 2004; Merino et al. 2005). Telephone administration of the Patient Health Questionnaire (PHQ9) has been validated in stroke patients (Lee et al. 2007). This instrument has demonstrated reliability as a screening tool for Post Stroke Depression (Williams et al. 2005). There is a need to determine the best modality for achieving the requisite goal in stroke survivors. These goals may be risk factor modification, patient and carer education, detection and management of post-stroke depression, carer support, strategy implementation, rehabilitation or simple surveillance of health service usage. Different modalities may be appropriate for different goals in that simple telephone calls may suffice for patient and carer education or support (Grant et al. 2002; Buckley et al. 2004), whereas videoconferencing would be required for a tele-rehabilitation programme (Hersh et al. 2006), or a psychiatric intervention for depression (Doze et al. 1999).

Use of Videoconferencing

Videoconferencing enables the patient, the caregivers, and the local and distant physicians to interact visually and audibly. However, minimum specifications need to be determined on the technical aspects including the degree of resolution of the computer screens and bandwidth to transmit videoconferencing and images. Some studies have also indicated that sound quality needs to be improved (Audebert et al. 2005; Meyer et al. 2008).

In order to address these technical issues, the following requirements have been proposed: a remote-control camera with zoom, tilt and rotation functions at the distant or "spoke" hospital, and large monitors with high resolution are needed in both the "hub" and "spoke" hospitals. To maintain sufficient visual quality (25–30 frames per second), a bandwidth of at least 300 kilobits per second is required (Audebert 2006). A controlled trial, allocating hospital-based or mobile teleconsulting and evaluating technical parameters, acceptability, and the impact on immediate clinical decisions showed that critical treatment decisions can be made on the basis of laptop-based telestroke consultations using the available European mobile network technology. However, although the technical quality was sufficient to make relevant immediate clinical decisions, the quality of the video examination was considered inferior to hospital-based consultations and there were critical comments regarding the lack of a video stream on the spoke side (Audebert et al. 2008).

Innovative Technologies

The literature reveals an interest in experimenting with new information and communication technologies from videoconferencing, Internet web-cams, to virtual reality haptic workbenches. Indeed, technological advances and developments in communication methods have led to new ventures within the field of telemedicine, and more specifically, telestroke. For example, Covotem™ Video Solutions is a telestroke tool that has been developed for emergency stroke treatment and secondary prevention. It comprises a software platform, HD videoconference and a high quality sound system. Covotem™ enables the neurologist to remotely manipulate a motorised camera in order to dynamically visualise the patient. A graphical editor enables medical imaging to be shared in real-time in DICOM format so that the type of stroke can be diagnosed and thrombolysis administered if necessary. Patient data can also be shared via an electronic file.This is just one example of the way in which information technology has taken giant strides in developing effective and efficient tools for delivering health services to widely dispersed populations.

3.2 Telestroke models: organisation and networks

Primary Stroke Centres (PSCs)

The overriding theme supporting the organisation of any model of telestroke care, particularly in the acute stage of stroke, is the availability of centres of excellence (PSCs) that are accredited and conform to requirements that enable them to not only be resources for the administration of rt-PA, but also act as "mentors" for hospitals receiving acute cases that are appropriate for thrombolysis, but which do not have the expertise or resources to implement the treatment without support.

Recommendations for such centres that would improve the treatment of stroke patients in the acute stage were determined by the Brain Attack Coalition (BAC) in 2000 (Alberts et al. 2000). These recommendations consisted of a number of constituent features such as the formation of acute stroke teams, the availability of 24 hour brain imaging and written protocols for the administration of rt-PA.

The BAC has determined optimum time-guidelines for patient triage and evaluation. They have determined that a stroke team should evaluate potential stroke patients within 15 minutes of arrival at the emergency department. This guideline in itself shifts priorities in a busy emergency department for the rapid evaluation of the stroke patient which is very different from the situation in the pre-thrombolytic period. Following this, computerised tomography (CT) of the brain should be performed within 25 minutes and reported on within 45 minutes. Ideally, in eligible stroke patients, intravenous rt-PA should be administered within 60 minutes (Switzer & Hess 2008).

The above rapid response has been sadly lacking, not only in community and rural hospitals, but also in major urban hospitals. The ideal of rt-PA administration within 60 minutes of arrival was only achieved in 16% of patients receiving thrombolytic therapy in a recent study by Reeves et al (2005) of hospitals from four states in the US.

Nevertheless, there have been gains and a demonstrated reduction of the delay between the presentation of a stroke patient at hospital and the appropriate administration of rt-PA, indicating that with guidelines and structure, systems of management can be changed.

Following the recommendations of the BAC, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) commenced the certification of these, and according to a review in 2008 by Switzer and Hess, there were over 300 JCAHO-accredited PSCs in 40 states as well as the District of Columbia.

The Complete Telestroke Model

A fully developed telestroke network involves the expertise from the PSC being directly applied to the clinical situation. Contact with the patient and family can be made via a video link, and NIHSS scoring performed by the PSC neurologist. Moreover, transfer of radiological data takes place, and CT reporting is done from the PSC. For this to function well, reliable video contact and ability for image transfer is mandatory. Another requirement is that the PSC or "hub" hospital has around-the-clock availability for teleconsultation. This will often only be possible from larger academic centres, with adequate staff components. Experienced stroke physicians will be able to read CTs adequately, but in large centres, radiological cover is frequently present for early evaluation of CT images.

For the most part, the model is a “fixed–site” one, which promotes high quality video and audio communication. In the “site-independent” model, connection is via the internet and often video quality is poorer than in the fixed-site model.

The “hub and spoke” model has been adopted widely in both the United States and Europe. Examples of such models of telestroke in the United States have been the Remote Evaluation of Acute isCHemic stroke (REACH) programme in east-central Georgia (2008–09.), the Partners Telestroke Center in Massachusetts and Stroke Telemedicine Initiative in New York State. In Europe, effective telestroke projects such as the Emergency Neurology Network in Franche Comte (RUN-FC) (Moulin et al. 2004), and the TEMPiS project in Bavaria (Audebert et al. 2005) have been in existence since the early part of the millennium. Despite varying emphases and differences in the model details, all have in common the expedition of treatment of acute stroke and the apposition of specialist stroke services and often remote, under-serviced hospitals by technology.

The development of variant interhospital collaborative models for acute treatments

Due to the large variation of hospital resources, both in urban and rural settings, the most efficient, practical and achievable model has to be identified (usually by the spoke hospital). This of course can change as the spoke hospital staff become more familiar with administering rt-PA. However, for the main part, between PSCs and spoke hospitals, established models of management of acute stroke cases have been developed. In addition, there is an increased risk of complications in situations where there is intermittent or infrequent administration of rt-PA, and an efficient mentoring relationship with a PSC is of great value to the community especially remote hospitals in managing the process (Heuschmann et al. 2003). In this regard, a mentoring role of academic hospitals and other PSCs has developed three major models of collaboration.

These models link community and other hospitals, especially geographically isolated ones, with centres that regularly and expertly use thrombolysis.

- *“Call and ship” model*

This is the most common model of expedition of thrombolysis in urban areas in the industrialised world. It is not a traditional telestroke model except that there is initial and sometimes ongoing contact (telephone or radio) between EMS and the PSC, but it emphasises a rapid response and evaluation on the part of the EMS with rapid transport to a PSC.

Here, the EMS identifies an appropriate stroke patient, contacts the PSC and then transports the patient via MICA ambulance or whatever is the most rapid means to the PSC or specialist stroke service.

One of the difficulties in this model is the misdiagnosis of stroke. Thrombolysis is only safe and effective in selected cases of cerebral infarction, and would be disastrous in the context of cerebral haemorrhage. Inherent in this model is the inability to identify cerebral haemorrhage accurately on clinical grounds (Crocco et al. 2003), as well as the variability of accurate stroke diagnosis by ambulance personnel. The sensitivity of stroke diagnosis varies widely (between 61% and 94%) and positive predictive values remain low (Rajajee & Saver 2005). Two screening tools exist; both designed to aid the pre-hospital identification of stroke by EMS. These are the Los Angeles Pre-hospital Stroke Screen (LAPSS) (Kothari et al. 1997) and the Cincinnati Pre-hospital Stroke Scale (Kidwell et al. 2000). Through use of the LAPSS in both California and Houston, Texas, the sensitivity of stroke diagnosis increased substantially. In Los Angeles, sensitivity was 91% and positive predictive value for stroke diagnosis was 97% (Switzer & Hess 2008).

Other factors do play a role, such as traffic conditions and misdirection to hospitals that do not have the expertise to administer rt-PA. In the United States there are only three states (Florida, Massachusetts and Texas) where it is legislated that the EMS takes stroke patients to a certified PSC (Switzer & Hess 2008).

Video assessment in ambulance cars was used in the TeleBAT system of the University of Maryland's Brain Attack Team (LaMonte et al. 2000). Low mobile transmission rates of 9.6 kbps only allowed transmission of two frames per second along with a voice channel. However the authors demonstrated the feasibility of performing the NIHSS evaluation in a specially-equipped dedicated ambulance. Video examination in the ambulance car is also currently being evaluated in Berlin using real patients and much higher transmission rates. The next step will be a controlled trial comparing stroke admissions by telemedicine-armed ambulance and by normal ambulance cars (de Bustos et al. 2009). It is clear that existing technology can provide some degree of interactive video and audio communication with pre-hospital units in transport, although current published applications have unacceptably low frame rates, and broad application of this technology to large fleets of EMS vehicles is not yet practical. Providing stroke expertise to the ambulance via HQ-VTC may increase diagnostic accuracy, provide earlier resource mobilisation, and increase appropriate triage. Furthermore, if effective pre-hospital neuroprotective interventions are available in the future, telemedicine may increase their appropriate use (Schwamm et al. 2009).

- *"Ship and Drip" Model*

This model embraces rapid communication between a community hospital and the expedited transport of an appropriate candidate for thrombolysis from that hospital to a PSC, where final evaluation and treatment can take place. Two PSCs in London and Ontario, Canada, have acted as hub hospitals for 33 spoke hospitals (Merino et al. 2002). Often basic facilities for evaluation and treatment such as CT scanners were not available in the spoke hospitals. In the London experience, of 82 consecutive patients undergoing thrombolysis in these two PSCs, 23 were transfers from rural spoke hospitals. Interestingly, patients referred had a shorter onset to treatment time compared to stroke victims presenting to London Emergency departments (148 minutes compared to 172 minutes). The essential decision in this model is whether the patient can be transported within the three-hour window. The Canadian study showed that this method can be applied with good effect. It is, however, not the most effective (Switzer & Hess 2008). The inherent difficulties in this model are availability of transport and time of transport. It is a model that could be greatly enhanced by telestroke communication.

- *"Trip and Treat" Model*

In this model, one that has been tested with good effect in both Houston and Cincinnati (Grotta et al. 2001), the stroke specialist is transported from a PSC to the patient judged appropriate for thrombolysis in a community hospital. It depends on several features that are different from the "Ship and Drip" model. These are: availability of CT facilities at the community hospital, adequate transport and availability of staff at the "hub" hospital to travel. This has been shown to be feasible in urban settings. For instance, the Cincinnati Stroke Team serves a ring of 22 surrounding hospitals. Inherent in this model is the problem of navigation of urban traffic. It is essentially an urban model reliant on large academic institutions with large staff components.

- *"Drip and Ship" Model*

In this model, which is closer to the ideal telestroke model, the appropriate patient is treated in a community hospital with intravenous rt-PA, and after this, is transferred to a PSC. In this model, the initial evaluation of the patient and CT are made at the community hospital site with thrombolysis commenced at that hospital. The initiation of thrombolytic therapy is done with telephone support from the PSC. There is no video contact between the two hospitals and no transfer of radiological data. Transfer of the patient takes place by whatever means is available. Intravenous rt-PA is frequently kept running during the transportation. On arrival at the PSC, the patient is evaluated for possible intra-arterial therapy. The deficits inherent in this system are inaccurate evaluation both of onset and physical status of the patient, and the inaccurate reading of CT scans. Non-neurologists making decisions and unavailability of radiological cover can give rise to less than optimal evaluation. Despite these drawbacks the model has been shown to be effective in several studies (Wang et al. 2000; Rymer et al. 2003; Frey et al. 2005).

4. Barriers to the implementation of telestroke models

4.1 Technical advances

One of the major barriers to the success of telestroke is that, despite the numerous advantages of recent technological advances, technical problems arise with telemedicine technology, including non-connecting or malfunctioning devices. This problem must be eradicated since it can lead to distrust by users and low levels of satisfaction, which can be further aggravated in cases of lack of interoperability due to fears of rapid obsolescence and wasted capital.

In terms of telemedicine-directed stroke care, there have been 3 different methods used for interaction: (1) telephone service; (2) HQ-VTC with an on-call stroke team using an Internet-based wireless or high-speed landline connection; and (3) a combination of telephone and video methods. Each of these methods has strengths and weaknesses, and several trials are seeking to determine whether videoconferencing is superior to exclusively telephonic interaction (Schwamm et al. 2009).

Despite innovative technological solutions making medical imaging available for simultaneous viewing by spoke hospital personnel and the telestroke consultant, which reduces the number of individuals required to make definitive recommendations regarding thrombolytic therapy or other time-critical interventions, many rural areas (as well as some urban and suburban areas) do not have access to consistent low-latency, high-speed bandwidth sufficient to support reliable, high quality video transmission and reception over open, standards-compliant networks. The presence of essential infrastructure (telephone lines, wireless broadband) must be assessed for hospitals participating in the exchange of telemedicine data as part of an SSCM implementation. Effective information technology systems and supporting infrastructure need to be put in place to initiate a telemedicine programme for stroke treatment. For example, the mode of data transmission must provide adequate bandwidth to transmit large amounts of data quickly, accurately, and securely.

The fact that the spectrum of IT options is expanding rapidly, whilst costs are decreasing, is perhaps more important. However, deployment of these options is not uniformly available across all geographical and demographic users. Fibre-optic cable is not yet as ubiquitous and high bandwidth mobile phone networks (such as G3) do not have the same coverage as GSM (Webb and Williams, 2006). More importantly, money is often spent on technical equipment but not sufficiently on the personal resources needed in telemedicine services.

4.2 Costs of infrastructure and staff

For a PSC to function as a centre of excellence that supports thrombolysis for remote hospitals, there are two main cost areas; one being the infrastructure set-up and the second has to do with staffing. In terms of infrastructure, the issues such as the acquisition of computers, the software related to these as well as the setting up of a system of data transmission that is in accordance with Privacy Guidelines for the specific country have to be resolved at a local level. The second problem of staffing relegates the setting up of telestroke networks to hub hospitals that have large numbers of staff, such as large academic departments. These hub hospitals take on the responsibility of providing access to stroke experts 24 hours per day, providing education to spoke hospital staff in how the process functions, providing systems for acquisition of images and, if necessary, having neuroradiological support available on a round-the clock basis.

Accessibility to necessary technology that is mandatory for the transfer of data from spoke to hub hospitals has varied in the past. However, increased availability of broadband nationwide has recently taken place due to a government initiative in Australia, and incentives for installation of fibre optic cabling to facilitate to high-speed Internet is an ideal that rural health care providers and local government should consider. However, due to economic factors, particularly in the developing world, there will always be barriers to attaining the ideal of good connectivity. Therefore the different modalities of telestroke connections such as Plain Old Telephone Service (POTS), cellular telephone network, HQ-VTC via Internet based wireless or high-speed landline connection as well as a model employing a combination of these methods, will vary from country to country, and the formation of a telestroke service should make use of existing and feasible technology as well as creativity.

Despite the fact that there is sufficient data to show that telestroke programmes increase the use of thrombolytics and in doing so reduce long term disability, there are few data concerning the economics of the programmes as a whole. Collection of health economic data concomitantly with clinical data is essential in future studies, not only in determining the economics of thrombolysis, but also the effect of telestroke programmes on risk factor management and thereby reduction of recurrent stroke and a step-wise decline into dependency. In a recent Danish study by Ehlers et al (2008), which looked at the cost-effectiveness of rt-PA administration between 5 centres and 5 clinics, the additional costs in this model over one year were $3 million. In the first year, the incremental cost-effectiveness ratio from Telestroke was around $50,000 per quality-adjusted-life-years (QALYs). In the second year, the telemedicine model was both less costly and more effective due to less expenditure in rehabilitation and long-term care.

Apart from cost-effectiveness, the cost in terms of resource utilisation, investment costs and maintenance costs has not been rigorously studied in the area of telestroke models (Johansson & Wild 2010). The German TEMPiS study was evaluated to cost €300,000 per year. When teleconsultation expenses were subtracted, the net cost ranged between €19,200 and €56,000 per year (Audebert et al. 2005). A telestroke system requires an initial capital expenditure in terms of equipment, maintenance, education of staff and support. Apart from these costs, telestroke networks require teams of on-call doctors as well as administrative and nursing staff. If the telestroke model uses the “drip and ship” approach, then the costs of transport have to be factored into the whole equation.

4.3 Funding and reimbursement

There are two main issues with reimbursement. The methods of how the referring and the consulting physician are reimbursed vary from situation to situation depending on the country. The situation becomes more complex when cross-border referrals are made. The second is the reimbursement of hospitals themselves. In the United States, as a result of the additional costs of special monitoring of patients who have been administered rt-PA, Medicare and others have developed a new coding system that covers the ancillary costs (Schwamm et al. 2009). There are complex issues regarding reimbursement in those patients who are transferred to a hub hospital. In particular this applies to cases where the “drip and ship” model is used. All in all, with a telestroke intervention, in addition to the cost of the drug itself, the overall cost includes the reimbursement of personnel and the cost of setting up the system, coupled with the training of all the healthcare participants.

4.4 Legal, deontological and ethical issues

General Background

The development of ICT over recent years is an incontrovertible fact and this has had an inevitable impact on medical practices. However, the majority of doctors have been unable to keep up with the speed and complexity of technological advances, and this has given rise to a number of bioethical issues (in the sense that ethical questions arise from the development of biotechnologies).

Just like progress in intensive care medicine has led to the concept of brain death or the potentials of medically-assisted procreation have led to reflections on assisted reproduction and filiation, the practice of telemedicine raises issues relating to the doctor-patient relationship and the freedom and responsibilities of the doctor. From a deontological perspective, the practice of medicine is an independent (exempt from material or moral pressures), personal and free act, but with this freedom comes responsibility. These principles are bound by competence, and the law specifies that if the attending physician does not possess the sufficient knowledge or technical know-how, he or she must call upon the expertise of a more specialised colleague. The attending physician assumes the responsibility for this step, even if only in the choice of specialist, and at this point is still the patient’s interlocutor, notably in deciding whether or not he or she will follow the advice given.

The doctor-patient relationship is therefore very much a two-way relationship, and should ideally be fostered in a safe environment, enabling the flow of inter-subjective and ultimately non-verbal information (mimic, jests, attitude, etc.).

The practice of telemedicine introduces a whole new dimension: communication is established at a distance using images and/or sound, in real time or asynchronously, and with a “virtual” doctor whose advice has a determining impact on the patient’s health. This advice may be given to the “real” doctor at the patient’s bedside (teleconsultation), or when reviewing a patient's file in the absence of the patient (tele-expertise). These situations do not result from any active choice made by the patient; they arise as the result of various "objective" constraints, some of which are linked to health policies such as doctor shortages, hospital closures, insufficient technical platforms, geographical remoteness of a centre of reference, etc. On the other hand, the use of telemedicine is also a clear expression of the progress that has been made, not only in the area of telecommunications, but also of medical techniques, some of which can only be employed at a highly specialised level. These ICT advances can be used to bring about real improvements in sound quality, and to compensate for certain insufficiencies or deteriorations to the healthcare environment. However, patients may be surprised, or even unsettled, by this wave of new technologies, which is why particular attention should be paid to ensuring that patients are sufficiently informed before giving their consent. In this regard, for instance, the fact that the French medical council recommends that patients sign an information letter is evidence of the unusual nature of the doctor-patient relationship. If a patient is unable to give his or her consent (reduced alertness or aphasia), the use of telemedicine is determined by therapeutic necessity (i.e., article 16-3 of the French civil code).

In the context of tele-expertise and teleconsultation, the roles and subsequent responsibilities of the different doctors who intervene can be particularly difficult to define. This issue is even more complex due to the general lack of legal provisions and clarity concerning this new practice. However, these difficulties should not be used as a pretext for inaction. The essential drive for the development of telemedicine will surely come from the willingness of doctors to collaborate with each other, to define and formalise their responsibilities (conventions, protocols) and to enrol their patients in these new practices if they are convinced of their effectiveness. In such circumstances, the general legal approach in terms of responsibility is that each actor (doctors and healthcare institutions) must answer for their actions according to their actual or assumed competencies. Thus the attending physician, for example, must gather the necessary information (through questioning, clinical examination, details from the patient file) which can be given when requested to the virtual doctor, who must therefore then take responsibility for his recommendations (Contis 2010).

Patient Confidentiality

Another characteristic of the doctor-patient relationship is that it is governed by the rules of patient confidentiality. It is the doctor who is responsible for ensuring that the existence and the nature of all patient consultations remain confidential. The digitisation of data, computerisation of patient files and the use of new ICT make it more complicated to monitor health-related information. It means that doctors have to hand over part of their responsibility to machines, procedures, software, and more generally to technologies of which they are not in full command. With the use of telemedicine, health-related data and its confidential nature is inevitably shared. The challenge involves limiting this information sharing to the necessary, and giving the patient a certain amount of say over what is transmitted.

The choice by the doctor of the relevant data can be difficult: in certain cases, it involves the results of complementary examinations or technical data, but in other cases, elements of the patient's personal life, his or her personality, or the tone of the relationship that he has with the doctor can be factors that influence the choice of treatment. It remains unclear how these more sensitive factors would best be communicated if patients were to exert greater control over the nature of the information transmitted, the risk being that it may become progressively excluded from the sharing process. For example, in France, although article n° 2002-303 of 4th March 2002 declared the principle of "express" consent for the hosting of health-related data, article n° 2007-127 of 30th January 2007 states that an exemption is possible when the host is in agreement and the data are transmitted by a professional or a healthcare institution. In other words, digitised personal health data can be physically transferred and stored without the patient knowing. It is therefore important to be able to trace, archive and store these multiple files which are essentially a record of an individual and personal medical event, and which may need to be shared, but must also remain confidential.

Community and emergency physicians' attitudes and medico-legal liability

In situations where intravenous rt-PA is administered by inexperienced physicians or by physicians who very infrequently use thrombolysis, it has been shown that complications such as intracerebral haemorrhage are more common than when the evaluation of the patient and the administration is performed by doctors who do it frequently (Katzan et al. 2000). Brown et al (2005) reported that the fear of complications is the main reason for 40% of emergency physicians not using rt-PA. This is driven by the fear of litigation. Conversely there is a medico-legal danger in not administering thrombolysis in appropriate patients. In a review of litigation related to the use or non-use of rt-PA (Demaerschalk & Yip 2005), in those cases where the outcome was in the plaintiffs favour, 83% related to failure to treat, whereas complications of treatment were only cited in 17%. Nevertheless, there is a significant number of doctors who choose not to expose themselves to situations where decisions regarding thrombolysis may need to be made for both these reasons and also because they do not wish to carry the on-call and after-hours responsibility.

Because of the risk of medical liability in not providing rt-PA in spoke hospitals, a telestroke programme involving expert "supervision" and, if possible, video assessment of the clinical status of the patient can be of great benefit for the spoke medical personnel. Accurate documentation of the clinical situation by both ends of the telestroke team ensures that medical liability for withholding treatment and complications resulting from the treatment is of great value for a spoke hospital (Liang & Zivin 2008).

Telestroke is a recent addition to the armamentarium of the community or rural physician and even urban physicians outside stroke centres. There is an understandable lack of trust and familiarity with the process because of this. Rates of telestroke referral and contact between spoke and hub hospitals vary considerably both in Germany (2% vs. 86% (Wiborg & Widder 2003), and the United States (Nesbitt et al. 2000). This lack of trust and reluctance to participate on the part of the spoke hospitals can be overcome in a number of ways. Involving the spoke hospital, nursing and administrative staff at an early stage in the process of setting up a spoke site, leads to them being able to "buy in" to the process. Other methods would be to have information and educational sessions with clear delineation of duties of nursing and medical staff. Ultimately, telemedicine is an indicator of the development of medical practices, and has an impact on both patients and doctors. It enables the diffusion of advanced treatments and techniques through the remote transmission of procedures and knowledge, and provides access to ultra-specialised expertise. It reveals the development of the doctor-patient relationship which is becoming more and more technical at the risk of becoming dehumanised. This may be accentuated by collaborative efforts between doctors which only take into account the objective elements, and overlook the importance of subjectivity when treating patients. Finally telemedicine highlights the dangers involved in the digitisation and diffusion of personal data.

5. Future trends and recommendations

Experiences have clearly demonstrated the wide-ranging current and potential benefits of telemedicine applied to stroke. Telestroke effectively links remote hospitals and underserved areas to PSCs, bringing effective therapies to patients in these areas. The impact of telestroke in implementing thrombolysis is well established and many other important benefits have now emerged, notably in the areas of stroke rehabilitation and secondary prevention. Therefore, as emphasised by Tatlisumak et al (2009), telestroke should be understood as a versatile tool which is not limited to delivery of thrombolysis, but offers numerous other benefits to stroke patients in underserved regions.

However, despite these demonstrated benefits, telestroke is currently not being used according to its full potential. Major advances will only be achieved in the future if the main barriers hampering the wider use of telemedicine, most of which have been identified, can be overcome.

As information technology continues to advance, it will be important to ensure that medicine is able to leverage and optimise the benefits of these developments. One of the top priorities will involve providing essential infrastructure to remote rural-based hospitals. The need for enhanced connectivity to rural areas urgently needs to be addressed. This could be partially achieved through the launch of dedicated programmes, such as the Federal Communications Commission's Rural Health Care Pilot Program in the United States, which offers huge discounts to collaboratives of rural health facilities that install commercial fibre optic cabling for access to high-speed internet. In addition, the rapid pace of technological advances will demand resolution of technical issues, facilitation of market development, and repeated assessment of the appropriate quality standards in health-related telecommunication (de Bustos et al. 2009). After all, patients will be much more inclined to partake in telemedicine if they believe they can do so privately and safely, and trust both the physician and technical provider. Alleviating patient concerns about the confidentiality of health-related information is therefore an important goal. This will be further facilitated by ensuring that all hospital staffed involved (specialists, emergency physicians, nurses, admin staff) have a positive attitude toward telemedicine practices by providing them with the necessary information and training.

As telemedicine also introduces a new form of interrelationship between health care providers, mutual trust and acceptance need to be developed here too. Indeed, in order to progress from small scale pilot projects to the national deployment of telemedicine, there is a pressing need for political will. This will help to overcome barriers such as the reimbursement issue, and will essentially involve convincing healthcare providers that telemedicine does have added value by providing them with information on evidence-based cases.

Further advances need to be made relating to legal clarity to ensure that the development of telemedicine is not hindered by legislation that is stuck in the past. Cross-border provision of telemedicine services requires legal clarification on an international basis. For instance, some EU states have clear legal frameworks for enabling telemedicine, whereas in other countries, the laws require that the acting health professional is physically at the same place as the patient. This is a clear obstacle to the deployment of telestroke and highlights the need for standardised regulations to address the medical liability associated with telemedicine-enabled care. As suggested by de Bustos et al (2009), the fact that teleconsultations in acute stroke are very similar to onsite stroke consultations should facilitate these regulations.

Finally, continued efforts must be made to continue to further develop the widespread deployment of telemedicine to the areas of stroke rehabilitation and secondary prevention in order to reduce the impact of problems such as post stroke depression in stroke survivors, and to stem the increase in stroke-related risk factors. Therapeutic inertia associated with the long-term management of these risk factors remains common at primary care level and in order to address this, a combination of a 'hub-and-spoke' case management model (care coordinator, with multiple stroke survivors) with a linear 'top-down' model (specialist, coordinator, carer, patient and primary care physician) could be advantageous. The ICARUSS model by Joubert et al (2006; 2008a; 2008b) provides an example of a telestroke model which specifically supports the implementation of secondary stroke prevention strategies and the detection of post stroke depression. Hersh et al. (2006) found that there were only a small number of well-designed telestroke studies, particularly in rural settings. There is a need for more rigorously designed randomised controlled trials and longitudinal observational studies of clinical outcomes to demonstrate the effective use of telemedicine in stroke survivors discharged from hospital (Lewis et al. 2006).

6. Acknowledgement

We are particularly grateful to Melanie Cole for her dedicated assistance in editing the manuscript.

7. References

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2

A Framework for Telestroke Network Design

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1. Introduction

Stroke is the third leading cause of death and leading cause of adult long-term disability in western industrialized countries. In stroke units providing special expertise, stroke patients receive highly efficacious care (Pollack et al., 2007). However, stroke units cannot be implemented in particular in sparsely populated rural areas because of a shortage of experienced neurologists (Audebert & Schwamm, 2009). As compensatory measures, telemedical solutions are increasingly applied within "telestroke" networks to provide neurological expertise from "hubs" to small primary care hospitals ("spokes") (Audebert 2006; Müller et al., 2006). Due to various environmental factors and personal preferences, different types of telestroke networks have emerged especially in Europe and the United States within the last ten years (Schwamm et al., 2009a; Günzel et al., 2010).

In these networks, various pilot studies have demonstrated that valid decisions on thrombolytic therapy, the most important and time-critical therapy for the majority of acute stroke patients, and on a variety of further special interventions can be made accurately with the aid of telemedical expert support (Audebert et al., 2006; Audebert et al., 2009). Since telemedicine has proven to be a valid supplemental procedure in the treatment of acute stroke patients, primary care hospitals, especially in less populated regions, increasingly show interest in complementing their range of care by teleconsultations (Ickenstein et al., 2010). Those primary care hospitals may have totally different characteristics, some are e.g. small and located far away from the next certified stroke unit, while others are medium-sized and have neurology experts available on weekdays, but need support for night shifts and weekends. From a health economic point of view, these and many other different types of hospitals could benefit from telestroke care.

However, current telemedicine networks focus in their approaches mostly on one specific group of primary care hospitals, thereby excluding others and thus withholding specialized stroke care from a large number of stroke patients. The situation may even worsen when national reimbursement regulations for telestroke care within the DRG system will be introduced. Those regulations will most likely be tied to current practice of the dominant telestroke network design in the respective country, thereby raising an entry barrier for all other primary care hospitals.

To address these important issues for the first time, comparative health economic research into optimizing health care provision by both local stroke units and combinations of established telestroke network concepts is needed – and it must specifically take into account different regional environments. In this study, we first attempt to systematically characterize telestroke network structures and identify parameters describing different established models. Second, we provide a novel structural framework and illustrate that fundamental but widely differing concepts do not compete with but rather complement each other from a primary care hospital point of view. Based on this framework, we suggest a proactive approach to customized network design.

This book chapter is organized as follows: in section 2 we give a brief overview of three leading telestroke network concepts. Section 3 presents a novel systematic taxonomy of telestroke network concepts based upon the central protagonist roles in telemedicine. Section 4 is devoted to presenting a hierarchical decision algorithm for choosing an optimal telestroke network design from the perspective of a primary care hospital. Finally, in section 5 we provide an exemplary case study of a fictitious hospital seeking to improve its stroke patient care by telemedicine.

2. International telestroke care

To identify the leading European and American telemedicine networks for acute stroke, a systematic literature review of the PubMed database (keywords "telemedicine" AND "stroke", "telestroke", "network") and ensuing expert interviews were conducted in 2008 and again in 2010. Thirty-four networks in seven countries could be determined that were actively using telemedicine to enhance stroke care. A sample of these networks representing a conceptually wide range of telestroke applications were visited, and additional in-depth knowledge beyond journal publications was gleaned from interviews with network representatives (Günzel et al., 2010). Telestroke network structures were examined from medical and technological as well as health economic viewpoints.

In all telestroke networks the teleconsultant can view the patient's brain scan (CT or MRI) that is uploaded onto a server platform via a DICOM interface. Furthermore, he is connected to the primary care hospital by a high-quality two-way video and audio transmission link and can observe the patient exam carried out bedside by the resident or attending physician. Having full control of the pan, tilt and zoom functions of the bedside camera, he can perform a thorough clinical assessment of the patient's neurological status. On the basis of the information thus gathered, the stroke expert communicates his diagnosis and related therapeutic recommendations to the physician and finally provides a medical report sheet (Schwamm et al., 2009b; Theiss et al., 2009).

Driven by personal preferences, national funding opportunities, regional factors and different foci in stroke care, a wide range of different telestroke network concepts has emerged beyond the common denominator of providing basic anamnestic patient data, CT-scan and high-quality two-way audio and video transmission.

From a structural perspective, the leading active telestroke network approaches belong to three different fundamental types: (1) the drip-and-ship concept (e.g. Partners Telestroke Center in Boston, MA, USA), (2) commercial neurological teleconsultation provider (CTP, e.g. Specialists on Call Inc. in Leesburg, VA, USA) and (3) the telestroke ward concept (e.g. The Telemedical Pilot Project for Integrative Stroke Care in Munich, Germany). Those are described below in more detail.

2.1 TeleStroke: Drip-and-ship concept for emergency rooms

The world's first telemedical stroke care network "Partners TeleStroke Center" started back in 2001 at the Massachusetts General Hospital (MGH) with two remote hospitals in Boston/USA (telestroke.massgeneral.org). Today, two academic stroke centers at MGH and

Brigham and Women's hospital provide about 200 acute stroke teleconsultations for 21 community hospitals in Massachusetts, New Hampshire and Maine per year. These primary care hospitals are mostly small community hospitals with CT-scan and laboratory available around the clock (Schwamm et al., 2004).

Implementing a "drip-and-ship" concept, the Partners TeleStroke Center network focuses on early identification of thrombolysis candidates in the network's primary care hospitals. Acute stroke patients admitted to a primary care hospital within the thrombolytic time window of 4.5 hours after symptom onset can be presented to the telestroke consultant, who discusses the findings with the on-site physician, and both together decide on a plan of care – in particular, the intravenous application of the clot-busting drug t-PA ("drip"). Up to 50% of the patients receiving t-PA, especially those developing complications, are transferred to one of the academic stroke centers ("ship"). Due to this narrow indication spectrum, all other acute neurological patients need to be treated or transferred by the primary care hospitals on their own.

It is the aim of the Partners TeleStroke Center network to promote the community hospitals to the status of an "acute stroke capable" hospital using the bridging concept within the first four hours of stroke. The neurological experts stress the relevance of the local network design and their personal educational relationship to the community hospital physicians, relying on the academic excellence of the university stroke centers (Farrell et al., 2008).

The total costs for both stroke centers and network hospitals are comparatively low, because Partners TeleStroke Center neurologists provide the teleconsultations as part of their in-house routine, and the community hospitals can request up to twelve consultations for an annual fee.

2.2 Specialists on Call: Commercial & global provider for teleneurological services

The first commercial provider of acute neurological teleconsultations, Specialists on Call (SOC), was founded in 2003 by a renowned Harvard neurologist at the Massachusetts General Hospital. With 30 appropriately accredited and licensed neurological consultants spread all over the country, SOC currently serves the biggest network worldwide and offers around 1,000 consultations per month to 100 hospitals in twelve US states. SOC uses a globally distributed network structure of both primary care hospitals and neurological consultants without any regional hub-and-spoke relationship around a stroke center. SOC has followed this global, scalable approach to teleconsultation from its inception, and addresses a wide spectrum of customer hospitals with solutions tailored to their demands to most perfectly supplement the existing in-house expertise (McDonald, 2008). This includes different service options as e.g. 24/7, night-shifts only or at the weekends as well as relocation management for urgent patient transfer. While stroke patients constitute approx. 71% of all incoming requests, SOC in principle answers all inquiries about neurological patients.

In practice, a hospital affiliated with SOC contacts a call center managing the distribution of incoming requests to the neurological consultants and making sure that these have the necessary anamnestic, CT and hospital data available. The neurological consultant "on call" then calls back to the inquiring hospital and arranges the consultation from his telemedical workstation.

Hospitals contracting with SOC pay a fixed initial fee for provision and installation of the hardware, with monthly rates depending on hospital size, average stroke incidence and type, but independent of the actual number of teleconsultations. Alongside the medical support service, SOC maintains the provided equipment (McDonald, 2009).

2.3 TEMPiS: Regional stroke care network with telemedical stroke ward

Germany's most renowned telemedical network TEMPiS (www.tempis.de) was founded in 2002 as a pilot project publicly financed by the Bavarian State, the German Stroke Foundation and Bavarian health insurances. In 2006, TEMPiS managed the transition to regular health insurance financing based upon a special reimbursement contract. Today, two comprehensive stroke centers (Munich and Regensburg) provide about 3,500 neurological teleconsultations per year to 15 community hospitals in eastern Bavaria (Vatankhah et al., 2008).

TEMPiS systematically follows an integrative, regional approach to stroke care which is based on the idea of transferring the stroke unit concept to hospitals lacking neurological expertise. Basically, TEMPiS network community hospitals set up full-blown regional stroke unit "minus 24/7 neurologists", and the neurological expertise is provided by teleconsultations with the stroke units in Munich and Regensburg (Audebert, 2006).

There are several essential building blocks of the TEMPiS concept. First and foremost, network hospitals have to establish a separate "telestroke ward" to accommodate stroke patients, and must provide monitoring beds, laboratory and CT around the clock. They also need to have specially trained personnel for early rehabilitation (e.g. physiotherapy, speech and occupational therapy). The implementation of standard operating procedures for stroke patient care is the third pillar of the TEMPiS concept, and goes hand in hand with the introduction of dedicated quality management and a regular education and training program both for physicians and nurses. TEMPiS strongly emphasizes the personal relationship between stroke center experts, network hospital physicians and nurses (Müller et al., 2006).

Due to the high telestroke ward installation and running costs, TEMPiS focuses on medium-sized hospitals which treat at least 200-250 stroke patients per year. The total annual expenses for both stroke centers are refunded by the network hospitals, which in turn receive a lump sum in excess of the DRG reimbursement from the health insurances for every stroke patient.

3. Telestroke network concept taxonomy

Starting from our observations in operational telestroke networks, we attempted to derive a generic, systematic classification of teleneurological consultation approaches in acute stroke patient care. To this end, we first identified the different protagonists participating in this process. In principle, there are many players involved in telemedicine on a formal level – from health care providers, health insurances, accrediting agencies and legislative bodies up to governments –, and they can have quite different impact e.g. in the United States or Europe. On an operative level, however, obviously three different key protagonists can be clearly distinguished in a telemedical scenario: the patient, the local primary care hospital, and the expert neurological consultant. In an attempt to illustrate the range covered by individual telestroke network concepts, we associated each protagonist role with a single (semi-) quantitative parameter varying along a one-dimensional axis. Eventually, we indicated the fundamental network type with the highest and lowest level of each parameter at the respective end of its axis.

The patient. We first linked the *patient* role in telestroke networks to the parameter "clinical indication spectrum" measuring which patients are actually eligible for the neurological teleconsultation. Among the fundamental network concepts described above, the drip-and-ship concept has the narrowest and most restricted clinical indication spectrum – it only provides neurological teleconsults for acute stroke patients eligible for thrombolysis or for neurosurgical or catheter intervention by referral to a tertiary care stroke center. On the other hand, commercially provided neurological teleconsults (CTP) are available to any patient in a hospital affiliated with the network, even way beyond the acute stroke condition. Therefore, the parameter axis "clinical indication spectrum" can be labeled as shown in Figure 1.

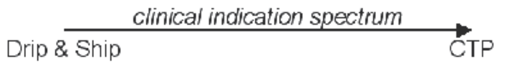

Fig. 1. The parameter "clinical indication spectrum" measures which patients are intended to benefit from neurological teleconsults.

The primary care hospital. In a second step, we associated the *primary care hospital* role with the parameter "required primary care hospital competency" measuring what amount of infrastructure and expertise is required for the hospital to receive the network's teleconsultation service. Clearly, the telestroke ward concept as practiced by TEMPiS is the most demanding network – primary care hospitals have to arrange a full-blown stroke unit except for the 24/7 available neurologist, and they must have a minimum annual stroke incidence of about 200–250 patients. On the other hand, neurological teleconsults offered either within a drip-and-ship network or by a commercial provider are available to any affiliated hospital, irrespective of its stroke care infrastructure. In order to stress the contrast between the telestroke ward and drip-and-ship concepts, we labeled the "required primary care hospital competency" parameter axis as shown in Figure 2.

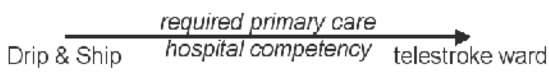

Fig. 2. The parameter "required primary care hospital competency" measures what conditions a hospital must fulfill to participate in a telestroke network.

The expert consultant. Finally, we characterized the *expert consultant* role by the parameter "consultant service spectrum" quantifying the degree of service offered by the teleconsult provider. Obviously, the regional TEMPiS telestroke ward concept ranks highest with respect to this parameter – it provides a wide range of educational and quality assurance measures beyond the actual teleconsult. In a drip-and-ship network, the tertiary care center still acts as referral hospital for stroke patients in need of neurointerventional procedures, while a non-locally distributed commercial teleconsultation network performs neither of these functions. Consequently, we labeled the "consultant service spectrum" axis as depicted in Figure 3.

Fig. 3. The parameter "consultant service spectrum" measures which services the telestroke consultant provides.

Available parameter space. Having associated the three principal protagonist roles in telestroke networks with semi-quantitative parameters, it is natural to examine whether these axes describe independent coordinates in an abstract three-dimensional space, i.e. if all combinations of values along theses axes indeed correspond to valid network concepts, or if constraints restrict the practically available parameter configurations. We will clarify this issue by two examples.

(1) If e.g. in an exemplary telestroke network the consultant service spectrum provided is rather comprehensive, this is best attained with a high level of stroke competency and infrastructure on the part of the primary care hospital to go along with the educational service measures. Furthermore, this is practically feasible only for an intermediate number of patients. An extensive service including in person education (as opposed to videoconference teaching rounds) and quality assurance can only be provided in a regional network and not from a distance. For a rather narrow clinical indication spectrum like in a drip-and-ship network, the low incidence of teleconsults does not warrant this big personnel effort, while for a maximally wide indication spectrum offered by a commercial provider the lack of regional relationship prevents in person attendance.

(2) If on the other hand only a rather narrow clinical indication spectrum is admitted to teleconsults in a second, exemplary low-throughput telestroke network, no particularly high stroke competency can reasonably be required to be kept at hand in the primary care hospitals for only very few patients. Furthermore, such a low-throughput consultancy cannot provide a wide service spectrum, and it would not find acceptance, if it only offered mere teleconsults without at least some interhospital transfer management. This is in line with the procedures implemented in drip-and-ship networks.

Triangular constraints. These examples motivate that constraints exist between the three parameters, and suggest to join the axes together in a triangular shape such that in each corner the same labels come together. This process is schematically depicted in Figure 4 (left), and leads to a symbolic representation of viable network concepts as points inside the triangle. As Figure 4 (right) explains, each network concept is characterized by suitable parameter values on the three sides (edges) of the triangle. Consider e.g. the concept represented by the center of the triangle where the three dashed blue lines intersect: each dashed blue line runs perpendicular to one edge of the triangle and marks the degree of the parameter on the respective side very much like in a conventional x-y-coordinate system, but with oblique axes. The telestroke network concept exemplarily depicted in Figure 4 (right) corresponds to an equal mixture of the three fundamental telestroke network types.

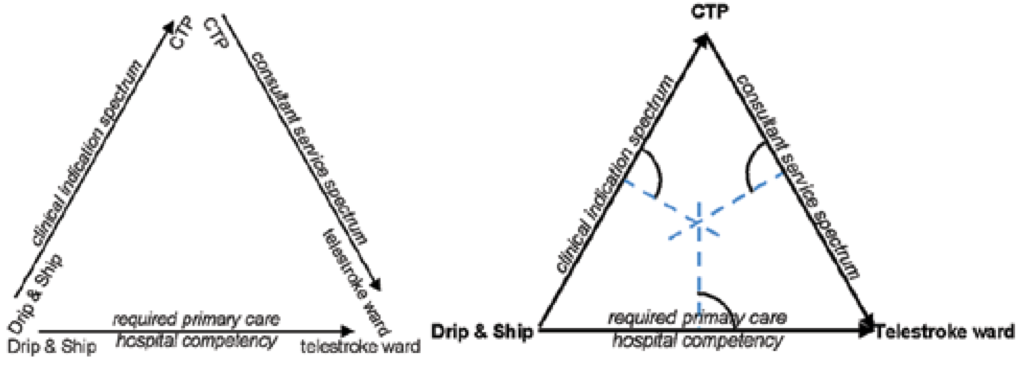

Fig. 4. Construction of the triangular classification scheme from the three individual parameter axes (left). For any valid telestroke network concept inside the triangle, the dashed blue lines indicate the respective associated parameter levels on the triangle's edges (right).

Implications for viable network concepts. Further conclusions can be drawn from this triangular parameterization of telestroke network concepts. First of all, the three fundamental telestroke network types are represented by the triangle's corners, and concepts similar to these types are placed close to the corners with similar parameter properties along both connecting edges. If a network similar to e.g. drip-and-ship is to be implemented, both "required primary care hospital competency" and "clinical indication spectrum" should be chosen "low".

Second, while for each viable network concept inside the triangle unique parameter properties can be read off along the edges (where the dashed blue lines end at right angles), the converse is not true: due to the constraints, we cannot choose all three parameter settings freely and end up with a workable network concept. This is exemplarily depicted in Figure 5: low required primary care hospital competency and wide clinical indication spectrum cannot be combined well with even a medium consultant service spectrum – it should be kept rather low.

There is not necessarily a single intersection of the three dashed blue lines starting at right angles from the desired parameter settings on the three edges of the triangle, since only any two of them can be chosen independently. The size of the small dashed blue triangle in the middle is a measure of the parameter settings' incompatibility: shifting the dashed blue lines appropriately indicates the necessary modifications of the initial "desired" settings that bring the intersection points closer together – and closer to a feasible solution.

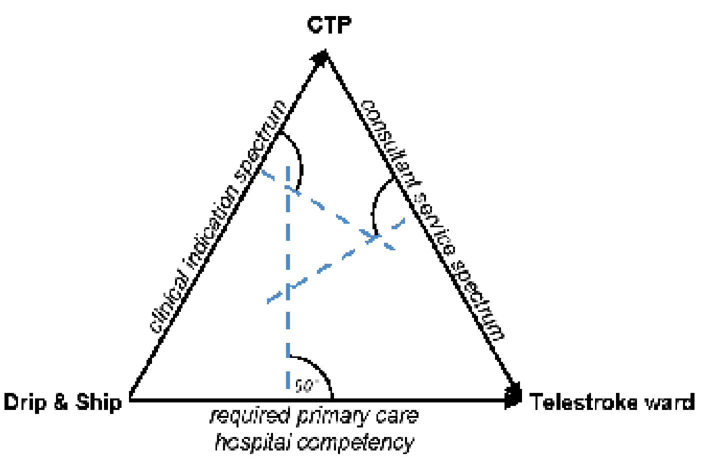

Fig. 5. Example of inconsistent "desired" parameter settings.

Practical consequences. How can a valid mixture of the three fundamental telestroke network concepts be implemented in practice, once it has been constructed according to the presented framework? A primary care hospital may choose a combination rather than any specific one of the fundamental types by associating with e.g. both a tertiary care center with neurointerventionalist specialties and a commercial teleconsultation provider. Specifically, only part of a telestroke ward could be implemented in the primary care hospital, patients eligible for neurosurgery could firstly be video-presented to a neurological consultant at a specialty center and then transferred to this clinic, and the remainder of stroke patients could be seen by a commercial teleconsultation service. **In this sense, the three concepts do not compete with but rather complement each other.**

4. Choosing optimal telestroke network design

Having posited a generic classification scheme for telestroke network concepts in the previous section, we now want to address rather practical issues of optimal telestroke network design. By construction, the classification scheme covers the views of all three principal telestroke protagonists – patient, primary care hospital and expert consultant. While the patient has no obvious part in *designing* a telestroke network, this process can be viewed from both remaining perspectives – service provider and recipient.

The first pilot telestroke networks have been driven by the initiative of stroke expert centers providing neurological teleconsultation. However, today's status in telestroke is entirely different, as various types of regional telestroke networks coexist with global commercial providers of neurological teleconsults. In this situation, it is rather appropriate to assume the viewpoint of a primary care hospital seeking to improve their acute stroke patient care, than that of a stroke center searching for potential network hospitals. Such a primary care hospital will typically have a clinic for internal medicine currently taking care of acute stroke patients, but no in-house neurological expertise. In an attempt to structure the process of deciding about a suitable telestroke concept, we present a hierarchical decision algorithm specifying which questions to answer along the road to a functioning implementation of telestroke. In this decision algorithm, we include the parameter axes introduced in section 3. In the following paragraphs we describe and exemplify the major decisions to be taken, while the entire decision algorithm is depicted in Figure 6.

Acute stroke incidence and regional stroke unit infrastructure. The most important data to start from is the incidence of stroke patients in the primary care hospital under study and the availability and accessibility of regional tertiary care infrastructure: stroke units, neurosurgery, neuroradiology and vascular surgery. Both these factors affect the levels of the two parameters "clinical indication spectrum" and "service spectrum provided" introduced in section 3. Local stroke incidence alone is the main determinant indicating whether it is reasonable for a primary care hospital to arrange a stroke unit of its own according to the recommendations of national and international stroke guidelines. Under a cost-effectiveness point of view, a certified stroke unit is only warranted for an annual acute stroke incidence exceeding about 450 patients (German Stroke Association, 2008). This first decision is shown in the leftmost column of Figure 6.

Preference: keep or transfer acute stroke patients? If the stroke incidence in the primary care hospital does not warrant arranging a stroke unit of its own, the next strategic decision is whether the hospital wants to keep and treat stroke patients or rather transfer them. This decision is reflected in the level of the parameter "service spectrum provided" of the above telestroke classification scheme. In the case of a primary care hospital with more than about 200-250 acute stroke patients per year, it is questionable to transfer all these patients for two reasons. First, a substantial loss of revenue would be associated with losing these patients, and second, there has to be a referral stroke unit sufficiently close by having the capacity to accommodate them. So in the case of high stroke incidence it will probably be preferable to establish a telestroke ward in the primary care hospital and acquire neurological expertise by teleconsult. Which clinical and administrative measures must be implemented in a telestroke ward to generate additional revenue for the hospital is to a large degree determined by national reimbursement regulations within the DRG system. For low incidence or a general preference to transfer acute stroke patients the main question is whether there is a tertiary care referral center sufficiently nearby that is willing and able to receive the transferred patients. Such a referral center could also offer neurological teleconsults to better select the cohort of patients benefiting most from a transfer. This step in the decision process is represented in the second column of Figure 6.

Targeted stroke competency in own hospital. In the next step, a primary care hospital preferring to keep acute stroke patients needs to specify the targeted degree of its own stroke competency. This corresponds to the parameter axis "required primary care hospital competency" introduced in the above classification scheme. In the case of high annual stroke incidence above 200-250 stroke patients it may well be reasonable for the primary care hospital to arrange a local telestroke ward of their own, including e.g. dysphagia diagnostics, early rehabilitation, speech and occupational therapy. Satisfying a set of conditions depending on national regulations, the hospital may become eligible for additional reimbursement for stroke patient treatment even without a local neurological department by acquiring teleneurological expertise. For low stroke incidence, it will probably be uneconomical to set up a whole telestroke ward, but patients will still benefit from some implemented measures and from neurological teleconsults – which along the way will also improve the hospital's reputation. This part of the decision process is depicted in the middle column of Figure 6.

Importance of regional relationship with the teleconsultant. Subsequently, the primary care hospital has to state its preferences regarding a regional relationship with the teleconsultant. There can be several good reasons for such a regional, even personal, relationship, e.g. a long standing successful collaboration with a nearby stroke unit already serving as a referral hospital, or a personal acquaintance with a stroke neurologist. These aspects become increasingly significant, if the hospital prefers to transfer acute stroke patients. In this case, the primary care hospital should ask the intended referral center for additional teleconsultation service. This part of the decision process is depicted in the second column from the right in Figure 6.

Economic viewpoint. Finally, if there is no nearby stroke unit available for teleconsultation, or if the regional relationship is not relevant, the primary care hospital should look for commercial teleconsultation providers and compare their value for money. First, it should assess the clinical indication spectrum covered by the provider and its relevance for the hospital and patients. For every network type considered, primary care hospitals should calculate a price per patient presented to the teleconsultant. To that end, it needs to add the annual costs for every model – including the running costs (e.g. additional staff, rent for rooms), the amortization rates of the investment costs (e.g. for new equipment, search costs for new employees) as well as the monthly fees paid to the provider. This should be compared to the additional incomes resulting from reduction in patients' length of stay, increase in the number of patients admitted to the hospital, additional reimbursement through the DRG system, which may vary significantly from system to system, and a better reputation. This part of the decision process is depicted in the bottom right section of Figure 6.

5. Exemplary case study

In order to round out the picture, we will consider an exemplary primary care hospital seeking the best way to improve stroke patient care by application of neurological teleconsultations. For the sake of the argument, we will work out our initial example sketched in section 4 and assume that the primary care hospital in question has a low-to-moderate annual incidence of 200 stroke patients, and the distance to the nearest stroke unit is slightly north of one hour by ambulance. Furthermore, suppose this nearest stroke unit is

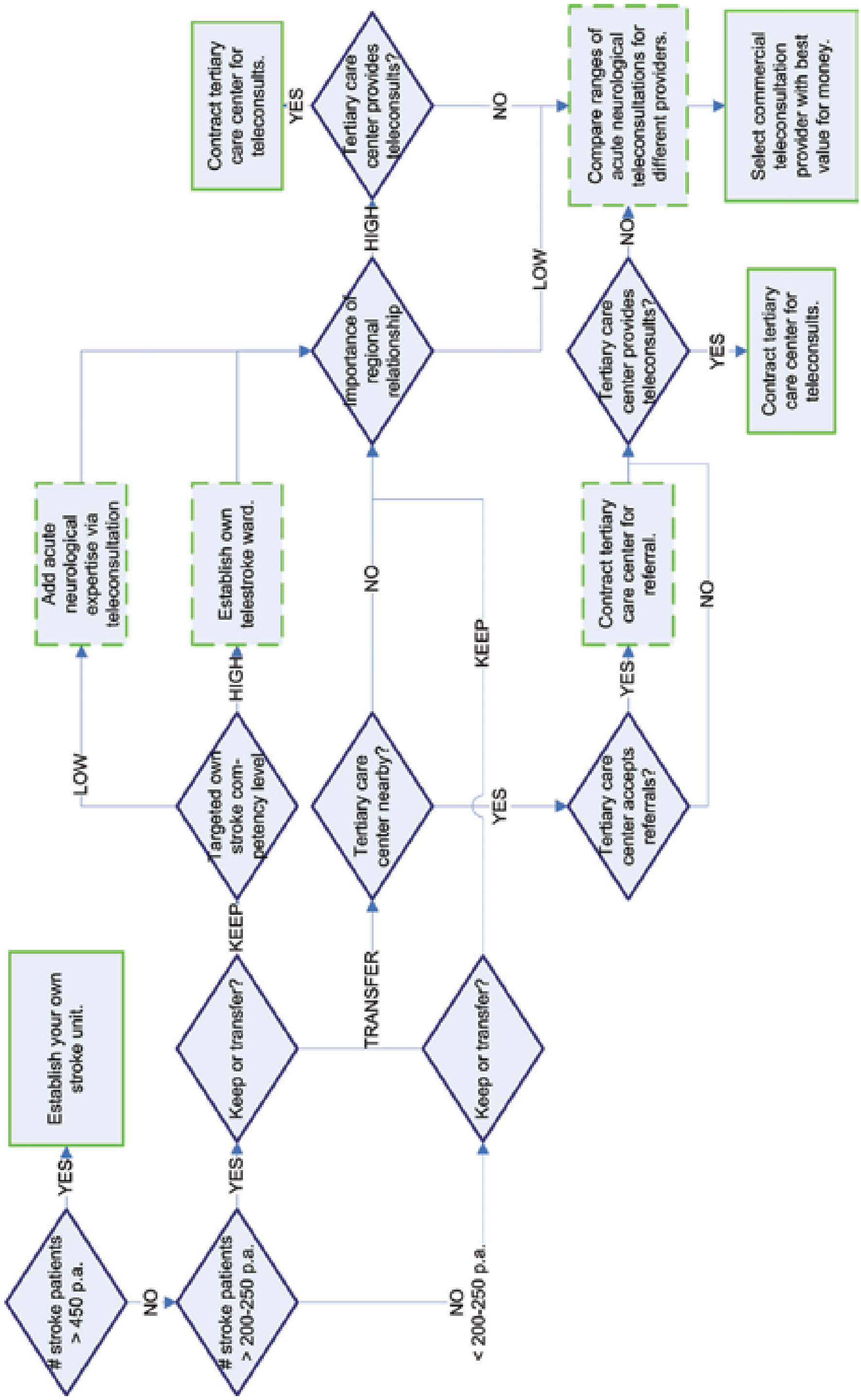

Fig. 6. Telestroke network concept decision algorithm.

part of a tertiary care center including neurosurgery and neuroradiology. Pondering the telemedicine options for stroke patient care, the hospital management may proceed along the decision tree in the following manner.

First of all, from the top level decision it is clear that it is not reasonable to arrange a full-blown stroke unit in this primary care hospital due to insufficient stroke incidence. Second, the hospital management realizes that it cannot reasonably transfer all acute stroke patients, since (1) that would mean a major reduction in revenue and (2) the potential referral stroke unit is too far away for the majority of patients to benefit. Thus, the general decision is to keep acute stroke patients. However, the physicians worry about their insufficient treatment options for severe acute strokes possibly requiring neurointervention, and would like to implement a bridging concept. Therefore they contact the tertiary care center and suggest to establish a neurological teleconsultation link in combination with a fast track (helicopter based) patient transfer option only for those severe acute stroke patients benefiting from neurointervention – maybe a few per month. The better the personal relationship to the tertiary care center already is, the more successful this endeavor will be in practice. The stroke unit in question is willing to cooperate within this setting, but they are unable to comply with any additional patient transfer requests. In order to provide supplemental neurological expertise to all patients presenting with acute neurological symptoms, the hospital management contacts a nationwide commercial provider of teleconsultations in this field. Thus, they treat different types of stroke patients according to different telestroke network concepts – and may even be using the same technology for both types of teleconsults.

Besides, the hospital's clinical directors have already been thinking about hiring a part-time speech therapist and an occupational therapist anyway, so with some stroke expert advice available these resources could be effectively used for acute stroke patients, too. Due to constraints in the hospital's staffing, however, it is impossible to arrange a completely certified telestroke ward, so the local stroke infrastructure is just improved by these two rehabilitation measures.

The clinical scenario described here is easily reflected in the triangular classification scheme presented above. The required primary care hospital competency is on an intermediate level, same as the clinical indication spectrum and the service spectrum provided: for a small number of severe stroke patients there is an intermediate spectrum of services provided (teleconsultation plus possible subsequent transfer within a bridging concept), and for all other patients with neurological symptoms, the teleneurological consult is available. So this scenario corresponds to a point close to the center of the diagram, as depicted in Figure 4 (right).

6. Discussion and conclusion

In this study, we present a novel approach to telestroke network design from the viewpoint of a primary care hospital seeking to improve its stroke patient care. The central conclusion of our systematic structural analysis is that a continuum of possible combinations of established network types is both feasible in principle and reasonable in practice. This conclusion constitutes a fundamental paradigm shift to the effect that telestroke network concepts do not compete with but rather complement each other.

Many primary care hospitals may well have refrained from implementing telestroke so far, because they felt that currently established network types would not meet their needs. Our results indicate, however, that they can in fact tailor a telemedical solution to their needs, combining features from a full range of different telestroke network types. Both in the systematic telestroke network taxonomy and by using the decision algorithm, such combinations or mixtures of telemedical concepts arise quite naturally.

Hence, from a health-economic point of view, many different kinds of primary care hospitals could benefit from implementing individual telestroke care solutions, and there is room for much more widespread applications. These unsatisfied customer needs should be met by designing innovative business models for telemedicine taking into account the problems arising from an ageing population and the projected increasing shortage of neurological experts in rural areas.

There are certain limitations to our study. Our formal representation of telestroke networks is based upon the identification of the central telemedicine protagonist roles and their association with semi-quantitative parameters. This association is not unique and different parameters could be constructed, but we are confident to have captured the most relevant protagonist properties in our model.

Moreover, the choice of network type as described in our triangular classification is not the single determinant of which specific measures the individual primary care hospital needs to implement in terms of local infrastructure and global telemedicine. These measures rather depend upon a number of additional aspects that go way beyond the presented telestroke classification scheme. A variety of environmental elements have to be taken into account: national, demographic, socioeconomic, infrastructural and regional factors like stroke incidence, hospital and physician availability or health care reimbursement regulations.

Complementary to these issues, each primary care hospital must take its individual economic perspective into account. It would therefore be highly desirable to determine the costs incurred and revenue generated by associating with specific telestroke network services. Any utility function derived from these costs and revenues will depend on the three parameters introduced in section 3, and can be pictured as a landscape above the triangular base, so that the network concept optimization task with respect to this utility function amounts to determining the minima (valleys) in this landscape. However, in order to actually perform such an optimization, quantitative economic data has to be collected first. Furthermore, the future savings by telestroke interventions in terms of healthcare and nursing costs remain quantitatively vague. Here, health economic studies are required to determine the actual added value of telestroke intervention and finally permit an economic comparison between different telestroke models.

7. Acknowledgement

The project TASC (*Telemedical Acute Stroke Care*) gratefully acknowledges financial support from the German Ministry of Education and Research (BMBF) within the framework of the program "ForMaT - Research for the Market in Teams" (ID 03F01242). The authors would like to thank the networks NeuroNet, Partners TeleStroke Center, REACHCall Inc., Specialists On Call Inc., SOS-NET, STENO, TEMPiS and TNS-NET for their kind hospitality and many stimulating and open discussions.

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3

Practical Operation of Telemedicine for Diagnostic, Therapy and Long Term Observation of Arterial Hypertension

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1. Introduction

Telemedicine increases quality of life dramatically. Patient's autonomy and responsibility are strengthened, that means a significant benefit. Patients realise a better safety with diagnostic and therapy as well as a decrease in therapeutic risks. This leads to a great acceptance of telemetric methods. Improvement of quality of life by telemedicine is demonstrable in heart failure, diabetes mellitus, rhythm disorders, psychiatric diseases and blood pressure. (Schmidt, 2009)

Telemetric medicine can be helpful in wide areas with low density of population like Africa and Asia, but also in rural regions in Europe (like Sweden, Scotland etc.) or North America or Canada with its large rural districts.

Worldwide, hypertension is common (Wolf-Meier et al., 2003) and regarded as a major public health problem. The prevalence of hypertension was found to be 28% in North America and 44 % in western Europe (Wolf-Meier et al., 2003).Though arterial hypertension was thought to be low in Africa in the 70ties and 80ties of the last century newer studies showed a prevalence between 15 % (Nigeria) and 28 % (Ghana) (Cappucio et al., 2004). Altogether patients in underserved rural areas have a higher prevalence of uncontrolled hypertension (Mainous et al., 2004).

Home monitoring can be a valuable tool in all populations. Patients who self-monitor can reach target BP goals with less medication (Verberk et al, 2007). Compared to office monitored patients they used an average of 1 drug or 1 dose less ($p<.0001$) at a reduced cost of $1124 per 100 patients for 1 month ($p<.001$) (Verberk et al., 2007).

The effectiveness of home monitoring is enhanced with Internet-based communications by health care providers (Green et al., 2008). A significant higher proportion of patients who received home blood pressure monitoring and Internet-based pharmacist care had controlled blood pressure (56%; 95%CI, 0,49-0,62) compared with those receiving standard care (31%; 95%CI, 0,25-0,37) or home-based care alone (36%; 95%CI 0,30-0,42) ($p<.001$) (Green et al., 2008)

Experience of safety and autonomy as well as responsibility for the own health is promoted by telemedicine. Numerous studies indicate an improvement of psychosocial factors. A deterioration of patient's psychosocial adaptation to the underlying disease by the used technology was picked up seldom.

Telemonitoring of blood pressure can be integrated into nearly every health care organisation. It can be realized in a regional as well as in a superregional model. Data are available at any place with Internet option. It's application is independent of national health care systems and allows their observation of patients far away from the treating centre. Beyond this every physician involved in the treatment is able to look to the data every time (via patient's password). This is of eminent importance to provide patients in large areas with a small number of physicians. Until now for Germany there are 110 national or superregional concepts integrating telemedicine into daily practise of treatment.

2. WHO Recommendations (Prevention of Cardiovascular Disease: guideline for assessment and management of total cardiovascular risk. WHO 2007)

Raised blood pressure is estimated to cause about 7 million premature deaths throughout the world, and 4.5% of the disease burden (64 million disability-adjusted life years (DALYs)) (World Health Organization, 2005; World Health Organization, 2002.; Lopez et al., 2006). It is a major risk factor for cerebrovascular disease, coronary heart disease, and cardiac and renal failure. Treating raised blood pressure has been associated with a 35–40% reduction in the risk of stroke and at least a 16% reduction in the risk of myocardial infarction (Collins et al., 1990). Raised blood pressure often coexists with other cardiovascular risk factors, such as tobacco use, overweight or obesity, dyslipidaemia and dysglycaemia, which increase the cardiovascular risk attributable to any level of blood pressure. Worldwide, these coexisting risk factors are often inadequately addressed in patients with raised blood pressure, with the result that, even if their blood pressure is lowered, these people still have high cardiovascular morbidity and mortality rates (Godley et al., 2001; Klungel etal., 1998; Trilling and Froom 2000).

Almost all clinical trials have confirmed the benefits of antihypertensive treatment at blood pressure levels of 160 mmHg (systolic) and 100 mmHg (diastolic) and above, regardless of the presence of other cardiovascular risk factors (Collins et al., 1990; Blood Pressure Lowering Treatment Trialists' Collaboration. 2000). Observational data support lowering of these systolic and diastolic thresholds (Van den Hoogen et al., 2000; Vasan et al., 2001).

Several trials in patients at high cardiovascular risk (Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. 2000; PROGRESS Collaborative Group. 2001; PATS Collaborating Group. 1995) have confirmed these observational data, showing reductions in cardiovascular morbidity and mortality in people whose blood pressure is reduced to levels significantly below 160 mmHg systolic and 90 mmHg diastolic. These trials support the view that, in patients at high cardiovascular risk, with blood pressures in the range 140–160 mmHg (systolic) and 90–100 mmHg (diastolic), lowering blood pressure reduces the number of cardiovascular events. These trial results suggest that treatment for such high-risk patients should begin at the lower blood pressure thresholds.

Although women are at lower total risk of cardiovascular disease for a given level of blood pressure, and randomized controlled trials generally include a greater proportion of men than women, the treatment thresholds for systolic and diastolic pressure should be the same in men and women (Gueyffier et al., 1997).

Total risk of cardiovascular disease for any given level of blood pressure rises with age. However, evidence from RCTs is currently limited and inconclusive about the benefits of treating those over 80 years of age. For now, the treatment threshold should be unaffected by age, at least up to 80 years. Thereafter, decisions should be made on an individual basis;

in any case, therapy should not be withdrawn from patients over 80 years of age (Bulpitt et al., 2003; Bulpitt et al., 1999).

3. Targets for blood pressure

In low- and medium-risk patients with elevated blood pressure, the Hypertension Optimal Treatment (HOT) trial found maximal cardiovascular benefit when blood pressure was reduced to 139/83 mmHg (Hansson et al., 1998). Clinic and population-based survey data continue to suggest that the lower the blood pressure achieved, the lower the rate of cardiovascular events (Gamble et al.,1998; Andersson et al., 1998; Liu et al., 2005). In people over 55 years of age, the systolic blood pressure is more important (Kannel 2000), so the primary goal of therapy is to lower systolic blood pressure to 140 mmHg or less. There is no apparent reason to modify this target for women or older patients.

Several trials (Hansson et al., 1998; Brenner et al., 2001; Parving et al., 2001; UKPDS Group. 1998; Zanchetti and Ruilope 2002) have shown that, in patients with diabetes, reduction of diastolic blood pressure to about 80 mmHg and of systolic blood pressure to about 130 mmHg is accompanied by a further reduction in cardiovascular events or diabetes-related microvascular complications, in comparison with patients with less stringent blood pressure control (Hansson et al., 1998; Brenner et al., 2001; Parving et al., 2001; UKPDS Group. 1998; Zanchetti and Ruilope 2002). In patients with high or very high cardiovascular risk, including diabetes or established vascular or renal disease, therefore, blood pressure should be reduced to 130/80 mmHg or less.

4. Methods for blood pressure measurement

Technical progress in blood pressure measurement is impressive in the last 20 years. The greatest advantage was the introduction of ambulatory blood pressure measurement and the telemetric transmission of home measured blood pressure into diagnostic and therapeutic follow up.

The different methods of blood pressure measurement are not competing but compiling. Each of the different techniques in blood pressure measuring contains certain advantages and power as well as disadvantages and weakness.

4.1 Blood pressure measurement (Mancia et al., 2007):

Blood pressure is characterized by large spontaneous variations both during the day and between days, months and seasons. Therefore the diagnosis of hypertension should be based on multiple blood pressure measurements, taken on separate occasions over a period of time. If blood pressure is only slightly elevated, repeated measurements should be obtained over a period of several months to define the patients ''usual'' blood pressure as accurately as possible. On the other hand, if the patient has a more marked blood pressure elevation, evidence of hypertension-related organ damage or a high or very high cardiovascular risk profile, repeated measurements should be obtained over shorter periods of time (weeks or days). In general, the diagnosis of hypertension should be based on at least 2 blood pressure measurements per visit and at least 2 to 3 visits, although in particularly severe cases the diagnosis can be based on measurements taken at a single visit. Blood pressures can be measured by the doctor or the nurse in the office or in the clinic (office or clinic blood pressure), by the patient or a relative at home, or automatically over 24 h.

4.2 Office blood pressure measurement

Office blood pressure measurement is considered to be the gold standard of blood pressure measurement. Blood pressure can be measured by a mercury sphygmomanometer the various parts of which (rubber tubes, valves, quantity of mercury, etc.) should be kept in proper working order. Other non-invasive devices (auscultatory or oscillometric semiautomatic devices) can also be used and will indeed become increasingly important because of the progressive banning of the medical use of mercury. However, these devices should be validated according to standardized protocols (O'Brien et al., 2001; http://www.dableducational.org), and their accuracy should be checked periodically by comparison with mercury sphygmomanometric values.

4.3 Blood pressure (BP) measurement

When measuring BP, care should be taken to:

1. Allow the patients to sit for several minutes in a quiet room before beginning BP measurements
2. Take at least two measurements spaced by 1–2 minutes, and additional measurements if the first two are quite different
3. Use a standard bladder (12–13 cm long and 35 cm wide) but have a larger and a smaller bladder available for fat and thin arms, respectively. Use the smaller bladder in children
4. Have the cuff at the heart level, whatever the position of the patient
5. Use phase I and V (disappearance) Korotkoff sounds to identify systolic and diastolic BP, respectively
6. Measure BP in both arms at first visit to detect possible differences due to peripheral vascular disease. In this instance, take the higher value as the reference one
7. Measure BP 1 and 5min after assumption of the standing position in elderly subjects, diabetic patients, and in other conditions in which postural hypotension may be frequent or suspected
8. Measure heart rate by pulse palpation (at least 30 sec) after the second measurement in the sitting position

4.4 Ambulatory blood pressure

Several devices (mostly oscillometric) are available for automatic blood pressure measurements in patients allowed to conduct a near normal life. They provide information on 24-hour average blood pressure as well as on mean values over more restricted periods such as the day, night or morning. This information should not be regarded as a substitute for information derived from conventional blood pressure measurements. However, it may be considered of important additional clinical value because cross-sectional and longitudinal studies have shown that office blood pressure has a limited relationship with 24-h blood pressure and thus with that occurring in daily life (Mancia et al., 2001; Mancia et al., 1995; Mancia et al., 2007). These studies have also shown that ambulatory blood pressure

1. correlates with hypertension-related organ damage and its changes by treatment more closely than does office blood pressure (Fagard et al., 1997; Mancia et al., 1997; Fagard et al., 1997; Verdecchia et al., 1990; Mancia et al., 2001; Redon et al., 1996),
2. has a relationship with cardiovascular events that is steeper than that observed for clinic blood pressure, with a prediction of cardiovascular risk greater than, and additional to the prediction provided by office blood pressure values in populations as

well as in untreated and treated hypertensives (Clement Det al., 2003; Sega et al., 2005; Fagard and Celis 2004; Dolan et al., 2005; Fagard et al., 2005; Hansen et al., 2005; Kikuya et al., 2005; Pickering et al., 2006), and

3. measures more accurately than clinic blood pressure the extent of blood pressure reduction induced by treatment, because of a higher reproducibility over time (Coats et al., 1992; Mancia et al., 1994) and an absent or negligible ''white coat'' (Parati et al.,1985) and placebo effect (Mancia et al., 1995; Staessen et al., 1994).

Although some of the above advantages can be obtained by increasing the number of office blood pressure measurements (Fagard RH et al., 1997; Mancia G et al., 1994), 24-hour ambulatory blood pressure monitoring may be useful at the time of diagnosis and at varying intervals during treatment. Effort should be made to extend ambulatory blood pressure monitoring to 24 hours in order to obtain information on both daytime and night time blood pressure profiles, day-night blood pressure difference, morning blood pressure rise and blood pressure variability. Daytime and night-time blood pressure values and changes by treatment are related to each other (Mancia G et al.,1995; Mancia G et al., 2007), but the prognostic value of night time blood pressure has been found to be superior to that of daytime blood pressure (Staessen JA et al., 1999; Sega R et al., 2005; Fagard RH et al., 2004; Dolan E et al., 2005; Fagard RH et al., 2005; Kikuya M et al., 2005). In addition, subjects in whom nocturnal decrease in blood pressure is blunted (non-dippers)(O'Brien E et al., 1988) have been reported to have a greater prevalence of organ damage and a less favourable outcome, although in some studies the prognostic value of this phenomenon was lost when multivariate analysis included 24-h average blood pressure (Staessen JA et al. 1999; Fagard RH et al., 2004; Fagard RH et al., 2005; Hansen et al., 2005; Ohkubo T et al.,2002; Verdecchia P et al.,1994; Metoki H et al., 2006; Hansen TW et al., 2006). Evidence is also available that cardiac and cerebrovascular events have a peak prevalence in the morning (Willich SN et al., 1992; Rocco MB et al.,1987; Muller JE et al., 1985; Elliott WJ. 1998), possibly in relation to the sharp blood pressure rise occurring at awaking from sleep (Millar-Craig MW et al., 1978; Kario K et al., 2003; Mancia G et al.,1980), as well as to an increased platelet aggregability, a reduced fibrinolytic activity and a sympathetic activation. Worsening of organ damage and the incidence of events have also been related to blood pressure variability as quantified by the standard deviation around mean values (Frattola A et al., 1993; Sander D et al., 2000; Verdecchia P et al., 1996). Although in these studies the role of confounding factors was not always excluded, an independent role of blood pressure variability has recently been confirmed by a long-term observational study (Mancia G et al.,2007).

4.5 Ambulatory blood pressure measurement

When measuring 24-hour blood pressure care should be taken to:

1. Use only devices validated by international standardized protocols.
2. Use cuffs of appropriate size and compare the initial values with those from a sphygmomanometer to check that the differences are not greater than ± 5mmHg
3. Set the automatic readings at no more than 30 min intervals to obtain an adequate number of values and have most hours represented if some readings are rejected because of artefact.
4. Automatic deflation of the equipment should be at a rate of no more than 2 mmHg/s.
5. Instruct the patients to engage in normal activities but to refrain from strenuous exercise, and to keep the arm extended and still at the time of cuff inflations.

6. Ask the patient to provide information in a diary on unusual events and on duration and quality of night sleep.
7. Obtain another ambulatory blood pressure if the first examination has less than 70% of the expected number of valid values because of frequent artefacts. Ensure that the proportion of valid values is similar for the day and night periods.
8. Remember that ambulatory blood pressure is usually several mmHg lower than office blood pressure. As shown in Table 5, different population studies indicate that office values of 140/90mmHg correspond to average 24-h values of either 125–130mmHg systolic and 80mmHg diastolic, the corresponding average daytime and night-time values being 130–135/85 and 120/70mmHg. These values may be regarded as approximate threshold values for diagnosing hypertension by ambulatory blood pressure.
9. Clinical judgement should be mainly based on average 24-hour, day and/or night values. Other information derived from ambulatory blood pressure (e.g. morning blood pressure surge and blood pressure standard deviations) is clinically promising, but the field should still be regarded as in the research phase.

4.4 Home blood pressure measurement

Self-measurement of blood pressure at home cannot provide the extensive information on daily life blood pressure values provided by ambulatory blood pressure monitoring. However, it can provide values on different days in a setting close to daily life. When averaged over a period of a few days these values share some of the advantages of ambulatory blood pressure, that is they are free of a significant white coat effect, are more reproducible and predict the presence and progression of organ damage as well as the risk of cardiovascular better than office values (Mancia G et al., 1997; Sega R et al.,2005; Fagard RH et al., 2004; Fagard RH et al., 2005; Sakuma M et al., 1997; Ohkubo T et al., 1998). Therefore, home blood pressure measurements for suitable periods can be recommended before and during treatment also because this relatively cheap procedure may improve patient adherence to treatment (Zarnke KB et al., 1997).

When advising self-measurement of blood pressure at home:

1. Suggest the use of validated devices. Few of the presently available wrist devices for measurement of blood pressure have been validated satisfactorily; should any of these wrist devices be used, the subject should be recommended to keep the arm at heart level during the measurement.
2. Prefer semiautomatic devices rather than a mercury sphygmomanometer to avoid the difficulty posed by having to educate the patient on its use and the error derived from hearing problems in elderly individuals
3. Instruct the patient to make measurements in the sitting position after several minutes rest, preferably in the morning and in the evening. Inform him or her that values may differ between measurements because of spontaneous blood pressure variability.
4. Avoid requesting that an excessive number of values are measured and ensure that those measurements include the period prior to drug intake so as to have information on the duration of treatment effects.
5. Remember that, as for ambulatory blood pressure, normal values are lower for home than for office blood pressure. Take 130–135/85mmHg as the values that approximately correspond to 140/90mmHg measured in the office or clinic (Table 1).
6. Give the patient clear instructions on the need to provide the doctor with proper documentation of the measured values and to avoid self-alterations of the treatment regimens.

4.5 Ambulatory and home BP measurements

Ambulatory BP

1. Although office BP should be used as reference, ambulatory BP may improve prediction of cardiovascular risk in untreated and treated patients
2. Normal values are different for office and ambulatory BP **(Table 1)**
3. 24-h ambulatory BP monitoring should be considered, in particular, when considerable variability of office BP is found over the same or different visits high office BP is measured in subjects otherwise at low total cardiovascular events risk there is a marked discrepancy between BP values measured in the office and at home resistance to drug treatment is suspected hypotensive episodes are suspected, particularly in elderly and diabetic patients office BP is elevated in pregnant women and pre-eclampsia is suspected

Home BP

1. Self-measurement of BP at home is of clinical value and its prognostic significance is now demonstrated. These measurements should be encouraged in order to:
   - provide more information on the BP lowering effect of treatment at trough, and thus on therapeutic coverage throughout the dose-to-dose time interval
   - improve patient's adherence to treatment regimens there are doubts on technical reliability/environmental conditions of ambulatory BP data
2. Self-measurement of BP at home should be discouraged whenever:
   - it causes anxiety to the patient
   - it induces self-modification of the treatment regimen
3. Normal values are different for office and home BP

	SBP	DBP
Office or clinic	140	90
24-hour	125-130	80
Day	130-135	85
Night	120	70
Home	130-135	85
Telemetric	135	85
Diabetes, renal failure, high cardiovascular risk (ESC/ESH 2010), office and clinic	130-139	80-85

Table 1. Blood pressure thresholds (mmHg) for definition of hypertension with different types of measurement. SBP indicates systolic blood pressure, DBP indicates diastolic blood pressure

5. Telemetric blood pressure measurement:

Self home blood pressure measurement has a number of potential advantages. These include avoidance of the "white-coat effect", possibility of multiple blood pressure readings over a long time, blood pressure reading at different times of the day and improvement of patient´s adherence to therapy (Yarows SA et al., 2000; Ogedegbe G and Schoenthaler A. 2006). There are however several difficulties in clinical practice. These include the use of nonvalidated devices, need of patient´s training, the risk of patients becoming neurotically obsessed by the procedure, not infrequently with self-modifications of the prescribed antihypertensive treatment (Imai Y et al., 2004), and the possibility of inaccurate report of home blood pressure values by the patients (Mengden T et al., 1998) as well as the difficulty for the physician to reach appropriate diagnostic conclusions from evaluation of often badly written patient´s blood pressure reports. It has been reported that in 54% of the cases, general practitioners fail to draw any meaningful conclusion out of patients´ blood pressure log books (Krecke HJ et al., 1996). Progress in technology over the last few years has led to the availability of a number of systems for digital storage of HBPM data and their transmission to remote sites (Mengden T et al., 2001).

5.1 Clinical background for the telemetric blood pressure measurement; methodical problems of blood pressure measurement:

In daily practice diagnostic and control of therapy of arterial hypertension are defined by blood pressure measurements at certain points in not exactly defined intervals. Between two office visits important uncertainties and lack of clarity exist in relation to adherence and compliance to therapy. We know, that the direct interaction between physician and patient increase adherence with therapy shortly before and after consultation. Motivation for taking the antihypertensive medication weakens considerably between the visits (Fig. 1). Lack of adherence to therapy ("compliance") is considered as the main factor for not reaching the target blood pressures. Medium therapeutic adherence in antihypertensive treated patients is about 50%. Adherence to therapy and quality of antihypertensive therapy can be increased by measures as increase of office visits, controls at home by ambulatory nurses, behaviour therapy, and specialized antihypertensive training programs. These measures are considerably limited by the available resources of Public Health. Telemedicine offers a promising approach by controlling chronically ills at their homes. The possibilities currently used to optimize the adherence of chronically ill patients are complex and unfortunately not very effective. The difficulties depend on the living and working conditions of our patients, their previous lifestyle (Bobrie G et al., 2007), fears and objections concerning the antihypertensive medication, and their other psychologically conditions like depressions or

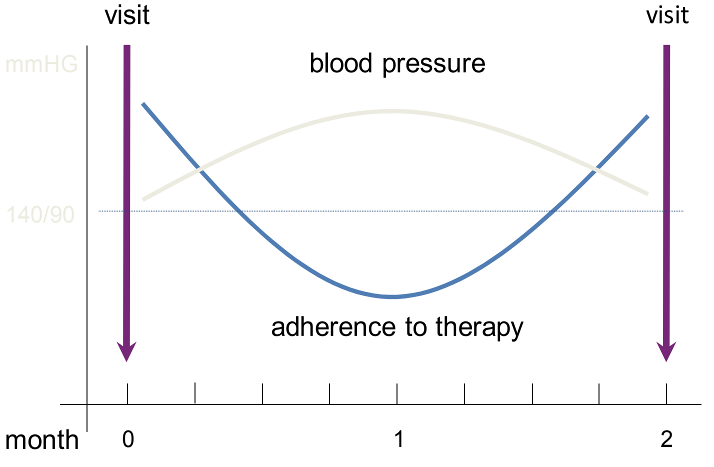

Fig. 1. Blood pressure control in 2 monthly intervals. Decrease of patient's compliance between two visits probably with increase of blood pressure between these visits. The supposed increase of blood pressure can not be recorded by office measurement.

negative emotions (Ashida T et al., 2008; Espinosa R et al., 2008). In addition to this there is the influence of the treating physician (Girerd X et al., 2008), possibly even her or his gender (Ericsson UB et al., 2008); even a specialized care can´t improve the compliance at least in men and older patients (Daghini E et al., 2008).

The assessments of quality of antihypertensive therapy differ between physician and patient (Sichkaruk I et al., 2008): the physician judges his patient better than patients do themselves – on the other hand side overestimates the physician his patient´s adherence (Zeller A et al., 2008).

In addition the physician is confronted with a conflicting problem in his daily practice. On the one site he wants and must have a good attitude to her or his patient, on the other hand site he must try to influence her or his patient´s lifestyle and/or supply them with antihypertensive medication. In this situation it is difficult to get a high amount of correspondence and/or mutuality. To be forced to control (controlling on the physicians side, to be observed on the patient´s side) conflicts with the effort to have a long-lasting good connection with the patients (physician respectively).

These difficulties and the need of medical care in wide areas with low density of population like Africa or Asia, but also in rural regions in Europe (like Sweden, Scotland etc.) North America or Canada with its large rural districts justify the development of new technical devices. Telemetric blood pressure measurements allow new dimensions for the cooperation between patients, physicians and public care. The assumption for a continuously therapeutic effort in cooperation between physician and patient is a therapeutic agreement with a clear definition of the target blood pressure. Randomized small studies show significant better blood pressure adjustment with telemetric monitoring compared to usual care (overview: Mengden T et al., 2001). The comparison shows a more intensive adaptation of antihypertensive medication in telemetric controlled patients. Beyond this the compliance of telemetric controlled patients increased significantly **(Tab. 2).**

6. Problems in home blood pressure measurement

Home blood pressure measurements are an effective and very helpful tool to support adherence to antihypertensive therapy (Mengden T et al., 2001). It can compensate partly the failing supervision by the treating general practitioner in diagnostic and therapy of arterial hypertension. It is helpful with "white coat hypertension", has a better correlation to the damage of target organs, improves the adherence to medical treatment, and allows a better control of long term treatment (Friedman RH et al., 1996 [Fig. 8]; Mengden T et al., 1998).

The acceptance of home blood pressure measurement by physicians is controversy. Less than 50% use it for diagnostic or therapeutic conclusions in their daily practice (Krecke HJ et al., 1996). The physicians justify this with:

- Uncertainty with the accuracy of the blood pressure measurement devices used
- Patient's insufficient training in the technique of home blood pressure measurement.
- Mistakes with documentation of home measured blood pressure.

Therefore automatically storing devices are recommended (Rogers MAM et al., 2001).

7. Telemetric blood pressure measurement in general praxis:

Telemetric blood pressure measurement is based on home blood pressure measurement. The blood pressure readings measured by the patient are send via handy (or an modem

literature	patients	design, duration	datarecord	data transfer	feedback to patients	Patient needs PC	results
Friedman 1996	267 uncontrolled hypertensive patients	UC vs. TM 6 months	patients protocoll	manuelly, weekly, public telefone network	yes, weekly	no	better blood pressure control with TM, especially if the compliance was bad
Rogers 2001	121 patients with arterial hypertension	UC vs. TM 8 weeks	device with storage, automatically	automatically, weekly, public telefone network	yes, weekly report of findings	no	significantly reduction of blood pressure (TM vs. UC)
Artinian 2007	387 uncontrolled hypertensive patients	UC vs. TM [b] 12 months	device with storage, automatically	manuelly, , public telefone network	yes, social health nurse- in TM	no	more decrease of systolic blood pressure (TM vs. UC)
Parati 2007	298 patients with grade I-II arterial hypertension	UC (I) vs. TM (II) vs. TM including feedback [a] (III)	device with storage, automatically	automatically, , public telefone network	yes, group III with memory-function	no	better blood pressure control in group II and III
Madsen 2008	236 patients with arterial hypertension	UC vs. TM 6 Monate	device with storage, automatically	automatically, PDA, Web-based	no	PDA	no difference between UC and TM
Green 2008	730 patients with arterial hyper-tension grade I - II	UC (I) vs. TM (II) vs. TM incuding feedback [b] (III)	device with storage, automatically	automatically, Web-based	yes, in II and III (WEB based)	yes	better blood pressure control in group III

abbrevations: UC - Usual Care TM – Telemonitoring
[a] automatically feedback including memory-function
[b] individualized telephone consultation by health care professional

Table 2. Randomised controlled studies comparing telemonitoring with standard care. Rogers (2001) and Parati (2007) showed moderate to missing effects in their studies. It can be summarised that telemonitoring is superior to usual care only with additional individualised interventions.

internet connection as well) to a data memory connected with a professional data base ("electronic post office"). The data are stored there and can be use by the treating physician and the patient. They are protected by a password and available wherever an internet connection is possible – even on smart phones (e.g. if the patient visits another physician). An alert system is part of the technique: information about exceeding of preliminary target values can be send automatically to the treating physician and/or if wished so) to the patient via e-mail, fax or SMS. The number of divergent blood pressures leading to alert can be selected freely. Alert is programmable concerning missing measurements in a given time interval as well. These technical features lead to a "virtually clinic for arterial hypertension" (Fig. 2), where visits of the patients are possible at any time and attention is attracted for those patients, needing a therapeutic intervention or those with poor compliance or adherence.

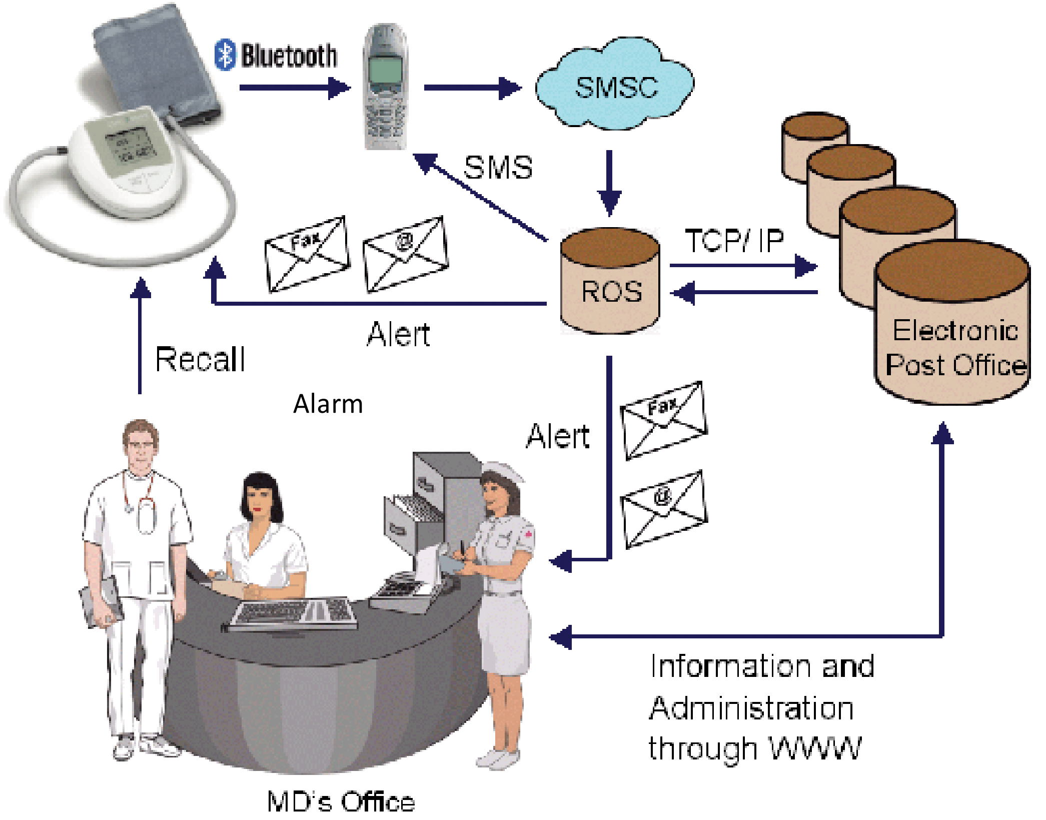

Fig. 2. Virtually clinic for hypertension. Home measured blood pressure is sent via "blue tooth" technique to a modem or handy. This generates a SMS-message to a national centre (ROS), which prompts them into a database. The patient and his physician are able to look to the data after logging in with their passwords. An additional alert-function informs the physician (and patient if she or he wishes so) if adjusted values are exceeded.

There are certain demands for a "virtually clinic for arterial hypertension":

1. A highly, clinically validated accuracy of measurement for the used blood pressure monitor devices according to the e.g. ESH protocol (Stegiou GS et al., 2010; O´Brien E et al., 2010) or one of the national protocols (see http://www.hochdruckliga.de, http://www.dableducational.org or http://www.bhs.soc.org).
2. Oscillometric measurement devices using the upper arm according to the ESC-guidelines (Mancia G et al. 2007).
3. Automatic data storing with a capacity of at minimum of 250-300 readings.
4. Acoustic and/or visual help remembering for blood pressure measurement and intake of medication.
5. Automatic periodically telemetric data transfer (fixed or mobile line network) to a service centre.

6. Standardised reports including statistical evaluations (mean, minimum and maximum), as well as trend plots for weeks and months.
7. Transfer of blood pressure reports to the patient and her/his general physician via letter, fax or web based e-mail.
8. Control function by general physician and/or a medical service centre.
9. Possibilities of intervention if adherence with the therapy is bad or blood pressure adjustment is insufficient.
10. Data protection and confidence.

Up to date there is no comparative assessment of the different technological possibilities for a virtually “Clinic of Hypertension”. Our own experience show that systems with automatically data transfer from patient to a service centre via mobile communications seems advantageously. Fixed line network based as well as PC based solutions have their limitations by installation problems especially in elder patients.

8. Application of telemetric blood pressure measurement in the daily routine of an office for internal medicine

We use telemetric blood pressure measurement in our routine daily care of hypertensive patients in an office for internal medicine. We make use of a validated (Westhoff TH et al., 2006) oszillometric blood pressure measurement device measuring at the upper arm. This devise has a Bluetooth interface and sends its data via Bluetooth-handy to a Regional Organisation System (ROS). From there the data are pushed forward to a database, analysed and stored there. If the measured blood pressure exceeds preliminary settings an alert is sent via ROS by e-mail, fax or letter to the treating physician and/or to the patient. The advantage of this system compared with other systems is that the patient can´t suppress measured blood pressures to endeavour to communicate optimal blood pressure values to his doctor. A small amount of technical solutions have been tested in a number of application studies (Mengden T et al., 2001). The virtually Clinic of Hypertension was tested successfully in several pharmacological studies (Ewald S et al., 2006; Mengden T et al., 2004; Möckel V et al., 2009). In all these studies telemetric blood pressure measurement was proved as practicable and was well accepted by the majority of the treated patients.

8.1 Methods

We used 36 telemetric blood pressure measuring devices (Stabilo-Graph i.e.m., Stolberg, Germany) in following indications:

- Making sure the diagnosis “arterial hypertension”
- First treatment of a newly discovered and to date untreated blood pressure
- Control and modification of a pre-existing antihypertensive treatment

We treated more than 400 patients with telemetric self blood pressure measurement until today. The assessment of the self measured blood pressure values was made in a weekly setting and in addition if there was an automatically alert by the system (we use e-mail and fax only to the doctor, not to the patient).

The patients are trained by a “hypertension assistant” (DHL®). After training the method of home blood pressure measurement according to the ESH guidelines the telemetric blood pressure measurement device is demonstrated and the use of the equipment is trained. According to the ESH guidelines (Parati G et al., 2004) measurements should be done at least between 06:00 and 09:00 hours in the morning before taking the antihypertensive

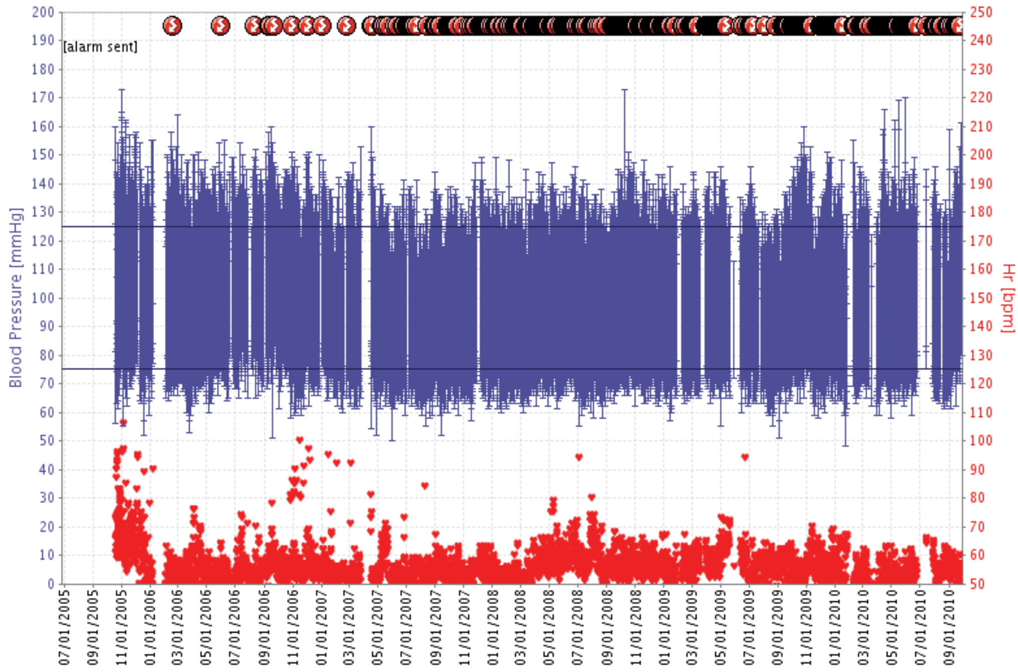

Fig. 3. High long-term adherence with telemetric blood pressure measurement in a type 2 NIDDM patient: 17,7 measurements per week from 10/18/2005 to 09/25/2010

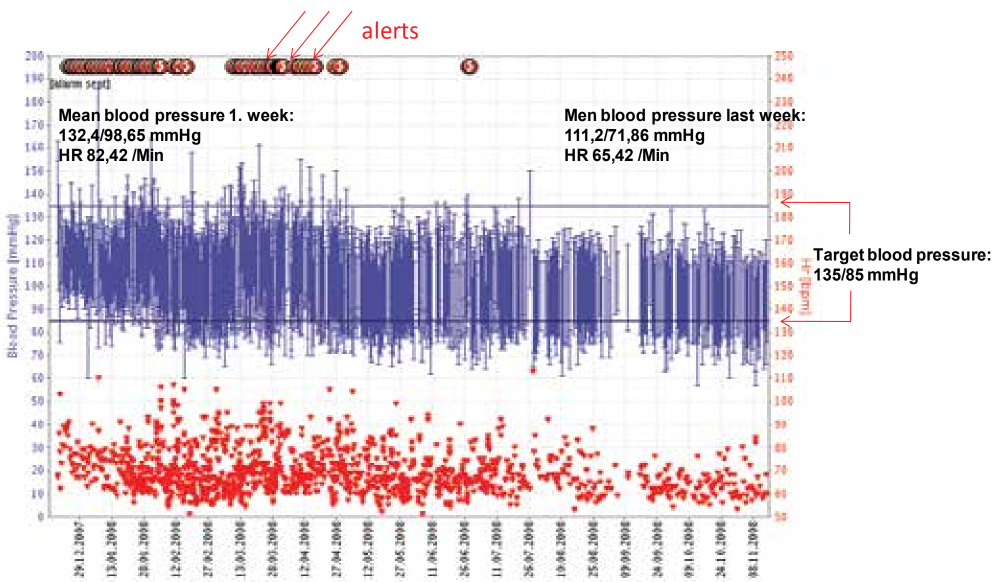

Fig. 4. Typical development of blood pressure under telemetric observation: high alert intervals at the beginning with corresponding mean weekly blood pressure and satisfactory blood pressure after 6 months.

medication. The alert limit is 135/85 mmHg in absence of other risk factors with adaptation of the target blood pressure according to the additional risks (diabetes mellitus or renal failure for instance) (Figure 3 and 4).

8.2 Statistic methods

We analysed the blood pressure of 147 patients. For that purpose all measurements at start of the telemetric home blood pressure measurement were set to a jointly zero point. The mean weekly blood pressure was calculated for every patient. We studied the hypothesis that telemetric blood pressure measurement would positively influence the quality of treatment by increase of adherence to the therapy. 95% confidence intervals (CI) of blood pressure were calculated.

An additional calculation was done for the dependence of blood pressure to the duration of an interruption of telemetric blood pressure measurement by an analysis of regression calculating the development of blood pressure in dependence to the interval of interruption of telemetric measurement. The increase of blood pressure over the time of interruption was calculated.

The acceptance of telemetric blood pressure measurement and management was analysed by a questionnaire. This was created together with 4 patients. 41 out of 71 questionnaires were answered and analysed.

8.3 Results

Mean age of the 147 patients (53 women) was 55,9 ± 11,6 years (women 56,5 ± 1,7 years, men 55,6 ± 11,6 years). A total of 30.217 single measurements were analysed, per patient 163 ± 172 measurements (median 106 ± 18 measurements). Mean measurements per week were 11,1 ± 5,2 (median 10,9; 1,7 – 26,8). There was no influence of the patient´s age on the frequency of measurements.

In the first measurement interval patients had an optimal adherence (i.e. ≥ 14 measurements a week) to the demanded number of measurements only in the first and second week of examination with 19,8 and 15,2 measurements per week. The frequency of blood pressure measurement fulfilled the criteria for a sufficient judgement until week 16 (i.e. a minimum of five measurements per week (Krecke HJ et al., 1996). This time was long enough to get 95% of the treated patients into their target blood pressure (< 135/85 mmHg). If a second measurement interval was carried out for control, the patients didn´t even reach the "optimal measurement frequency" (i.e. 14 measurements/week) at begin of this period – the minimally necessary number of 5 measurements per week was realized only until week 6 of the second interval (Figure 5).

The duration of measurement periods was between 3 and more than 52 weeks. Only patients with a minimal measurement period of 4 weeks were analysed.

9. Blood pressure under telemetric observation

At the begin (week 0) of a new or changed therapy mean systolic blood pressure was 136,8 mmHg (95%-CI 136,1 – 137,4 mmHg), and mean diastolic blood pressure 85,2 mmHg (95%-CI 84,5 – 85,2 mmHg). Under therapy mean blood pressure decreased to systolic 134,1 mmHg (95%-CI 133,4 – 134,9 mmHg) and diastolic 81,95 mmHg (95%-CI 81,4-82,5 mmHg) after 4 weeks, that means below the target blood pressure of 135/85 mmHg. This reduction remained constant over the observational time of maximal 51 weeks (134,2 mmHg [95%-CI 133,4-134,9 mmHg]/81,95 mmHg [95%-CI 81,4-82,6 mmHg], (Fig. 6).

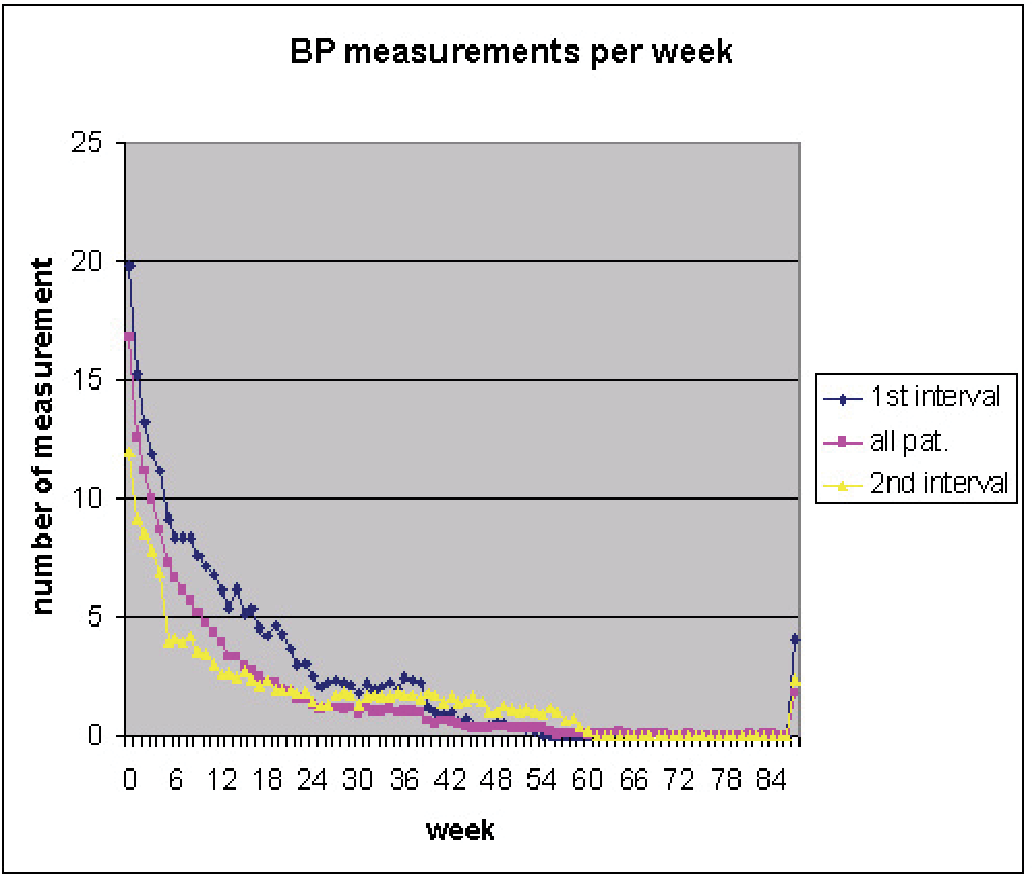

Fig. 5. Number of measurements per week for all patients, patients in first and second measurement interval

10. Does this success remain only under continuously telemetric observation?

32 patients had a telemetric blood pressure control for documentation of the quality of their therapy and to clarify, if the therapeutic success is influenced by the interruption interval due to deterioration of compliance or adherence. In these patients blood pressure decreased from 137/85 mmHg to 131/81 mmHg in the first therapy interval (Fig. 6). Blood pressure at begin of the second telemetric measurement interval continuously was in the target range of <135/85 mmHg measuring 132/81 mmHg. During the second observation interval blood pressure decreased slightly to 130/80 mmHg. The regression analysis showed an blood pressure increase of systolic 0,01242 mmHg (r=0,36) and diastolic 0,007374 mmHg (r= 0,54) per day without telemetric monitoring of blood pressure. That means: The adherence with an antihypertensive therapy started under telemetric observation is very strong. An increase of blood pressure by systolic 1 mmHg is expected not until 12 weeks, and by diastolic 1 mmHg even not until 19,4 weeks.

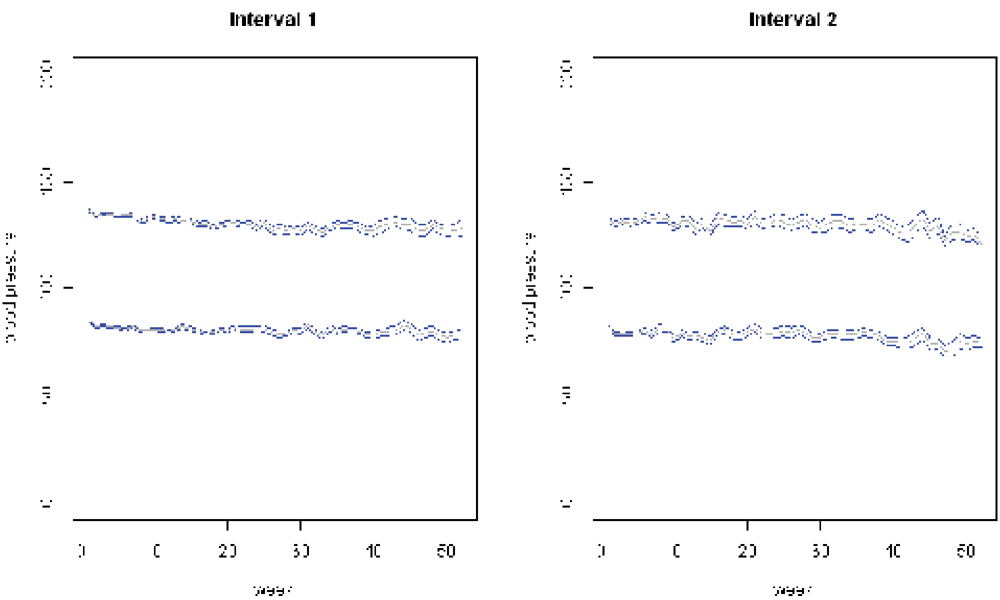

Fig. 6. BP during first interval and during recurrent measurement (interval 2) in 32 patient

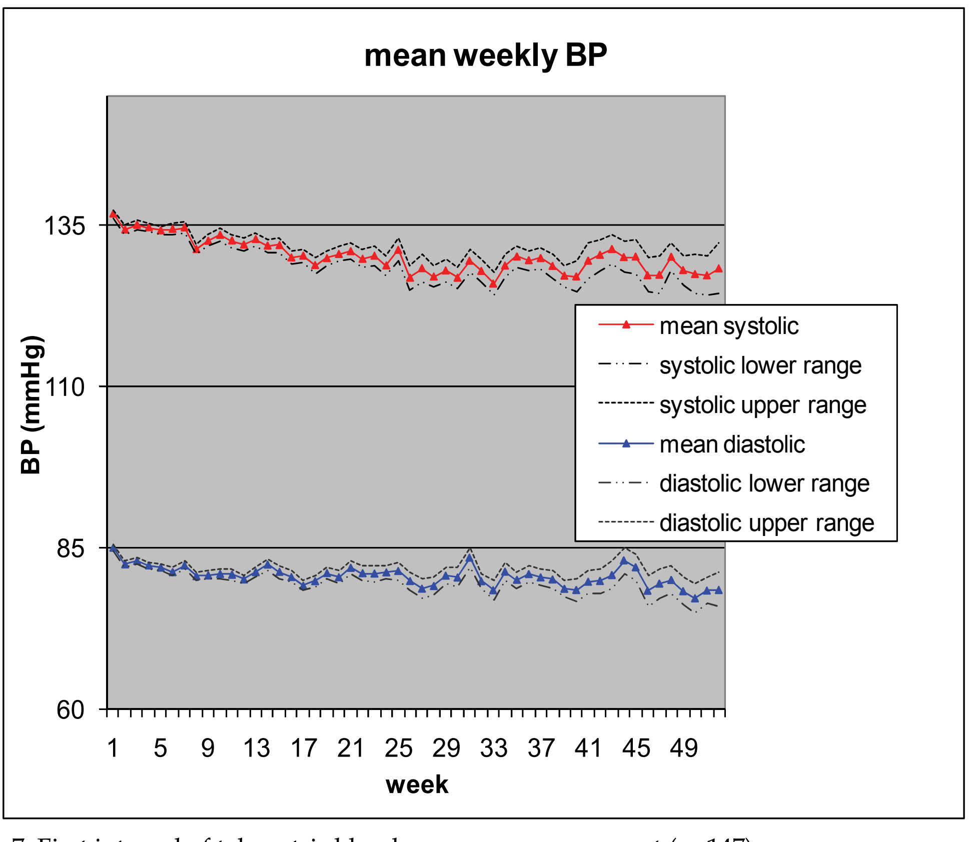

Fig. 7. First interval of telemetric blood pressure measurement (n=147)

11. Acceptance of telemetric blood pressure monitoring

15 out of 39 patients asked in a survey had no objections against the publication of personal data in the internet; no objections (less than a quarter) were existent against publication of blood pressure, diagnoses, and informations on therapy in the internet. Their own blood pressure history was observed in 18% periodically, seldom, and 47% never. Two thirds of the telemetric observed and treated patients wished a possibility for interaction with their physician via internet. Particularly if they would have special causes (62%) or problems with the therapy (i.e. side effects etc.) they would like to contact their physician and communicate directly with him in the internet.

The opportunity to be alarmed automatically by the Telemonitoring system was judged very different: 67% considered alerts as necessary, 22% as desirable, and 17% felt insure by alerts. In her/his daily life no one patient wished to be disturbed or made unsure by automatically generated alerts. On the other side the patients felt reassured upon the information that their physician gets an alert in the case of violation of adjusted target values.

Three quarters of the patients were willing to pay for the hardware of telemetric blood pressure measurement (about 90 €) fully or in part. Two thirds of the patients were willing to pay full or in part even the monthly costs for the database (about 10 €).

12. Discussion

Friedman et al. (Friedman RH et al.,1996) studied 267 patients for 6 months in a randomized trial. Telemetric controlled patients showed an additional decrease of systolic 11,5 mmHg and diastolic 5,5 mmHg as compared to usual care (Figure 8). The adherence to therapy was increased by 36% with Telemonitoring. This improvement with Telemonitoring was the crucial predictor for the improvement of blood pressure. In this study the blood pressure data were transferred by a call centre to the general physicians. This was judged as a helpful additional information for therapeutic decisions in > 85%. In Friedman´s study from 1996 an interactive computer based telecommunication system was used weekly telephone calls. The blood pressure data were transferred to the database by the patients themselves assisted by a standardized automatically working telephone interview system. In such a system communication mistakes are possible and the documentation of the blood pressure data is not patient independent.

Another study (Rogers MAM et al., 2001) compared a Telemonitoring interventional group with usual care treated patients. The blood pressure readings were transferred automatically and regularly to a medical centre of competence. The treating physicians as well as the patients of the intervention group were informed weekly about the quality of blood pressure adjustment. The telemetric intervention group showed a significant reduction of mean arterial pressure by 2,8 mmHg whereas the control group had a increase of 1,3 mmHg. Even patients without adaptation of their medication had superior blood pressure reduction in the telemetric treated group. This indicates that the telemetric measurement promoted the adherence with their therapy.

Friedman et al. (Friedman RH et al., 1996) discuss if solely the telemetric blood pressure transfer improve the blood pressure adjustment, or if the specific intervention on basis of the telemetric measurements is decisively. For this discussion there are interesting data generated by an internet based long term study using Telemonitoring (Tab. 2, Green BB et al., 2008; page 10) in three arms:

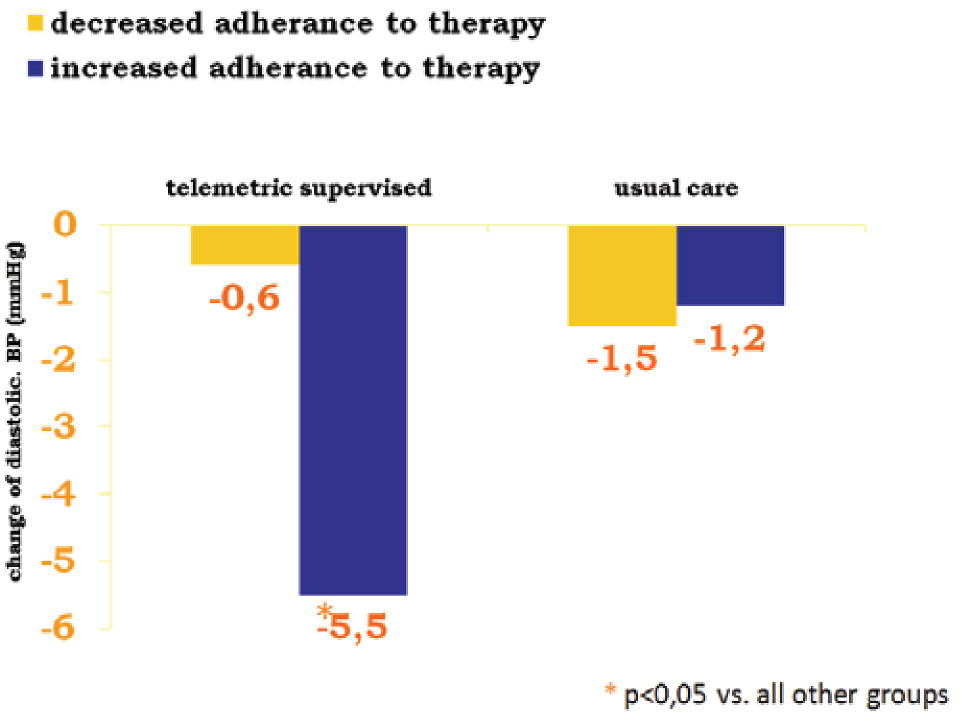

Fig. 8. Blood pressure decreased in 267 randomized patients by systolic 11,5 mmG and diastolic 5,5 mmHg in they were controlled telemetrically with an improvement of adherence by 36%. Friedman RI et al. (1996)

1. Blood pressure adjustment by general physicians ("usual care")
2. Home blood pressure measurement plus internet based training and blood pressure evaluation
3. Home blood pressure measurement plus internet based training and blood pressure evaluation plus phone intervention by a pharmacist

The target blood pressure in group 2 and 3 was <135/<85 mmHg as for home blood pressure measurement. Phone intervention in group 3 was carried out every two weeks by a specially trained pharmacist until target blood pressure was reached. Just the group 3 had a significant improvement of blood pressure compared to group 1 (Tab. 2).

Without an additional intervention other studies showed only a moderate (Rogers MAM et al., 2001; Sehnert W and Maiwald G. 2008) to absent (Madsen LB et al., 2008) effect of Telemonitoring. It can be concluded, that telemetric blood pressure monitoring has a better effect compared to a usual therapy only if there is an additional individualized intervention.

Telemetric blood pressure monitoring may have a big potential in hypertension in pregnancy due to the dynamic of blood pressure in this state (Mengden T et al., 2001; 19: 71suppl 2). Blood pressure changes may be very quick in pregnancy and it is important to realize even small increases of blood pressure.

Further investigations should be done in high risk populations in future. These are hypertensives with coronary artery disease, heart failure ok cerebrovascular problems. A prognostic benefit from such a telemetric observation can be expected in these high risk groups.

Patients' adherence to therapy is the biggest problem in the therapy of high blood pressure. Hypertension is a chronically illness requiring a maximum of understanding from our patients. They are involved in a therapy with possible side effects without substantial symptoms, which mean a therapy causes no symptomatic benefit for the patient. The classic "traditionally authoritarian" relation between patient and physician must be changed from into a dynamic model. In this the patient gets an active part. Home blood pressure monitoring is recommended by the ESH as a sensitive toll for therapy adjustment. Telemonitoring with alert system presents innovative possibilities to improve adherence to therapy by patients and physicians. It improves the patient´s relation to her/his disease – and thereby improves the basis of therapy.

Telemonitoring helps to control the adherence and compliance of an patients without time limits. We observed some of our patients now more than 4 years (Figure 3). A "severe deterioration" of adherence "after 6 months of therapy" (Osterberg L and Blaschke T. 2005) could not be proved with telemetric blood pressure monitoring. We could not observe therapy failure – caused in 50% by insufficient up-titration of the antihypertensive medication (Mengden T et al., 2001) – in our telemetric controlled patients.

Telemonitoring of blood pressure can be integrated into nearly every health care organization. It can be realized in a regional as well as in a superregional model. Data are available at any place with internet option. It´s application is independent of national health care systems and allows the observation of patients far away from the treating center. Beyond this every physician involved in the treatment is able to look at the data every time (via patient´s password). This is of eminent importance to provide patients in large areas with a small number of physicians.

For Germany there are no national or super national concepts integrating telemedicine into daily practice. Demographic development with a high part of older women and men will push Telemonitoring. The elderly want to stay as long as possible in their homes. Telemonitoring can be used as early warning system and continuously control in their homes. The correct use of telemedicine can save costs in a public health system considerably. The wrong use of telemedicine however can force up costs. Public health organizations hesitate to accept telemedicine. They will be overtaken by the "silver generation", which demand an optimal medical supply. There is a good chance for a broad use of this innovative meaningful new technique.

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Part 2

Applications for Diabetes, Pregnancy and Prenatal Medicine

4

Overview of Telemedicine Applications in the Follow-Up of the Diabetic Patient

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1. Introduction

Diabetes Mellitus is a growing health problem worldwide and will reach epidemic proportions in the next years. Chronic complications of diabetes cause an important rate of morbidity, from ischemic heart attacks to lower extremity amputation. The total number of excess deaths attributable to diabetes worldwide for the year 2010 was estimates in 3.96 million for the age group 20-79 years-old. This represents 6.8% of the global mortality for all ages. (Gojka and Unwinb, 2010)

A tight glycemic control and a close monitoring of all cardiovascular risk factors is essential to prevent serious complications of diabetes and to reduce mortality. Health care systems need to look for new approaches to afford the overload of diabetic patients and to provide them with an effective and cost-effective assistance.

Telemedicine-based systems for sharing information between patient and health professional may facilitate the high level of assistance required by diabetes.

Transmission of capillary blood glucose values by the patient and a regular feedback from the professional are the basis for patient education in the self-management of their disease. The exchanged information could be much more complex, including data on food intake, level of exercise, dose of insulin…Taking into account all these parameters, health professionals may adjust the therapy in a more accurate way. Certain groups of patients may benefit more due to their special care needs: type 1 diabetes, patient treated with a continuous insulin infusion system, pregnant woman with diabetes, among other situations. All of them require close monitoring. Telemedicine may help to reconcile the care process with patient's lifestyle.

However, the real presence of Telemedicine in clinical practice is still very limited in most centres attending diabetic patients. Many studies have been performed in the last years in order to evaluate different Telemedicine approaches to diabetes care. Most of these studies involve a small number of patients and can be just regarded as pilot experiences. The heterogeneity among the evaluated systems makes difficult to provide strong conclusions about the effectiveness of Telemedicine in the control of the diabetic patients. Wider research in this area is required in order to create a more reliable perception about these systems among patients and health professionals.

Our group from the Endocrinology and Nutrition Department of Hospital Clinico San Carlos (Madrid, Spain) carried out a clinical trial in the year 2007 to evaluate the feasibility of a Telemedicine system based on Internet and short message service in the follow-up of women with gestational diabetes. 100 women were followed during their third trimester of pregnancy, 50 of them using Telemedicine. This experience provided a useful view of the possibilities of these systems, but also of the difficulties and how to improve them for the application in clinical practice.

On the other hand, Telemedicine has been applied successfully in the diagnosis and management of chronic complications of diabetes such as diabetic retinopathy. The transmission of digital images of the retina to specialized centres where they are properly interpreted may increase the access to specialized care, improve the screening of diabetic retinopathy and make possible an early treatment.

A screening protocol of diabetic retinopathy using Telemedicine has been developed in Hospital Clinico San Carlos from the year 2008. The programme has shown to be effective in selecting the patients that must be evaluated by ophthalmologists with more experience in the management of retinopathy. This implies an optimization of resources and an improvement in patient satisfaction.

The application of Telemedicine in the follow-up of other chronic complications of diabetes is also a very interesting area of research: the evaluation of foot ulcers through digital images that could be transmitted to experts, the monitoring of patients with cardiovascular disease, and many other applications that we will see in the next years. Therefore, Telemedicine represents an amazing advance in the care process of the diabetic patient.

2. Definition of telemedicine

Telemedicine covers a wide variety of procedures with very different stages of complexity. From a simple telephone conversation between two health professionals sharing information, to complex diagnostic or therapeutic procedures long distance and in real time.

Telemedicine is a technological tool that enables the optimization of health care services, allows saving time and resources and facilitates access to remote areas in order to provide them with specialist care.

It enables the exchange of information between different health professionals, including primary care physicians and specialists, or between professional and patient. This latter form is known as Telecare, which aims to improve the quality of care through an increased communication between the patient and the healthcare professional. In this process there is a unit of the patient and a health professional station. The shared information may include electronic documents, digital images and any data of interest in patient monitoring.

The amazing advances in the area of information technology and communication in last decades has allowed the development of multiple approaches to Telemedicine. Communication tools used so far are very diverse: fixed telephony, modem, mobile phone short text messages (SMS), Internet e-mail, Web application, video-conference, GPRS technology, Bluetooth, Integration Computer Telephony, and Multi-Access Systems: Web application, dial through interactive voice response, palms (PDAs)... The available systems are becoming more diverse and higher quality through constant innovation in this field, but they are also more reasonable in cost.

The field of information technology and telecommunications has started offering to health professionals new Telemedicine systems to facilitate their daily work. However, there is still

a lack of knowledge about the possibilities of these systems and, occasionally, some resistance of health authorities for the implementation of Telemedicine in clinical practice.
The European Commission launched in 2009 a consensus document to encourage member states in the effort to integrate these new services in health systems. The actions proposed to undertake in the next three years are aimed at the following points:

- Improve the confidence and acceptance of Telemedicine systems by conducting large-scale studies of effectiveness and cost-effectiveness.
- Build a stable legal framework, with the adaptation of the regulations of each country.
- Solve technical problems and facilitate market development, promoting interoperability and improve their quality and safety.

3. Telemedicine applications in diabetes: why to apply telemedicine in diabetes care?

Telemedicine has been applied in the follow-up of chronic diseases such as hypertension, obesity, chronic obstructive pulmonary disease, asthma, even in the monitoring of oncology patients. But no doubt Diabetes is the chronic disease with more approaches using Telemedicine. This is due to the special characteristics of the monitoring and treatment of this disease.
Multiple evidences show that complications of diabetes can be prevented by a tight metabolic control and an adequate monitoring of the patient. However, to achieve this control is essential a close relationship between the practitioner and the patient, which should be consistent and prolonged in time. As an example, patients from the intensive group in the DCCT study visited the medical centre every week until reaching the target, then every month, and received weekly telephone contact to adjust the treatment. (DCCT Research Group, 1989). This level of support is difficult to implement in clinical practice because of the increasing prevalence of diabetes and the incompatibility with the patient's lifestyle (work or school activity).
The level of involvement required from the diabetic patient in the control of his own disease is higher than in any other disease. That's why such close contact with the health professional is necessary. The patient with diabetes should self-monitor his capillary blood glucose, as directed by the health team (nurse educator and doctor). There must be a constant feedback to adjust their treatment according to these values of blood glucose.
This communication is also essential to evaluate and modify if necessary dietary habits and instructing patients on the interpretation of their blood glucose levels in relation to nutrition and physical activity. The patient must be always guided by the health professional in order to gradually learn to make decisions about his own treatment.
This requires, in all its developments but more importantly in the early stages of diagnosis and at specific situations, constant and close supervision by medical staff, an individualized treatment and continuous education.
In other cases, the metabolic control is affected by the motivation of the patient over time. In many cases a positive encouragement is needed to implement the self-management of diabetes, for example in certain life stages such as adolescence.
Therefore, professionals look for new solutions in order to facilitate the contact with the patient, to create a more dynamic and motivating communication and that may be compatible with the patient's lifestyle.

4. Review of the literature: what has been done by other researchers?

In the early 80s, Telemedicine systems started to be implemented in monitoring the diabetic patient and, since then, many approaches have been developed following the quick evolution of information technology and communication in the last 30 years.

The first systems allowed the transmission of blood glucose values from the patient to the healthcare professional by fixed telephone or modem. The practitioner replied to the patient by telephone and gave him recommendations for treatment. Using this system in type 1 diabetic patients, the study of Chase et al. (Chase et al., 2003) showed that modem technology can be useful and cost-effective in the process of patient care. 70 patients were followed for 6 months. The control group performed visits every three months, while the intervention group sent their blood glucose data by modem every two weeks, receiving a "feedback" via telephone by the professional. At the end of the follow-up, there were no significant differences in HbA1c value or number of severe hypoglycemia. However, the use of telemedicine system was more cost-effective and reduced the number of school and work absences during the follow-up.

A subsequent meta-analysis (Montori et al., 2004), including controlled clinical trials using only the modem transmission of glucose data from the glucometer of type 1 diabetic patients, found a difference of 0.4% (95% CI 0 to 0.8) in mean change in HbA1c from baseline between intervention and control group. They were paediatric patients, type 1 diabetics with poor glycemic control and women with pregestational diabetes. However, the follow-up time was short (average 6 months), and a small number of patients (average of 50 patients), so can not assess long-term feasibility.

Internet development was a breakthrough in the field of Telemedicine. In the following studies, the patient is able to communicate with the healthcare professional via the Internet, existing Web-based applications. The patient access the application from home or from a pocket computer, sending their values of blood glucose, and other data necessary for the interpretation of blood glucose levels as the dose of medication, diet and physical activity level. The health professional receive this information in the medical station (usually a PC) and replies with individualized recommendations, which are received via the Internet in the terminal of the patient (Kwon et al., 2004).

In other studies, the communication by telephone or by text message service is used as a complement of Internet communication. (Kwon et al., 2004; Tasker et al., 2007). More recent studies integrate several forms of telemedicine, as in the M2DM project developed by the European Commission in different centres in Europe (Bellazzi et al., 2003; Bellazzi et al., 2004), which uses a multi-access system consisting of a Web application, dial through interactive voice response, palms and intelligent modems. This project aims to assess clinical, organizational, economic and patient satisfaction, with encouraging results.

Some studies tested educative modules associated with the Web application as a source of information and patient training on basic concepts and skills for managing their diabetes (McMahon et al., 2005). The ability to access to these educational resources has been shown to improve patient motivation, which has a positive influence in their glycemic control.

Available studies of telematics systems applied to diabetes are generally short in follow-up and small in sample sizes. To date, the study that has evaluated over a longest time the usefulness of a glucose monitoring system based on Internet, had a follow-up of 30 months (Cho et al., 2006). It concluded with a significantly greater reduction in HbA1c and a reduction in the rate of fluctuation of HbA1c in the intervention group compared to control.

Patients in the intervention group with baseline HbA1c ≥ 7% had HA1c levels markedly lower than the corresponding control group patients during the first 3 months (7.9 ± 1.0 vs. 7.3 ± 0.7, p = 0.023) and levels remained stable throughout the study (HbA 1c fluctuation index of 0.47 ± 0.23 vs. 0.78 ± 0.51, p = 0.001).

The development of decision support systems in the last years offers another very interesting field in Telemedicine. These systems can help the practitioner in making decisions about the management of their patients, by identifying problems and suggestions of treatment modifications in diet or physical activity levels, based on intelligent algorithms. In a Korean study (Kim et al., 2007), patients sent their data of blood glucose recorded in the glucometer, exercise data recorded on a pedometer and a food diary. Data were processed in a "matrix of knowledge" that generated automatically by an intelligent algorithm messages with recommendations and positive reinforcement directed to patients. After a follow-up of 12 weeks, a significantly greater reduction in HbA1c was achieved in the intervention group compared to controls (0.72 ± 0.80 vs. 0.15 ± 0.85%, p = 0.005). These results could be explained simply because the patients in the intervention group received more frequent recommendations based on current data compared with the control group, which encourages patients to more actively modify their lifestyle to achieve better glycemic control.

One meta-analysis (Verhoeven et al., 2007) reviewed 39 clinical studies (1994-2006), of which 22 used Telecare, 13 video and 4 combined Telecare and video conferencing. Telecare systems, involving monitoring of clinical, education and personalized feedback were most effective in achieving change in habits and reducing costs. They conclude that they are all practical, cost-effective and safe in the diabetes care system. However, the heterogeneity in study designs and results make difficult to give definitive conclusions about the benefits of telemedicine in the management of diabetes.

Thus, well designed clinical trials are needed to provide consistent evidence on the usefulness of Telemedicine systems, so that they can gradually overcome the barriers to its implementation in clinical practice.

5. Telemedicine applications in gestational diabetes

The patient with gestational diabetes requires a careful monitoring for a short period of time, from the diagnosis of gestational diabetes to the moment of delivery. Tight glycemic control in gestational diabetes is critical in reducing perinatal morbidity and mortality and avoiding maternal complications. During that short period of time, the patient should adopt nutritional and physical activity recommendations, must self-monitor her capillary blood glucose frequently, and in some cases must start using insulin. It therefore requires close monitoring and frequent visits to the medical centre.

The prevalence of GDM in Spain is increasing in the last years, especially in the immigrant population. It means an overload of care, so new strategies for their attention are needed.

So far there are few studies published that specifically evaluates a telemedicine system in the management of gestational diabetes. In one of these studies was provided Internet access to women of low economic level to communicate with health professionals. There were no significant differences in the values of pre-and postprandial blood glucose, but more patients from the intervention group were treated with insulin (31% vs. 4%, p <0.05). The system showed no improvement in maternal and fetal parameters, although women in the telemedicine group reported greater satisfaction with their diabetes control.

6. Experience in Hospital Clinico San Carlos:

A Telemedicine system based on Internet and short message system as a new approach in the follow-up of gestational diabetes mellitus. Es-Te-Dia Project. (Pérez-Ferre et al., 2010; Pérez-Ferre et al., 2010)

In order to test the feasibility of a Telemedicine system in the follow-up of gestational diabetes, a pilot study was conducted at Hospital Clínico San Carlos.

6.1 Subjects, materials and methods

Patients.

A prospective randomized interventional study with two parallel groups was designed. All women diagnosed as having gestational diabetes (GDM) according to Carpenter-Coustan criteria before 28 weeks of gestation and referred to the Unit of Gestational Diabetes of San Carlos University Hospital (HCSC) from June to December 2007 were invited to participate in the study. Women with inability to understand or to comply with the protocol were excluded.

100 women signed written informed consent and were randomized by age and obstetric history, allocated to an intervention group (A, n = 50), provided with a Telemedicine system detailed below, and a control group (B, n = 50) that was followed in accordance with the usual monitoring face-to-face based protocol in HCSC. Patients were followed until the delivery. 97 women completed the study (48 from group A and 49 from group B, respectively).

Experimental design

At visit 0 (between 24-28 weeks of pregnancy), patient data were collected: age, nationality, educational level, employment status, problems to access the medical centre, family history, personal history (hypertension, smoking habit, obesity, thyroidal disease, other co morbidities), obstetric history (number of pregnancies, abortions, gestational diabetes in previous pregnancies), use of medications, body weight and height.

Patients were instructed by the nurse educator as regards to nutritional habits and self-monitoring of capillary blood glucose, and informed about the goals of glycemic control: fasting and pre-prandial blood glucose <95mg / dl, and 1-hour postprandial blood glucose <120mg / dl. Body weight, blood pressure, HbA1c and first morning urine sample albumine-to-creatinine ratio were assessed.

At visit 1, one week later (before 28 weeks gestation), capillary blood glucose values were evaluated. Six capillary blood glucose determinations a day were recommended during the first week. If more than 4 of 5 fasting and pre-meal glycemic values were <95mg/dl in the first week, only 1 hour post-meals capillary blood glucose determinations daily or each other day were recommended until delivery.

Patients were randomized in two groups (control and intervention), according to age and obstetric history. However, those patients most likely to require insulin after the evaluation of the first 7-days blood glucose profiles (at least 50% of post-meals blood glucose values>115mg / dl) were allocated to the Telemedicine group, because this subgroup of patients was expected to need more provider contacts and could benefit more from the Telemedicine system.

During the follow-up of both groups, 4 face-to-face visits were scheduled until delivery (before 28 weeks of gestation, and between 32-34, 36-38, 39-40 weeks). Body weight, blood

pressure, HbA1c and first morning urine sample albumine-to-creatinine ratio were determined in every visit. Capillary glucose values recorded by the patient in her log-book were evaluated, and episodes of mild or severe hypoglycaemia and insulin requirements were collected.
Patients in the control group (B) were followed according to the usual protocol for gestational diabetes at HCSC, including the same capillary blood glucose targets, in a way that gave them the opportunity to attend to the medical centre without prior appointment (non-scheduled visit) to show their log-book when their blood glucose values were above the objectives or for any queries regarding nutritional recommendations or insulin dose. The total number of non-scheduled visits to the medical centre, number of work absences and number of hospital admissions were regularly recorded.

Telemedicine System

The Telemedicine system consists of a central database and peripheral units, consisting of cellular phones and a Glucometer capable of transmission via infrared port.
The intervention group received a Glucometer (Accu-Chek Compact Plus) with a cellular phone (Nokia E50-1). The cellular phone has a preinstalled application that allows the transmission of capillary glucose values to the central database through short message service (SMS). This application has also an interface that allows the infrared transmission of the glucose values stored in the glucometer to the cellular phone. The system enables the patient to regularly transmit blood glucose values and also to maintain contact through short text messages with health professionals as required.
They were recommended to send blood glucose values recorded in the glucometer to the medical terminal once a week.
An endocrinologist and a diabetes nurse educator evaluated patients´ data accessing into Emminens Conecta Plus Web Application (www.emminens.com) from any PC with Internet connection. Entering a personal password, they had access to blood glucose values sent by the patients, accompanied by their identification by initials, date and time of measurement. The application provides graphics with the trend of glycemia over time, charts of everyday and weekly glucose values, and the daily glycemic values of every patient. Health professionals can send text messages from their computer, which are received via Internet on the cellular phone of the patient. Through these messages, the professional makes recommendations on nutritional changes or adjustments in insulin doses. Patients can send text messages from their cellular phones to the medical terminal via Internet with questions as required, or answering to questions about their nutritional patterns or treatment.

Statistical analysis

Sample size was estimated for the hypothesis that the Telemedicine-based intervention will be no inferior to the traditional face-to-face usual treatment. A primary end point difference of the percentage of GDM patients achieving HbA1c values <5.8% more than 20% has been used. With 50 patients in each group, the study had 80% power to detect a 20% difference between groups at 5% significance.
The statistical study was performed by using SPSS 15.0 program for windows. Descriptive data are expressed as median and Q1-Q3 or mean ± SDM. Non-parametric Mann-Whitney and Kreskas-Wallis test were carried out to detect significant differences between groups.

6.2 Results

All women achieved HbA1c values <5.8% during pregnancy. The Telemedicine group transferred a median of 94 (34-127; Q1-Q3) values per patients of capillary blood glucose along a follow-up period of 9 (7-12) weeks. Five patients (10.2%) were not able to transmit any data. The professional posted a median of 5 (3-9) text messages per patient. The distribution according to the content of the messages is described in **Table 1**.

Telemedicine Contacts	*Patients to Health Care Providers*	*Health Care Providers to Patients*
Number of SMBG values	93.12 $\pm$ 70.77	
Number of SMS	1.63 $\pm$ 3.87	6.39 $\pm$ 4.84
Contain of the SMS	Answers about diet (60%)	Positive reinforcement (40%)
	Questions about diet (10%)	Questions about diet (30%)
	Questions about insulin (5%)	Reminding transfer (15%)
	Need of strips (10%)	Need of insulin (6%)
	Reporting technical problems (9%)	Adjusting insulin dosage (4%)
	Other issues (6%)	Other issues (5%)

Data are Mean ±SDM or (%)
SMBG denotes self-monitoring glucose values; SMS: short message service

Table 1. Use of the Telemedicine system (Adapted from Pérez-Ferre N. et al, 2010)

There was some kind of fault in the data transmission of 10 patients (20.4%), which forced the health professional to use the telephone to contact the patient. The major defects that were detected were caused by the use of the meter (modification by accident of the hour configuration that blocked the transmission of successive glucose values for security reasons, or inadequate use of the meter), pitfalls of the mobile terminal (not appropriate configuration of the mealtimes, not receiving text messages due to problems of the line), or technical problems with the web application. The patients had access to a telephone service to solve the fault in the transmission.

The use of Telemedicine services compared with conventional monitoring reduced by 62% the number of non-scheduled face-to-face visits (1 ± 1.347 per patient in the control group to 0.38 ± 0.684 per patients in the Telemedicine group; p <0.03).

Seventeen patients (34. 7%) in the Telemedicine group required insulin versus 9 (18. 8%) in the control group. Differences in the week starting insulin treatment were not found (week 26 (25-30) versus 28 (25-30), respectively; p=0.727), but a reduction of 82.7% in the number of non-scheduled visits in the Telemedicine group was observed (from 2. 89 ± 1.054 per patient to 0.50 ± 0.730 per patient, respectively; p<0.001). Data are displayed in **Table 2**.

Differences in clinical and laboratory data during the follow-up were not found.

In a similar way there were no differences in delivery and new born outcomes (**Table 3)**.

	CONTROL Group	TELEMEDICINE Group	p
Total Population (n)	48	49	
Face-to-face Visits	4.34 ± 1.73	3.98 ± 0.99	0.733
Non-scheduled visits	1 ± 1.35	0.38 ± 0.68	**0.033**
Insulin-treated patients	9 (18.75%)	17(34.69%)	**0.013**
Gestational weeks at insulinitation	28.22 ± 3.80	27.73 ± 3.13	0.727
Face-to-face visits	6.22 ± 1.48	4.25 ± 0.93	**0.002**
Non-scheduled visits	2.89 ± 1.05	0.50 ± 0.73	**0.0001**

Data are Mean ± SDM or n (%)

Table 2. Visits at setting office. (Adapted from Pérez-Ferre N. et al, 2010)

	CONTROL Group	TELEMEDICINE Group	p
N	48	49	
Gestational Weeks at Delivery	39.42 ± 1.42	39.12 ± 1.66	n.s.
Mother Weight Gain (kg)	6.446 ± 4.988	5.820 ± 3.950	0.712
Delivery Outcomes			
Eutocic	26 (54.2%)	20 (40.8%)	
Distocic	17 (35.4%)	27 (55.1%)	0.068
-Caesarean Section	12 (25%)	17 (34.7%)	
-Forceps	5 (10.4%)	10 (20.4%)	0.427
New born gender (M/F)	22 (47.9%) / 18 (37.5%)	20 (40.8%) / 26 (53.1%)	0.240
Birth weight (g)	3370.6 ± 479.1	3308.2 ± 488.8	
Male	3407.1 ± 492.2	3214.5 ± 435.7	0.385
Female	3346.9 ± 481.3	3380.2 ± 522.9	
Mother / New born Outcomes	14 (29.2%)	11 (22.5%)	
Macrosomia	4 (8.3%)	3 (6.1%)	0.115
Hypoglycemia	0 (0%)	1 (2%)	
Hypokaliemia	0	0	0.500
Hypocalcemia	0	0	
Poliglobulia	0	0	
Loss of fetal wellbeing	5 (10.4%)	3 (6.1%)	
Umbillical cord patology	2 (4.2%)	1 (2.0%)	
Shoulders distocia	1 (2.1%)	0 (0%)	
Abrupto placentae	1 (2.1%)	0 (0%)	
High blood pressure-proteinuria	0 (0%)	2 (4.1%)	

Data are Mean ± SDM or n (%).

Table 3. Delivery characteristics and new born data. (Adapted from Pérez-Ferre N. et al, 2010)

6.3 Conclusions from the study

The present study shows that this Telemedicine system based on mobile technology and the Internet applied to the monitoring of gestational diabetes is feasible in clinical practice. A significant reduction in the number of visits was reported, mainly in the insulin-treated patients. Neither the evolution of pregnancy and delivery nor the newborn outcomes worsened.

The reduction in the number of face-to-face visits means a significant saving of time and an important improvement on patient convenience, especially in cases with difficulties in accessing the medical centre, either because of incompatibility with the working schedule, long distance to the medical centre or need for resting at certain times of pregnancy. Such a reduction became conspicuous in the subgroup of insulin-treated patients who require a higher number of contacts with the health professional to adjust the insulin dose. A trend toward an earlier insulinitation in the Telemedicine group was observed, but did not reach a significant difference in the week starting insulin treatment.

The use of the Telemedicine system as an alternative to non-scheduled face-to face visits did not determine differences in the evolution of pregnancy (in terms of the parameters of metabolic control) or the final delivery parameters, nor in the newborn data, despite the higher proportion of patients using insulin in the Telemedicine group.

The extent of the use of the Telemedicine system was very variable, highly depending on the cultural level and the skills in the management of the system. Patients who were unable to transmit any data had usually a lower educational level, difficulties with the language, or were not used to new technologies. At visit 1, all the patients assigned to the intervention group received information about the management of the system and were recommended to send the values of capillary blood glucose at least once a week. In contrast to other studies using similar Telemedicine-based services (Yoon et al., 2008), the patient does not require to access to a website in order to send and receive information, that is important in the group of patients with low resources and no access to a computer.

The option to send text messages was generally underused by patients. The messages posted during the follow-up were mainly in response to questions from the professional. Most patients preferred face to face interview or the use of fixed telephony for questions they considered important, probably because they considered them more reliable media.

The professional also used fixed telephony to contact the patient in certain cases, such as in the moment of start insulinitation or doubts about the implementation of capillary blood glucose determinations at appropriate time intervals. In some cases, an inappropriate setting of meal times in the mobile phone could lead to confusion in the interpretation of the pre- and postprandial blood glucose values during the first week of monitoring, which led to consultation with the patient by fixed telephone.

Professionals employed an average of 10 minutes per patient in the assessment of capillary blood glucose profiles sent to the terminal and the doctor weekly broadcast messages in response to the interpretation of the data. The face-to-face visit is estimated in about 15-20 minutes. Therefore, the standard telematic visit saves time to the professional, in addition to significant savings in time for the patient, avoiding displacements to the medical centre and waiting to be attended. This savings in professional and patient time and working absences would result in a reduction of the overall costs of the process of patient care.

When the Telemedicine system was offered, patients accepted the proposal in a positive way and showed their satisfaction at the end of the follow-up; however it was not

specifically measured in the present study, in contrast to others (Mair et al., 2000; Long et al., 2005; Trief et al., 2008). They highly appreciated the possibility to communicate with the healthcare team as required. In next studies a specific quality of life questionnaire will be implemented (Bakken et al., 2006).
We conclude that this Telemedicine system can be a useful tool in the treatment of diabetic patients, as long as a complement to conventional face-to-face monitoring, especially in cases requiring a tighter glycemic control, or with difficulties to access to the medical centre.

7. Telemedicine application in the screening of diabetic retinopathy

Diabetic retinopathy is the leading cause of blindness in people under 60 years old and a major cause in older people. It is a specific microvascular complication of diabetes, depending on the duration of diabetes and is associated with the degree of glycemic control. It is estimated that after 20 years from the onset of diabetes, over 60% of type 2 diabetic patients will have retinopathy. Hypertension is a risk factor for the development of macular edema and is associated with the presence of diabetic retinopathy. Glaucoma, cataracts and other changes may occur early in patients with diabetes and should also be evaluated.
Retinal lesions with high risk of develop in blindness are often asymptomatic. Patients are not aware of these lesions if they are not examined periodically. When lesions are detected late in their evolution, the prognostic becomes worse: lesions can be irreversible at this moment. The systematic screening of diabetic retinopathy is an effective tool for the reduction in the incidence of visual deficiencies and blindness.
The transmission of digital images of the retina to specialized centres where they are examined and properly interpreted may increase the access to specialized care, improve the screening of diabetic retinopathy and make possible an early treatment.
A screening protocol of diabetic retinopathy using Telemedicine has been developed in Hospital Clinico San Carlos from the year 2007 (Fernandez Romero et al., 2009).
Diabetic patients are referred from their primary care physicians to be examined with a non-midriatic digital camera in 2 specialized centres. The pictures from the retina are transmitted by Internet to Hospital Clinico San Carlos. Three endocrinologists evaluate the images once a week and select the patients that should be evaluated by the ophthalmologist. The report that can be read by primary care physicians from the area.
Until January 31, 2010, 1473 patients were evaluated. Of them, only 15.3% were remitted to the ophthalmologist because of lesions of diabetic retinopathy. 13.5% of patients were remitted to the ophthalmologist because low quality of the images with non-midriatic camera. 56.7% of the patients are not referred to the specialist, and they are derived for a new examination with non-midriatic camera in one or 3 years, according to HbA1c level and other risk factors (hypertension, smoking habit, and microalbuminuria).
The evaluation of diabetic retinopathy with non-midriatic camera, the interpretation by trained endocrinologists and the use of Telemedicine emerge as the best method for the screening of diabetic retinopathy. It allows optimizing sources and reducing the overload of diabetic patients at ophthalmology departments. This method also improves patient satisfaction.

8. Future research in the field of telemedicine applied into diabetes

Since January 2008, our group from Hospital Clinico San Carlos is participating in a European study promoted by the European Commission into the Seventh Framework

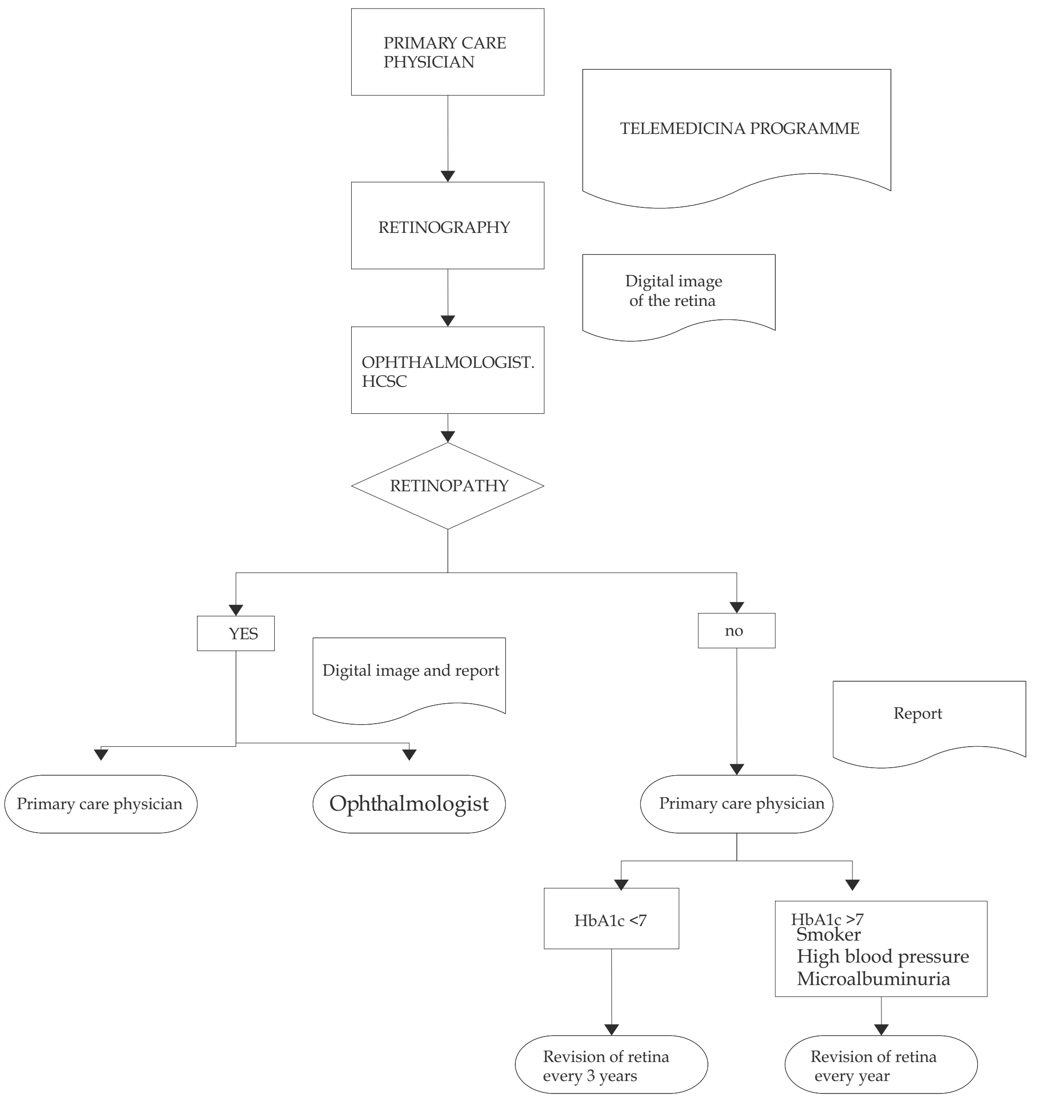

Fig. 1. Algorithm for the screening of diabetic retinopathy in Hospital Clinico San Carlos. (Adapted from Fernández Romero N. et al, 2009)

Programme. METABO project tries to create a global platform for the monitoring of all the parameters involved in diabetes. It not only monitors glucose values, but also food intake, level of exercise, energy expenditure, dose of insulin, other treatments, stress, environment... The control panel of METABO will be a graphical interface that will provide complete information about the patient, to be used by the patient and the health care team. It will display all the data well organized, with easy access for care providers anywhere with the frequency required by them. The final objective is to generate individual recommendations for the patient to improve his metabolic control and to make easier for the doctors the management of their patients. But also, data from a wide sample of patients may provide intelligent algorithms to relate the different parameters and predict behaviours. That is known as **modelling in diabetes**, a really interesting area on which many groups are working.

The application of Telemedicine in the follow-up of other chronic complications of diabetes is also a very interesting area of research.

- Telemedicine applied to the follow-up of diabetic neuropathy

Diabetic neuropathy may lead to foot ulcers that need a very careful examination and an accurate and timely treatment to prevent a fatal evolution. The evaluation of foot ulcers through digital images that could be transmitted to experts (endocrinologists, podiatrists, vascular surgeons) would be a very useful system to improve the follow-up of lesions of diabetic neuropathy. An early detection of the lesion and the selection of the best management for each ulcer may improve the prognostic, even prevent a lower-extremity amputation. Images could be remitted from primary care physicians to specialised centres. Specialists will decide which patients must be referred to the hospital for advanced treatment (debridement of the ulcer, intravenous antibiotics). It will prevent the overload of patients in specialised centres.

- Telemedicine applied to the follow-up of cardiovascular disease (ischemic heart disease)

Diabetic patients who have suffered an ischemic heart event need an intensive follow-up after the event in order to control the glucose levels and the other important cardiovascular risk factors: blood pressure, lipids, weight and smoking habit. The tight control of all these factors can definitely prevent the occurrence of another heart event. Many of these patients are diagnosed of type 2 diabetes after their first heart event, and they have to start using insulin at that moment. They need an intensive education about diet, glucose monitoring, the use of insulin and/or glucose-lowering medications, the management of hypoglycemias, physical activity they can practise without risks… Other patients were diagnosed of diabetes before having the heart event but they must change their treatment after the event in order to improve their global control. The close monitorization of these patients by care providers will be crucial for the evolution of the disease.

The application of telemedicine to the control of this group of patients would be very useful for the physicians and the patients.

Data to monitor would be: patient's profile (medical background, treatments, clinical and lab parameters), glucose monitoring, physical exercise, food intake and other events. In this group of patients, the cardiac function should be accurately defined in the medical background. It should include data from the electrocardiogram and the echocardiogram, systolic function, ventricular ejection fraction; last exercise test, data from the angiography (state of the coronary vessels, presence of stents or surgical coronary bypass). The

collaboration with Cardiologists would be recommendable for the inclusion and better evaluation of this information.
There is also special interest in monitoring the cardiac response to exercise: heart rate, heart rate variability, blood pressure, modifications in ST in the electrocardiogram, adaptation to exercise after a cardiac event.
- Other groups of patients with co-morbidities that could be interesting to monitor using Telemedicine would be: diabetic patient with renal disease, diabetic patients using steroids for a short period of time, diabetic patient with obesity. They all could beneficiate from a close monitoring from the health care team.

9. Conclusions

- Telemedicine can provide significant improvements in monitoring of diabetic patients, mainly in selected groups for their special care needs.
- Telemedicine may help to achieve an intensive treatment of diabetes and to save time and cost in the care process.
- A better monitoring of the diabetic patient may reduce the incidence of chronic complications of diabetes. This means an important reduction in morbi-mortality and the cost derived from the interventions.
- The feedback from users is essential to increase the confidence of the professional and patient in the use of Telemedicine in clinical practice.

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5

Telemedicine in Pregnancy Complicated by Diabetes

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1. Introduction

Recent studies have indicated that strict glycemic control is a very important factor for reducing maternal and fetal complications related to diabetic pregnancies (Metzer et al, 2007; Kitzmiller et al, 2008), both in cases of pregestational diabetes (types 1 and 2) and in cases of diabetes diagnosed during pregnancy (gestational diabetes mellitus, GDM). It is often difficult to ensure a good metabolic control in these patients, however, due not only to their diabetes *per se*, but also to a number of practical problems. Pregnant diabetic women need frequent contact with their physician, not only for routine care but also to clarify their doubts arising, for instance, from sudden changes in their glycemic levels that need short-lived adjustments to their therapy. Attending Metabolic Care Units can also prove difficult for various reasons (for women living too far away, or with no independent means of transportation, or needing to rest to avoid preterm delivery).

In principle, telemedicine could be a useful method to apply to the care of diabetic women, but few studies have been published on this topic so far, the most important of which are discussed below.

2. Telemedicine systems

An adequate communication structure is fundamental to optimal interaction and coordination between caregivers, and between caregivers and patients. Information and communication technology (ICT) has the potential to solve certain problems in the management of diabetes care because it can enhance care coordination and support patient self-care. The chance to exploit ICT can reduce the costs while maintaining the quality of health care, and the fact that ICT can help respond to an increasing demand for care with a decreasing availability of personnel is of real interest.

Previous reviews on diabetes care reported modest benefits of ICT-based care compared to conventional face-to-face care, but they focused primarily on the technology's usability and mainly considered one-sided issues such as clinical improvements (glucose and diet) rather than looking at the diabetic patients' various problems, including the influence of interactive technology on the caregiving process (patient-caregiver cooperation, care coordination, costs), the patient's quality of life and self-care (Ouwens et al, 2005; Jennett et al, 2003; Balas et al, 1997).

ICT-based care is not just a technological tool, it is a different way to provide health care with the aid of ICT. The most important ICT-based care modalities are teleconsultation and videoconferencing. Teleconsultation is a form of telemonitoring involving patient-caregiver communication (monitoring and delivering feedback) via email, phone, automated messaging systems or other equipment without face-to-face contact, or the Internet. Videoconferencing involves real-time, face-to-face contact (image and voice) using videoconferencing equipment (television, digital camera, videophone, etc) to connect caregivers and one or more patients simultaneously, usually to provide instruction.
In a recent review, Verhoeven et al showed that teleconsultation programs, with daily clinical data monitoring, providing education and personal feedback, are the most successful in inducing behavioral changes and containing costs. The benefits of videoconferencing related to its effects on socio-economic factors such as education and cost reduction, but also on disease monitoring. Videoconferencing also seemed to be able to assure a good quality of care while achieving cost savings.
The studies selected for review suggest that both teleconsultation and videoconferencing are practical, cost-effective and effective ways of delivering a health care service to diabetics, although the diversity of study designs and reported findings makes it impossible to draw any final conclusions. Interactive systems integrating patient monitoring and personalized feedback functions warrant further development in diabetes care in the near future.

3. Studies on pregnancy

Few studies have reported to date on the application of telemedicine to diabetic pregnancies (Tables 1 and 2).

3.1 Studies on type 1 diabetes in pregnancy

Di Biase et al investigated whether the use of telemedicine could be useful in the management of pregnant type 1 diabetic woman. A completely automated system (the DIANET system) was used and 20 type 1 pregnant women participated in the study: 10 were treated using telemedicine and 10 using the conventional approach. The DIANET system was performed at 4 different times: "entry" (9.5 weeks), "basal" (9.5-16.8 weeks), "1st month" of investigation and "end" (near delivery). All the women adopted intensified insulin administration protocols. The DIANET ensured a better metabolic control than the conventional approach, judging from the profiles of the women's absolute blood glucose values. These results were associated with higher insulin doses being used by women in the DIANET group, and a significant reduction in hypoglycemic episodes in both groups at the "end", "1st month" and "basal" times with respect to "entry" time. On the basis of these results, the authors suggest that telemedicine (DIANET) is a practical way to provide specialist care in pregnancy.
Frost et al studied whether diabetological care for pregnant women can be improved by using telemedicine, which facilitates communications between clinicians and patients. They adopted the prototype of a remote data management system (CareLink; Abbott-MediSense, New Bedford, MA) and 11 pregnant women with type 1 diabetes (all given intensified insulin therapy) were monitored with this system from the 15th gestational week onwards, in addition to providing the usual diabetological care, which consisted of regular outpatients visits every 2-3 weeks. A control group was formed of 10 pregnant women with type 1 diabetes with comparable age, diabetes duration, self monitoring practice, and insulin

regimen, who received standard diabetological care during the same time period as the CareLink group, but without the addition of telemedicine.

The mean time between 2 visits was 3.3 weeks for the CareLink group and 2.9 weeks for the control group. HbA1c improved in the CareLink group from 6.1 ± 1.0 to 5.4 ± 0.3% and in the control group from 6.2 ± 0.8 to 5.7 ± 0.6% (the difference between the two groups was not significant). Mean blood glucose (all values) in the CareLink group dropped from 141 ± 90 to 110 ± 18 mg/dl, and mean fasting glucose from 111 ± 17 to 101 ± 23 mg/dl ($P < 0.05$). Blood glucose variability was also markedly reduced: the standard deviation in individual patients fell from 51.6 to 44.4 mg/dl ($P<0.01$) for mean blood glucose and from 41.4 to 31.0 mg/dl for mean fasting glucose. There was no significant difference in the number of severe hypoglycemic episode in both groups during the study. The authors concluded that the system adopted for glucose monitoring is easy to use and helpful in the care of pregnant diabetic women, even when the patient attends the diabetes clinic less frequently. This telemedicine approach thus appears to be particularly suitable for women who have difficulty adhering to the prescribed regular check-ups at the clinic.

Wojcicki et al evaluated the therapeutic effectiveness of a telematic intensive care system designed and applied for the intensive treatment of pregnant type 1 diabetic women. The system operates automatically, transferring every night all the data recorded in the patient's glucometer memory during the day to a central clinical unit. To assess the efficiency of the system, a 3-year randomized prospective clinical trial was conducted, using a study group and a control group, each consisting of 15 pregnant type 1 diabetic women. All patients were treated by the same diabetologist. Two indices, calculated weekly, were used to assess glycemic control, i.e. mean blood glucose (MBG) levels and the universal J-index, which is sensitive to glycemia levels and their variations. The main results of the study were: a better glycemic control in the study group than in controls during the course of treatment, based on the mean differences in weekly MBG levels and J indices (n=24) ($\Delta MBG = -3.2 \pm 4.3$ mg/dl, $p = 0.0016$, $\Delta J = -1.4 \pm 2.3$, $p = 0.0065$); much more similar results in glycemic control among the women in the study group, than among those in the control group, as demonstrated by significantly lower variations in the glycemic control indices considered (SD_{MBG}:11.9 vs 18.7 mg/dl, $p = 0.0498$; SD_J: 6.5 vs 10.9, $p = 0.0318$); a tendency for a better glycemic control in patients with a lower intelligence quotient (IQ < 100) using the telematic system than in all other assessed groups of patients. This last result was not statistically significant, however. The telematic intensive care system thus improved the efficacy of diabetes treatment during pregnancy and enabled the diabetologist's strategy to be much more precise than if it had been conducted without any telematic support.

Ladyzynsky et al implemented a telematic system for supporting the intensive insulin treatment of pregnant type 1 diabetic outpatients and assessed the technical efficiency of the system. The system consisted of a patient teletransmission module (PTM) and a central clinical control unit (CCU). The PTM contained a one-box blood glucose meter and electronic logbook, a modem and a dial-up or cellular phone set. The CCU consisted of a PC computer with a modem and DIAPRET – an original program designed to monitor intensive insulin treatment.

The system was tested for 166 ± 24 days on 15 pregnant type 1 diabetic women. Patients' data were telemonitored automatically. No major technical problems were noted. Total effectiveness (expressed as the percentage of days in which data were transmitted successfully from a patient's PTM to the database in relation to the total number of days of the system application) was 69.3 ± 13.0% and technical effectiveness 91.5 ± 6.1%. The efficacy of the system was not significantly influenced by the patient's IQ, formal education or place of residence ($p<0.05$). There was a significant improvement in metabolic control while the system was in use. In short, the telematic system developed and implemented by the authors seems to have a positive influence on the quality of diabetes treatment during pregnancy.

Ladyzynsky et al also examined the influence of a home telecare system on metabolic control in pregnant women with type 1 diabetes. The system stored blood glucose values and was integrated with a simple electronic logbook: the data collected by patients were automatically transmitted via the telephone network every night. Thirty patients with type 1 diabetes were considered, randomly allocated to the home telecare group or to a control group treated by means of clinical check-ups every three weeks. In the home telecare group, the data collected by patients were transmitted to the hospital daily, enabling the doctor to take action more frequently. The mean study period lasted 180 days (SD 22) for the home telecare group and 176 days (SD 16) for the control group. The mean level of metabolic control and the insulin dosage adjustment patterns were similar for the two groups despite the much higher (15-fold) reporting frequency in the home telecare group. The data collected by patients were not fully utilized, mainly because of an excessively high within-day variability in glycemic control and a high workload for daily data analysis.

The mean frequency of reporting patient-collected data in the home telecare group was 0.7 times a day (15 times more often than with routine care procedures), but the mean metabolic control was only slightly better in the home telecare group than in the control group, and the insulin dosage adjustments were similar. A possible explanation for the lack of any significant differences may relate to: general issues interfering with the day-to-day usage of the telecare system, such as a high workload associated with the daily data analysis or the physician's attachment to conventional treatment methods; a marked variability in the glycemia of individual patients during the course of the day, masking medium-term changes in insulin requirements; the study design and the characteristics of the study group.

These findings led the authors to conclude that using a home telecare system during intensive insulin treatment for pregnant patients with type 1 diabetes improves glycemic control, but that real-time data transmission, accompanied by algorithms supporting data analysis and decision making, may be necessary to achieve further improvements in the quality of care.

3.2 Studies on gestational diabetes mellitus (GDM)

As for GDM patients, in a preliminary paper, Hernando et al proposed a method for assessing the performance of DIABNET, a knowledge-based system designed to aid doctors with treatment planning in gestational diabetes. The system is a qualitative model, implemented using a Causal Probabilistic Network, that can detect insulin effectiveness on a daily basis: the DIABNET analyses monitoring data and then recommends quantitative adjustments to insulin therapy and qualitative dietary changes.

The methodology includes: subjective analyses based on questionnaires and objective analyses based on quantitative comparisons of the system's and experts' proposal. The authors also reported the results of two approaches in which diabetologists evaluated the treatment recommendations provided by the DIABNET during the follow-up of 9 patients with gestational diabetes. The DIABNET detected the need to adjust the therapy in 92% of

Authors	Study group	Control group	Results
Di Biase et al (1997)	DIANET system	Regular ambulatory visits	1. Better metabolic control and higher insulin doses in the study group.
Frost et al (2000)	CareLink system	Regular ambulatory visits	1. No differences in HbA1c improvements between the two groups. 2. MBG and MFG markedly lower in the study group.
Wojcicki et al (2001)	Telematic Intensive Care system	Regular ambulatory visits	1. Better glycemic control in the study group, as assessed by MBG and J-index variations. 2. Significantly lower variations in the glycemic control indices applied in the study group.
Ladyzynsky et al (2001)	PTM and CCU system	---	1. Significant improvement in metabolic control
Ladyzynsky et al (2007)	Home Telecare system	Clinical examinations every 3 weeks	1. Similar levels of metabolic control and insulin adjustment in the two groups

Table 1. Brief outline of the studies conducted on telemedicine for type 1 diabetes mellitus in pregnancy

cases, demonstrating its appropriateness for automatically triggering an alarm. Around 80% of the system's proposals were approved by the experts, whose review of the results enabled a characterization of the system's performance in proposing changes to a patient's treatment. This study demonstrated the usefulness of DIABNET as a decision-guiding tool in gestational diabetes.

Pèrez-Ferre et al showed that the outcome of GDM after using a telecare approach is no worse than after traditional visits to the outpatients clinic. The authors evaluated the feasibility of a telemedicine system based on the Internet and txt messaging in pregnancy, and its influence on delivery and neonatal outcomes for women with GDM. A hundred GDM women were randomized to form two groups: a control group followed up with traditional check-ups at the outpatients clinic and a study group of women equipped with a telemedicine system for transmitting capillary glucose data and text messages and receiving weekly professional feedback. Ninety-seven women completed the study (48 controls and 49 in the study group) and the rates of women with HbA1c values < 5.8%, normal vaginal deliveries and babies large for their gestational age (LGA) were evaluated. Women in the study group had more contacts with health personnel (15.09 vs 9.11), taking up less time (3.8 vs 4.6 hours for each insulin-treated patient, $p<0.001$). No significant differences were seen between the two groups in terms of HbA1c levels, normal vaginal delivery and LGA newborn. The authors concluded that this system significantly reduced the need for outpatient clinic visits while achieving similar pregnancy, delivery, and newborn outcomes.

More recently, the same authors demonstrated that, compared to a control group, a telemedicine group reduced by 62% the number of unscheduled face-to-face visits, and by 82.7% in the subgroup of insulin-treated patients, improving patient satisfaction, and achieving similar pregnancy and newborn outcomes.

Homko et al randomized 57 indigent women with GDM to an Internet group (n=32) or a control group (n=25); patients in the Internet group were provided with computers and/or Internet access if necessary. A website was used to record glucose values and for communications between the patient and the healthcare team. The women in the control group kept paper logbooks, which were reviewed at each prenatal visit. Maternal feelings about "diabetes self-efficacy" were assessed at study entry and before delivery.

The women in the Internet group accessed the system and sent a mean 21.8 (± 16.9) data sets. There was no difference between the two groups in terms of fasting or after-meals blood glucose values, though more women in the Internet group received insulin therapy (31% vs 4%; $p < 0.05$). There were also no significant differences in pregnancy and neonatal outcomes between the two groups. The women in the Internet group showed a significantly stronger sense of self-efficacy at the end of the study.

The benefits of monitoring blood glucose in indigent women with GDM via the Internet was limited by their infrequent use of the telemedicine system. Although use of the system was not associated with better pregnancy outcomes, the women in the telemedicine group did experience a stronger sense of being self-sufficient in coping with their condition.

Authors	**Study group**	**Control group**	**Results**
Hernando et al (2000)	DIABNET system	---	Two different experiments evaluated the system's performance compared to physicians, based on answers to questionnaires and quantitative comparisons of the system's and experts' recommendations
Pèrez-Ferre et al (2009)	Telemedicine system (Internet and text messages)	Traditional face-to-face visits at the outpatient clinic	1. Women in the study group went significantly less to the outpatients clinic. 2. No differences in HbA1c levels between the two groups 3. No significant differences in delivery modality between the two groups 4. No difference in the rate of LGA babies between the two groups
Homko et al (2007)	Telemedicine system (website for recording of glucose values)	Information recorded in a paper logbook	1. No differences between the two groups regarding fasting or after-meals glucose values 2. No significant differences in pregnancy or neonatal outcomes 3. Study group patients had stronger "feelings of self-efficacy"

Table 2. Short outline of studies on telemedicine for pregnancies complicated by gestational diabetes mellitus (GDM)

For our study, we considered 235 pregnant women (203 with GDM and 32 with type 1 diabetes mellitus), who were trained to monitor their blood glucose levels with a glucometer (One Touch Ultra-Lifescan) and to send their glycemic profiles by means of a standard phone call to Glucobeep. The clinical and metabolic parameters we considered were age, pre-pregnancy BMI, mode and timing of delivery, macrosomia, maternal and fetal morbidity. Subjective outcomes were also investigated using the following questionnaires: CES-D for depression, SF-36 for health-related quality of life (QoL), Stress and Distress for the impact of diabetes.

All the women were given standard care according to the Recommendations of the American Diabetes Association.

They were sequentially assigned to two groups: one patient was followed up using the telemedicine approach (study groups: T for GDM, and T1 for diabetes type 1), and the next using the conventional approach (control groups: C for GDM and C1 for diabetes type 1). Women in groups T and T1 were trained on the use of the Glucobeep and asked to submit their glycemic data once a week, or more often if necessary, while they had a medical check-up at the diabetes clinic once a month. Women in the C and C1 groups had a medical check-up every two weeks. All patients could contact the physician whenever they wished (Table 3).

	T **88**	**C** **115**	**T1** **17**	**C1** **15**
Clinical parameters				
Age (yrs)	34.2±4.4	33.8±4.5	30.8±4.2	32.7±3.1
GDM diagnosis (g.w.)	24.9±4.8	25.1±5.9	-	-
Duration of type 1 diabetes (yrs)	-	-	16.1±7.7	17.4±5.8
Prepregnancy BMI	25.0±5.2	25.1±5.9	23.3±4.2	24.9±4.8
Weight gain (kg)	10.6±4.3	11.0±4.8	11.0±4.0	11.7±7.5
HbA1c at booking (%)	5.1±0.5	5.2±0.5	7.5±1.2	7.1±1.1
HbA1c in 3rd trim.(%)	5.1±0.6*	5.3±0.5	6.7±0.7	6.5±0.8
Insulin therapy (%)	48	39.1	100	100
Pregnancy outcome				
Delivery (g.w.)	38.8±1.5	38.7±1.8	36.1±1.9	35.1±7
Cesarean section (%)	38.6°	53.0	70.6	73.3
Maternal morbidity (%)	3.4	6.9	29.4	13.3
Birth weight (g)	3268±531	3249±566	3307±698	3467±686
Neonatal morbidity (%)	7.9	5.2	47.2	40.0
Macrosomia (%)	4.6	6.7	23.5	20

Table 3. Clinical and metabolic parameters, and pregnancy outcomes in 32 pregnant type 1 diabetic women, 17 of them followed up with the telemedicine system (T1), 15 using the traditional approach (C1), and in 203 GDM women, 88 of them followed up with the telemedicine system (T) and 115 with the traditional approach (C) * p = 0.008 T vs C; ° p = 0.02 T vs C.

Women with diabetes type 1 were enrolled in the study at their first visit after conception, while women with GDM were included a week after GDM was diagnosed (after a mean 28±1 weeks of gestation).

Type 1 diabetic pregnant women revealed no differences in clinical and metabolic parameters, or pregnancy outcomes, whether they were followed up with the telemedicine system or conventionally.
Conversely, the GDM women followed up with the telemedicine system had a better metabolic control, as demonstrated by their HbA1c levels at the end of the pregnancy ($p=0.008$), a lower rate of caesarean sections ($p=0.02$), and also of macrosomia (though the difference was not statistically significant) than the GDM women followed up conventionally.
Using the telemedicine approach for pregnant type 1 diabetic women resulted in fewer visits to the diabetes clinic. Most women reported being satisfied with the system because they could contact the physician whenever they felt it necessary to do so.
As for GDM patients, the telemedicine approach led to improvements in their metabolic control and in some maternal and fetal outcomes. Our data differ from the report from Homko et al, who found no significant differences in pregnancy and neonatal outcome between GDM women followed up with a telemedicine approach and those in conventional care, but their patients' poor economic conditions and scarce adherence to the study may well explain the different results they obtained.
To our knowledge, our study is the first to examine the influence of telemedicine systems on quality of life in diabetic pregnant women. We were unable to document any major differences between the study group and controls, but the scores for some areas explored by the SF-36, e.g. general health perception, vitality and mental health, improved significantly after delivery only in the telecare group, suggesting a positive impact of the system on subjective health perception. In both groups, the diabetes-related frustration and worry decreased markedly after delivery, physical functioning substantially improved, and women perceived fewer role limitations as a result of their physical problems.
A strength of our study is that we adopted a straightforward telemedicine system (using the telephone) that was easy for all patients to handle, demanding no IT expertise or computer literacy.
Use of the telemedicine system was associated with a positive impact on quality of life. The system also reduced the number of visits to the diabetes clinic and helped the diabetic women to maintain a better metabolic control with fewer medical consultations.

4. Conclusions

In conclusion, the above-reported studies all show that the telemedicine approach can be a practical way to provide specialist care in pregnancies complicated by diabetes.

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6

Prenatal Telemedicine – Advances in Fetal Monitoring

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1. Introduction

Current medical research aims to continuously improve diagnostic tools, and thus to develop new assessment methods, less invasive and - when long-term monitoring is the case, as in telemonitoring systems - less annoying for the patient. Many improvements of clinical investigations are directed by cost reduction; therefore, upgrading existing inexpensive techniques such as the direct recording of biosignals from the body surface is of utmost interest (Groves, 2008).

Currently, research and development are mainly focused on offering reliable medical devices and techniques for disabled and elderly people (Alemdar et al., 2010; Feng et al. 2010; Tay, 2009; Mestre, 2005; Corchado, 2010; Fleury, 2010). Concomitantly, there are ethical and social aspects that make medical care also focus on the first years of life, including the prenatal period, since disorders and handicaps acquired during this time will be long lasting and an extreme load for the subject, for the family, and for the society, as well. Since these individuals are not autonomous, but totally dependent on the adults, the society is also responsible for their health for obvious ethical reasons. Therefore, prenatal health care is an important topic in biomedical research, and fetal monitoring is one of its most important components (Di Lieto et al., 2008; Ippolito et al., 2003; Kosa et al., 2008; Hod and Kerner, 2003; Dalfra, 2009; Kerner, 2004; Di Lieto, 2002). Fetal electrocardiogram (fECG) and electroencephalogram (fEEG) can be used to investigate the general wellbeing and the brain development.

The current clinical methods are mainly based on the fetal heart rate variability (fHRV) analysis (Kovacs et al., 2000; Varady et al., 2003; Horvath et al., 2007). Currently, the noninvasive cardiotocographic technique is the standard clinical approach because its use is possible during both pregnancy and labor. Alternatively, the fetal Doppler ultrasound is used during pregnancy, but not during labor (1) because of its sensitivity to the movement either of the mother or of the fetus, and (2) because of the errors induced by the uterine activity. Furthermore, the side effect of long-term ultrasonic exposure on the fetus and young infants is not completely clear, and that is why this method is not recommended for hours-long monitoring. All of the above drive to the conclusion that alternative methods are necessary. Consequently, alternatives offered by other non-invasive recording techniques are extensively analyzed for fECG monitoring. Beside the fetal phonocardiographic signals (Kovacs et al., 2000), abdominal recordings are especially investigated due to the fact that the recording devices were improved significantly and simple low-cost long-term recording is allowed, considering the modern data storage technologies. Fetal monitoring through the assessment of abdominal signals (ADS) allows the screening of the fetal well-being, based on the analysis of the fetal heart rate (fHR) and of the waveform of fECG (Sato et al., 2007). The latter implies a strong advantage of this noninvasive recording method for fetal monitoring over methods such as Doppler ultrasound (Jezewski et al., 2006).

The morphology analysis of fECG is a quite important point in fetal monitoring, since the information about the fHR does not really provide all the necessary information about the development of the fetus and fetal electrocardiography (Oostendorp 1989). Rather, the analysis of the fetal P- and T-waves, the QRS complex, and the ST segments are extremely important for an accurate diagnosis of the fetus, indicating when hypoxia occurs during pregnancy. Till now, this type of information is only available during labor, through direct fetal scalp recordings. The advantage of the abdominal fECG recordings is that this information will be optionally available all the time during pregnancy and labor, as demanded by fetal telemedicine. After extracting the fECG, the relation between the fECG and mECG needs to be investigated under different conditions.

The uterine activity will also be detected and analyzed in order to investigate, how it affects the fHR knowing that the fetus has the ability to adapt to the altering conditions induced by uterine contractions translated into temporary reduction in oxygen supply and increased pressure to the fetal head. With the adequate processing techniques, the uterine activity can be investigated from the abdominal recorded signals (Diab 2007).

As the morphology of the mECG is different between ADS channels (Roche et al., 1965; Sturm et al., 2004), the methods which analyze each ADS channel independently from the others seem to be more suitable for fetal monitoring as they provide superior preservation of the fECG morphology due to the channel specific disturbance canceling. Combined with a contactless recording (Peters et al., 2007), they could be used even for long-term continuous monitoring of high risk pregnancies.

This chapter is structured as follows: Section 1 present a short introduction into the topic; Section 2 is dedicated to the information and communication strategies available in the prenatal telemedicine; the currently in use fetal monitoring techniques are described in Section 3, revealing that recording techniques appropriate for long-time fetal monitoring; Section 4 presents the methods used to extract the information about the fECG, fHR and the uterine activity from the abdominal recorded data, pointing out the contribution of the group, and reveals their performance; the last section summarizes the problems that the prenatal telemedicine could face, showing possible research directions in the field.

2. Communication networks used in the prenatal telemedicine

The solutions for long-term fetal monitoring, necessary when a high-risk pregnancy is assumed, include different levels of complexity and technological challenges, depending on the supplied information: images, videos, signals, (multimedia) electronic patient records (EPR). The lowest complexity is given when only alarm systems are implemented (Fleury et al., 2010) (e.g., birth alarm systems). This kind of systems usually provides a button that allows to contact a call center of a medical system serving the alarm situations. The next level of complexity appears in the store-and-forward systems; here the relevant data (signals, images and processed information) are stored and forwarded for a medical examination. These systems are cheaper, due to the asynchronous transmission, and they are widely used when the real-time monitoring is not demanded (Pandian, 2007; Britt, 2006). The highest complexity is involved by real-time applications, based on the synchronous transmission. For these telemedicine systems, the use of some kind of video-conferencing equipment is common (Kyriacou et al., 2003).

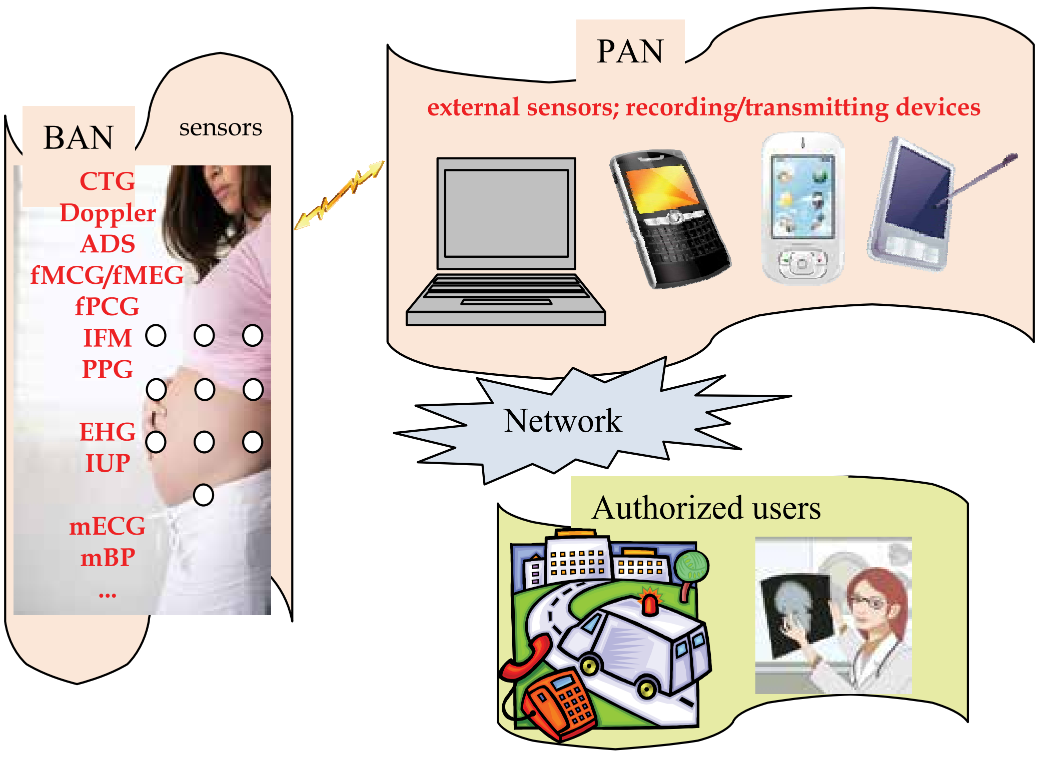


Fig. 1. A simple fetal telemedicine application scenario. Several biosignals were recorded continuously from the pregnant woman through the BAN (CTG, Doppler, ADS, fMCG/fMEG, fPCG, IFM, PPG, EHG, IUP, mECG, mBP) and monitored. They are transmitted to the PAN and further integrated into the prenatal telemedicine system to be available to authorized users.

A simple fetal prenatal application is presented in Fig. 1. The Body Area Network (BAN) ("on-body network" – OBN) consists of a group of sensors placed on the body of a pregnant woman and can be used with wireless local area network, radio (Xiao et al., 2007), Bluetooth (Omre, 2010), RFID, and Zigbee communication technique, to deliver the recorded data to the Personal Area Network (PAN).

The PAN includes (mobile) medical data acquisition devices that belong to the monitored pregnant woman (laptop, cell phone, PDA, Smartphone), and, eventually, environmental sensors spread around her (at home for example); it represents a "network of OBNs" (Alemdar et al., 2010; Dabiri et al., 2009).

The prenatal telemedicine system includes at least a base unit (doctor's unit) and a portable patient unit that communicates with each other through a wired/wireless wide area network (WAN). The traditional wired telemedicine networks, based on the Plain Old Telephony Systems (POTS) and the Integrated Services Digital Network (ISDN), and wired LAN, are lately replaced by the wireless networks (Kyriakou et al., 2003; Faddle et al., 2005) and its recently improved version, the cognitive radio approach (Feng et al., 2010; Phunchongharn & Hossain, 2010; Haykin, 2005; Matila & Maquire, 1999), using mobile phone (GPRS, GSM, G3) (Lin, 2010), or Satellite technology (Tyrer, 2009).
The communication technology for BAN, PAN, WAN is selected by considering the information transferred within/by the telemedicine system: i) CTG (cardiotocograph)/ Doppler ultrasound data, abdominal signals (ADS), fetal magnetocardiogram (fMCG), fetal magnetoencephalography (fMEG), fetal phonocardiogram (fPCG), invasive fetal monitoring (IFM – scalp electrodes), Photoplethysmography - to extract the fHR/fECG; ii) electrohysterogram (EHG), intrauterine pressure (IUP) – to analyze the uterine contractions, for labor prediction; iii) maternal ECG (mECG), maternal blood pressure (mBP), etc. – to evolution the state of the mother during pregnancy/labor.
When the medical images are of interest (e.g., Doppler ultrasound), it is necessary to implement an appropriate image communication system (Fig. 2), by designing a database for these images in such a way that the medical information can be retrieved no matter which technical method is used when the image is recorded.

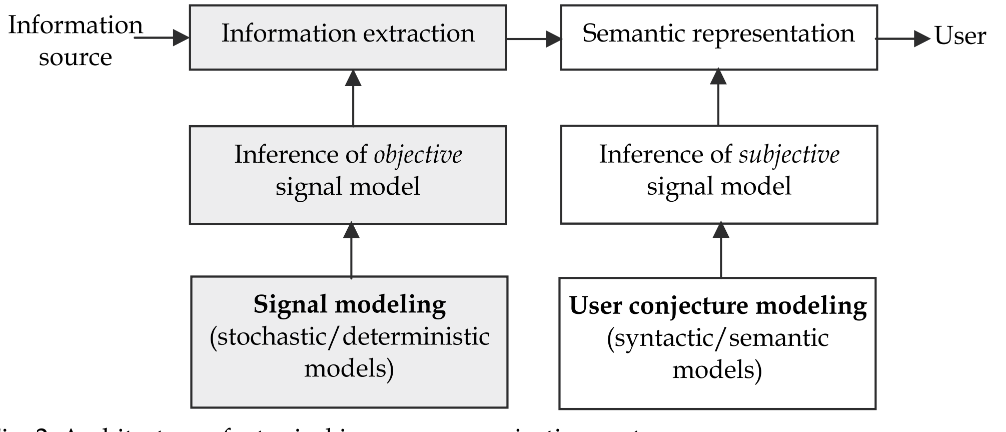


Fig. 2. Architecture of a typical image communication system

The information must be also achieved for any imaging orientation, for different body regions, considering the analyzed biological system. The challenge is then to develop tools that efficiently represent the medical images allowing physicians an easy search and comparison and a fast clinical interpretation. There is an increasing trend towards the digitization of medical images and the formation of good archives. The resulting picture archiving and communication systems (PACS) are available within a hospital allowing a global access to the shared resources. The PACS must be supplemented by a Content-Based Image Retrieval (CBIR) system so that the information the physicians are looking for is self-contained. In order to support data mining considering huge medical image databases, all approaches for CBIR systems compute a certain set of features, which are stored in the database and linked to the original image. Regarding the integration of CBIR systems into PACS there is no need to analyze whether these features are global, local, and hierarchical or of other more complex structure. This information is integrated internally by the CBIR system. The CBIR system must have a manual interface for data entry and a mechanism for relevance feedback and query refinement (Strungaru et al., 2006). In Table 1, some of the telemedicine systems available for prenatal/pregnancy monitoring are mentioned; their transmitted signals and communication technology for BAN/PAN/network are specified.

No	Author(s)/Publication/Monitoring System	Year	Data transmitted	Transmission Communication Technology
1.	Graatsma E., Jacod B., van Egmond L., Mulder E., Visser G. (2009)/ Fetal electrocardiography: feasibility of long-term fetal heart rate recordings. *BJOG*, Vol. 116, (2009) 334–338./ Monica AN 24	2009	**ADS:** fHR/mHR/UA (uterine activity) data, fetal position	BAN: bluetooth PAN/network: mobile phone
2.	Kerner R., Yogev Y., Belkin A., Ben-Haroush A., Zeevi B.&Hod M. (2009)/ Maternal self-administered fetal heart rate monitoring and transmission from home in high-risk pregnancies. *Int. J. Gynaecol. Obstet.*, Vol. 84, No. 1 (Jan 2004) 33-39	2004	**ADS:** (fetal movements, uterine contractions)	network: telephone
3.	Kovacs F, Horvath C, Torok M, Hosszu G. (2005)/ *Conf Proc IEEE Eng Med Biol Soc.* 2005;4(1):3946-3949	2005	**PCG:** fHR and additional PCG data	PAN/network: mobile phone (GPRS)
4.	Di Lieto A, De Falco M, Campanile M, Török M, Gábor S, Scaramellino M, Schiraldi P, Ciociola F. (2008)/ Regional and international prenatal telemedicine network for computerized antepartum cardiotocography. *Telemed J E Health.* 2008 Jan-Feb;14(1):49-54./ TOCOMAT	2008	**CTG:** fHR UC	network: modem
5.	Dalfrà MG, Nicolucci A, Lapolla A; TISG. (2009)/ The effect of telemedicine on outcome and quality of life in pregnant women with diabetes. *J Telemed Telecare.* 2009;15(5):238-42.	2009	Blood glucose	

Table 1. Implemented telemedicine systems for prenatal/pregnancy monitoring

3. Available pregnancy/fetal monitoring techniques

The available fetal/pregnancy monitoring techniques as presented in Fig. 1 are all potential sources of information for a prenatal telemedicine system; they will be described in this section in some detail.

3.1 Investigation of the fetal heart

The usual investigation of the fetal heart means to analyze the fHR, i.e. the instantaneous fHR (Ungureanu et al., 2009; Bemmel, 1968) or its spectrum (Cerutti et al., 1996). In addition some other statistical analyses can be performed (see the CTG section below). The recent progress in recording techniques and information technology encourage research to extend the analysis over the morphological parameters of the fECG, such as: PR-interval, PR-Segment, QRS-Interval, QT-Interval, ST-Segment, ST-Interval, QRS-Amplitude, T-Wave Amplitude, shape of the QRS, P-Wave (Taylor et al., 2003; Vrinson et al., 2004; Hayashi et al., 2009).

Doppler ultrasound

Doppler ultrasound is used to evaluate the hemodynamic components of vascular impedance and it is usually used in cases of fetal growth restriction (FGR). It is also applied to investigate the blood vessels (maternal uterine artery, fetal middle cerebral artery and the fetal ductus venosus) when evaluating the FGR (Farley & Dudley, 2009). The hypoxia related with FGR generates a brain-sparing reflex similar to that noticed in other fetal hypoxemia cases.
The parameters usually measured are: peak systolic flow velocity, the diastolic flow velocity at the end of the cardiac cycle (end-diastolic flow velocity – EDV), the systolic/diastolic ratio (S/D ratio), resistance index: $\frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{peak systolic velocity}}$, pulsatility index: $\frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{average frequency shift over entire cycle}}$.

Cardiotocography

The ultrasound Doppler method combined with the recording of the uterine activity by applying an external pressure transducer is known as *cardiotocography* (CTG) (Signorini et al., 2003; Warrick et al., 2009). The fHR is measured and analyzed by investigating the baseline, the fHRV, the accelerations and the decelerations. In addition, the uterine pressure (UP) is used to extract the following parameters that describe the uterine activity: the contraction frequency, duration, intensity. Based on the fHR and UC the physician can recognize when the well-being state of the fetus is affected by the hypoxia.

Abdominal recordings

Abdominal recording (ADS), including the fECG, is a non-invasive method suitable for long-term fetal monitoring, and it involves the recording of the electrical signals which arise on the mother's abdomen, using surface electrodes. With the ADS it is common to monitor the fHR and the fECG, throughout pregnancy and in labor. The parameters extracted from the fECG give vital information about the fetal health status and its development. Thus, monitoring starting early in the pregnancy can observe whether the fetus is stressed, whether some critical health problems (i.e. cardiac dysfunction) could appear, or whether asphyxia appears. The method is preferred because it has no potential risk and greatly increases the comfort of the mother and the fetus. In addition, the method can be used continuously throughout pregnancy when using a belly belt of sensors.

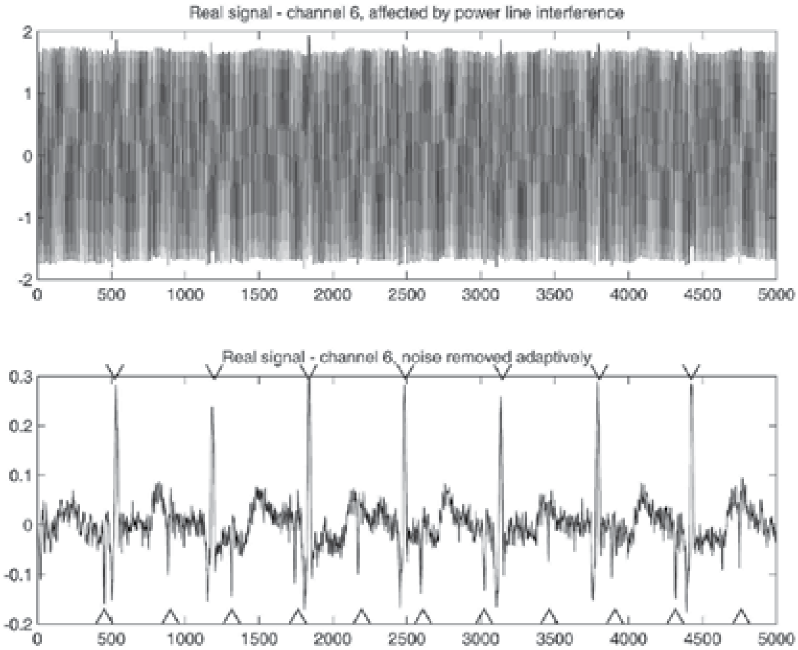
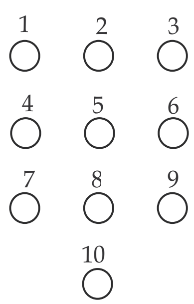


Fig. 3. Real ADS signal – chanel 6, noisy (upper plot) and adaptively filtered (lower plot). fECG (∧) and mECG (∨) are indicated in the plot.



Recording configuration
BIOPAC System
Unipolar recording: 10 active electrodes and
1 reference electrode placed on the lower back;
Gain – 5000;
Sampling Frequency – 1000Hz

Fig. 4. Electrode placement for unipolar ADS recordings.

The fECG is not the only biosignal projected on the maternal abdomen; the disturbing biosignals are the mECG, the electromyogram (EMG) generated by maternal abdominal muscle activity, and electrohysterogram (EHG) which is the electromyogram originating from the uterine activity. In addition, the following disturbances must be considered: noise of the measurement sensors and systems, the power line interference, and the baseline wander (Matonia et al., 2005; Ungureanu et al., 2009). The main source of disturbances is the mECG. The transabdominal fECG R-peak amplitude ranges from 10 to 100 µV, while the amplitude of the maternal QRS complex shows 0.5 - 10 mV. The uterine contractions are strongly disturbing the fECG, too, especially during labor. The slow baseline wander of the signals is caused by the respiratory process and by changes of the skin-electrode-contact. All these noise sources overlap the transabdominal fECG in the time and frequency domain, and a simple high-pass filter cannot be applied to the ADS, for fECG extraction. Another problem would be the unwanted phase distortion of the fECG, introduced by filters in signal preprocessing. The amplitude of fECG obtained through the ADS depends on the electrode configuration and varies among subjects due to the different body size of the mother and due to the position of the fetus. Considering these hard conditions, a processing of the ADS to extract the fECG is a difficult task. The ADS usually provides the fHR (or the RRI – R-R Interval), but depending on the method applied to get the information about the fetal heart, a more complex analysis that considers the fECG morphological features (waves, segments) can be applied (Ungureanu et al., 2009; Sato et al., 2007). Figure 3 shows an example of an ADS segment, obtained when using the recording setup described in Fig. 4.

Fetal magnetocardiography

The fetal heart is lately more and more investigated by using the fetal magnetocardiography (fMCG), a non-invasive method not affected by the appearance of the vernix caseosa. It provides fECG signals of a quality good enough to allow not only the instantaneous fHR monitoring but also the analysis of the fECG morphology (Comani et al., 2007; Hoyer et al., 2009; Lewis, 2003; Comani et al., 2009).

Fetal phonocardiography

The fetal phonocardiography (fPCG) represents a good alternative to the ultrasonic cardiotocography, since it is a non-invasive recording technique suitable for long-term fHR/fHRV (tele)monitoring. Like the ADS-based fetal monitoring technique, it requires complex signal processing methods that extract the cardiac information from these noisy recordings (Ruffo et al., 2010).

Invasive (internal) fetal monitoring

The fetal cardiac activity can be detected, recorded and analyzed using the scalp fetal electrocardiogram, an invasive (internal) fetal monitoring method (IFM) that can be applied during labor; it can cause discomfort and complications for both the mother and the fetus. In addition, this recording technique can be applied only after the membrane rupture. This method is usually used for research purpose, to evaluate the noninvasive fetal monitoring techniques, due to its major shortcoming, its invasiveness, relying on a direct contact needle-like fetal scalp electrode (FSE) to obtain the fECG signal during labor (Taylor et al., 2003).

Abdominal Photoplethysmography

Zahedi and Beng proposed in 2008 an efficient algorithm to extract the fetal cardiac rate from the noisy abdominal photoplethysmographic signals (APPG) recorded from the maternal abdomen (Zahedi and Beng, 2008). Since the method analyzes the maternal and fetal blood pulsations, it does not allow the identification of the ECG waves and segments.

3.2 Investigation of the Uterine Activity

The current methods to monitor the uterine activity analyze either the mechanical uterine activity (using a tocodynamometer, i.e. CTG, or applying invasive methods that record the intrauterine pressure - IUP), or the electrical uterine activity (uterine EMG - an invasive method that is not applied on humans usually, and the electrohysterogram, recorded non-invasively from the maternal abdomen, usually filtered bellow 5Hz) (Devedeux et al., 1993).

Electrohysterogram

The EHG has a slow wave in the frequency range of 0.01 – 0.03 Hz, and a fast wave that can be divided in a low-frequency band (FWL), present in any contraction, and a high-frequency band (FWH), a sign of an efficient parturition contraction (Devedeux et al., 1993). There is also a slow wave with a period equal to the contraction duration (0.01 – 0.03 Hz), usually undetectable in a standard recording. The following parameters are extracted from the EHG: i) Burst duration (D); ii) Peak-to-peak action potential amplitude (Amp); iii) frequency of bursts (F1); iv) the intrinsic spike frequency within each burst (F2). They allow to identify a normal labor (Amp > 400 μV), to analyze the efficiency of the contractions (a high enough F2; a shift of FWL to higher frequency, indicated by the FWH power/ FWL power ratio), to predict the term and preterm labor (Maner et al., 2003; Khalil & Duchene, 2000), to detect the preterm labor or to recognize the fetus motion. A variation of the F2 within a burst is noticed when the IUP increases.

Intra-uterine pressure

The intra-uterine pressure (IUP) measured invasively is the most accurate recording technique in use for monitoring the uterine activity. Unfortunately, it cannot be applied in early pregnancy, and it is exposed to a high risk of infection or of induction of labor (Schlembach et al., 2009). The parameters measured are usually: the strength, the frequency and the duration of contractions. The values of the maximum rate of rise of pressure and the extrapolated maximum muscle velocity are also used, to make the difference between dysfunctional uterine activity and contractions specific to delivery (Devedeux et al., 1993).

4. Signal processing methods to extract the fetal ECG and the uterine activity from abdominal signals

The fundamental problem in extracting fECG from ADS is that they do not contain only the signal of interest, the fECG, but also other disturbing signals which have higher amplitudes than the fECG component and, in addition, are overlapping with it in the spectral domain. Some recent publications (Vijila et al., 2005; Guerrero-Martinez et al., 2006; Najafabadi et al., 2006; Assaleh 2007) underline that this topic currently attracts huge research efforts. Among the "noise" signals in ADS, the mECG is clearly the most salient source of disturbance, since its R-peak shows amplitudes 2 to 10 times greater than the amplitude of the fetal R-peak (Cicinelli 1994). The fECG R-peak amplitude ranges from 10 to 100 μV (Shao et al., 2004; Bemmel 1969) in a good ADS recording where the fECG can be detected.

Other disturbing signals which must be considered are the electronic noise (introduced by amplifiers etc), the baseline wander of signals, the myoelectric crosstalk, and, in particular during labor, the uterine contractions. The latter evoke electrical activity which can be recorded by unipolar or bipolar electrodes placed on the abdomen of the mother and can be extracted by applying a bandpass filter set at 0.1 – 5 Hz to the ADS; the resulting signal is called EHG, and shows an amplitude range from 100 μV to 500 μV (Devedeux et al., 1993).

The large amplitude of the EHG, particularly during labor, is hiding the fECG, and a simple high-pass filtering of abdominal signals for fECG extraction cannot be applied due to the overlapping spectra of the EHG and the fECG. Also, a filter would introduce some phase distortion of the fECG. The amplitude of the fECG depends also on the electrode configuration and varies among subjects due to the different body mass index of the mother and also due to the different positions of the fetus. In addition, the fECG changes with time, especially with the appearance of the vernix in the last three months of pregnancy, when the R-peak of the fECG is hardly detectable (Bemmel 1969).

All these confounding factors reveal the need for reliable methods for removing the mECG and EHG when analyzing the fECG based on ADS recordings. Some methods have been

proposed to extract the fECG for fHR computation, such as principal component analysis (PCA), independent component analysis (ICA) (de Lathauwer et al., 2000) and nonlinear state-space projections (NSSP) (Richter et al., 1998), but the increasing interest of physicians to consider not only the instantaneous fHR but also the waveform of the fECG introduces new requirements, thus filtering methods in general are getting more demanded. For example, adaptive noise cancelling using standard mECG recordings in addition (Widrow et al., 1975) and the event-synchronous cancelling method (Ungureanu and Wolf, 2006; Ungureanu et al., 2009), as well as an adaptive maternal beat subtraction using an approximation by some previous linearly combined segments (Comani et al., 2004; Vullings et al., 2007) are applied to remove the mECG and to extract the fECG. All these methods require a template for the mECG time course within one beat cycle estimated from the recorded signal; for this purpose, first the maternal R-peaks are detected in either the ADS or the standard mECG recording by applying some pattern recognition algorithm (Friesen et al., 1990); then, the mECG template is estimated from ADS signal segments around the detected R-peaks. Most of the methods apply some preprocessing steps to remove the baseline wander, the power line interference and the mECG (Taylor et al., 2003; Martens et al., 2007), indicating again the importance of providing valuable methods for noise removing and fECG extraction. An additional standard mECG recording in addition to the abdominal channels will contribute to a more precise detection of the mQRS complex.
The analysis of the uterine contractions provides useful information about the development of the pregnancy and parturition. The most important point in the uterine activity analysis is to predict the pre-term delivery, as the premature birth is the leading cause (85%) of infant death and the source of neurological, mental, behavioral and pulmonary problems in later life (Garfield et al., 2005). Nowadays, the only method to absolutely detect pre-term labor is the permanent contact and care from physicians (Maner et al., 2003) in a hospital, which represents an expensive solution. An alternative to early detect pre-term labor by an effective automatic procedure for uterine activity monitoring (home care solution within a prenatal telemedicine system) is not yet available. Some attempts to accurately detect the preterm labor involve the invasive recording of uterine activity (Shi et al., 2008; Jiang et al., 2007).

4.1 Event Synchronous Interference Canceller

Event Synchronous Interference Canceller (ESC) removes a repetitive disturbing signal available from an additional recording channel n from the recorded signal y in order to extract the signal of interest. A 'Compensation' block performs the gain adaptation that considers the intersegment variation for the repetitive disturbing signal. The additional recording of the noise signal is not necessary when the disturbance has an amplitude strong enough to allow the detection of the repetitive segments, as is the case of fECG extraction from abdominal signals. However, the recording of the additional standard mECG improves the extraction and the analysis of the resulting fECG. ESC simply subtracts an artificial repetitive reference (which represents an approximation of the disturbing signal) from the input signal, for denoising. The artificial reference signal is determined by repeating the template disturbing segment, obtained by averaging the noise segments contained in the recorded disturbed signal y (Ungureanu & Wolf, 2006).
The subtraction performed to obtain the cleaned signal, includes the linear and non-linear distortions of the noise signal associated with the signal path and the recording techniques. The adaptive gain a^* applied to the averaged template includes the amplitude variations in the real periodic noise signals and is obtained as the value which minimizes an error

function over $[a_1;a_2]$. In order to avoid the instability, the interval of minimization is chosen to be $[0.9,1.1]$. An example of fECF extraction from ADS signals is shown in Fig. 5.

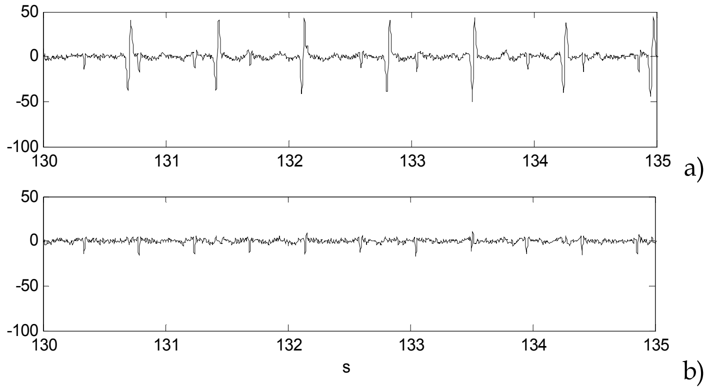


Fig. 5. Results obtained when applying the ESC for fECG extraction from a real ADS signal, recorded at 1000 Hz. a) ADS signal; b) fECG extrated by the ESC algorithm.

4.2 Principal component analysis

PCA procedure reduces the number of uncertainties and identifies the major components based on the fact that they have the most significant variance. Let us consider that we have *N* samples for each channel, x_i, and that the data vector is *D*-dimensional: $\mathbf{x} \in \mathbf{R}^D$. PCA replaces these vectors by lower-dimensional vectors with dimension *C*, where $C < D$. Considering the linear transformation for these vectors, we obtain:

$$\mathbf{x} = \mathbf{W}\mathbf{s} + \mathbf{b} = \sum_{j=1}^{C} \mathbf{w}_j s_j + \mathbf{b} \tag{1}$$

where the matrix W is described by $\mathbf{W} = \begin{bmatrix} w_1 & w_2 & \cdots & w_C \end{bmatrix}$.

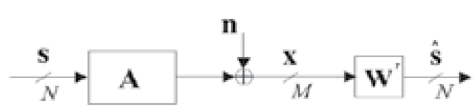


Fig. 6. PCA method - Data decorrelation

This corresponds to a real case where we have a set $\{x_i(k)\}$ of measurements, each with *N* samples (k = 1,2 ,..., *N*), and from it we want to extract the set $\{s_i(k)\}$ for a further analysis; **b** is the average component. There are two different approaches to compute the matrix **W**, namely the eigenvector method (EVD) and singular value method (SVD). The algorithms are the following:

PCA (EVD)

1. Let $\mathbf{b} = \frac{1}{n}\sum_i x_i$ be the mean vector.

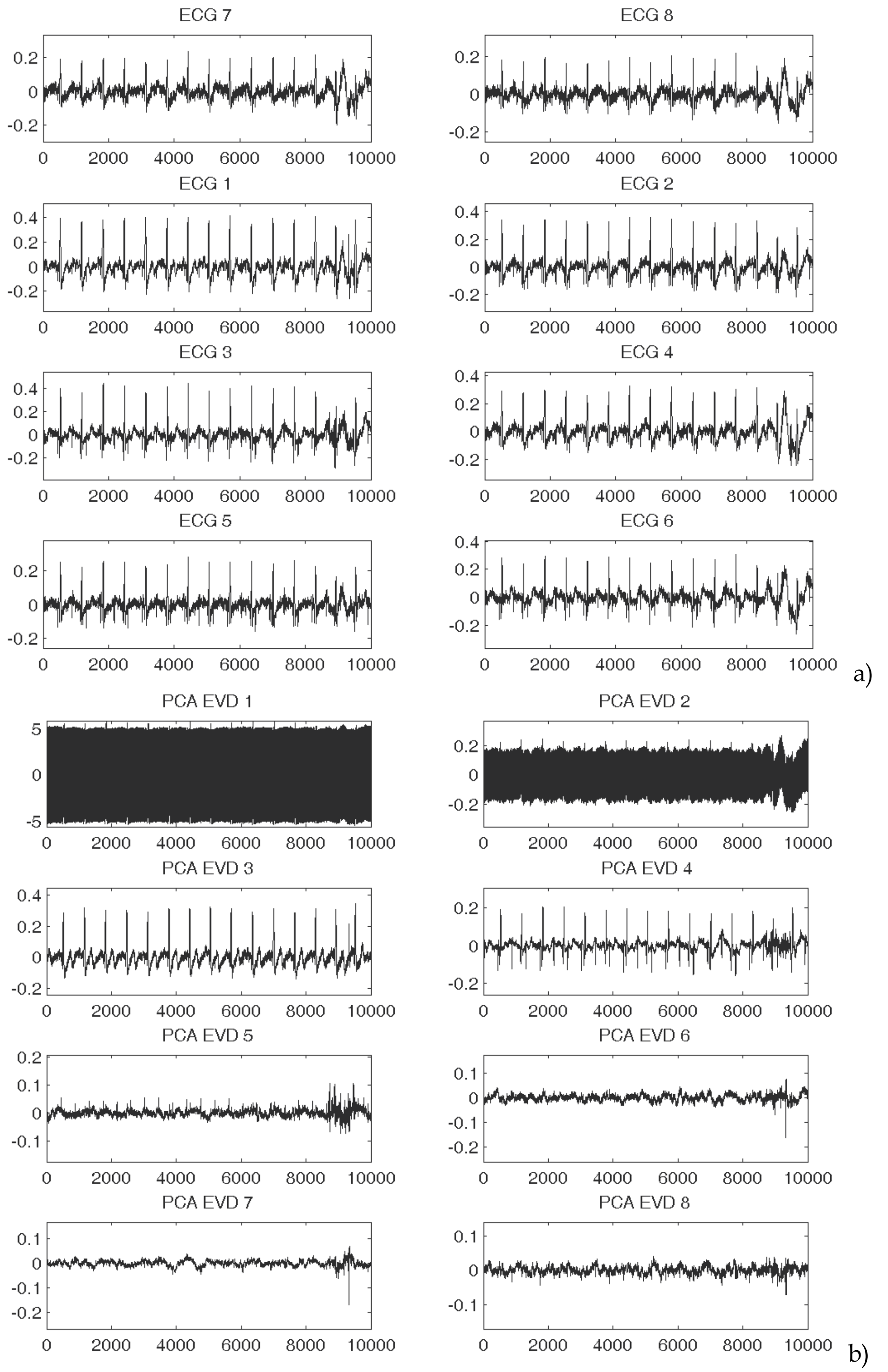


Fig. 7. Results obtained when applying the PCA-EVD method to ADS signals, to extract the fECG. Note that the fECG is not extracted properly. a) real signals; b) extracted components.

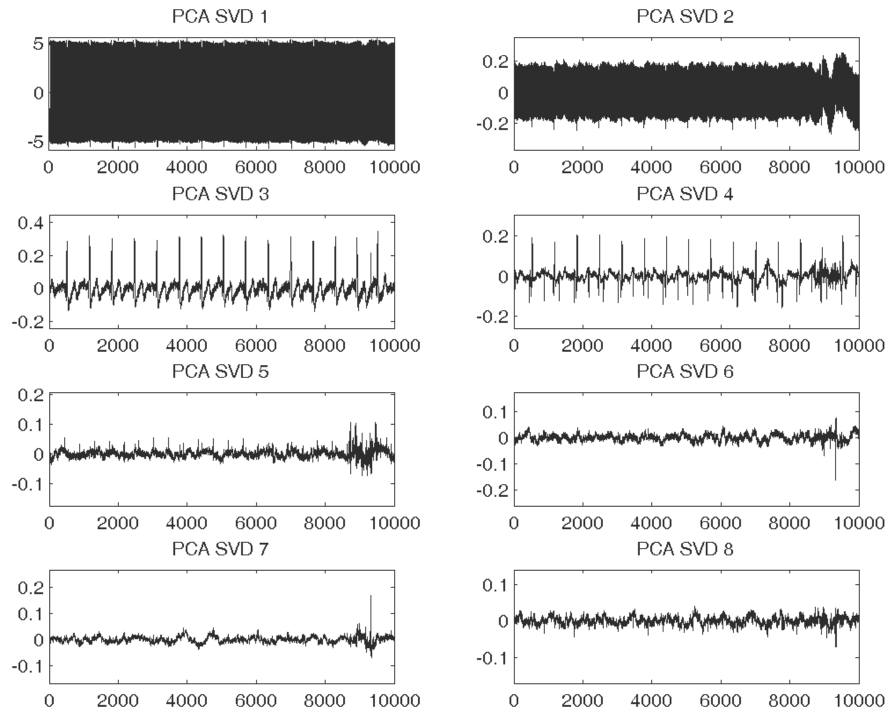


Fig. 8. Results obtained when applying the PCA-SVD method (the real signals are shown in Fig. 7.a). Note that the fECG is not extracted well.

2. Let $\mathbf{K} = \frac{1}{n}\sum_i \left(x_i - \mathbf{b}\right)\left(x_i - \mathbf{b}\right)^T$ be the covariance matrix.
3. Let $\mathbf{V}\Lambda\mathbf{V}^T = \mathbf{K}$ be the eigenvector decomposition of $\mathbf{K}$. $\mathbf{\Lambda}$ is a diagonal matrix of eigenvalues $\mathbf{K}$ ($\mathbf{\Lambda} = \mathrm{diag}(\lambda_1, ..., \lambda_D)$). The matrix $\mathbf{V}$ contains the eigenvectors: $\mathbf{V} = [\mathbf{v}_1, ...\mathbf{v}_D]$ and is orthonormal $\mathbf{V}^T\mathbf{V} = \mathbf{I}$.
4. Let us assume that the eigenvalues are sorted from the largest to the smallest one ($\lambda_i \geq \lambda_{i+1}$). If this is not the case, then we firstly sort them (and their corresponding eigenvectors).
5. Let us consider the estimated noise variance: $\sigma^2 = \frac{1}{D-C}\sum_{j=C+1}^{D} \lambda_j$ (it is equal to the average marginal data variance over all the directions that are orthogonal to the C principal directions; i.e., this is the average variance per dimension of the data that is lost in the approximation of the data in the C dimensional subspace).
6. Let $\tilde{\mathbf{V}}$ be the matrix comprising the first C eigenvectors: $\tilde{\mathbf{V}} = \left[\mathbf{v}_1, \cdots, \mathbf{v}_C\right]$, and let $\tilde{\mathbf{\Lambda}}$ be the diagonal matrix with the C leading eigenvalues: $\tilde{\mathbf{\Lambda}} = \left[\lambda_1, \cdots, \lambda_C\right]$.
7. Compute $\mathbf{W} = \tilde{\mathbf{V}}\left(\tilde{\mathbf{\Lambda}} - \sigma^2\mathbf{I}\right)^{1/2}$.
8. Compute $\mathbf{s}_i = \mathbf{W}^T\left(\mathbf{x}_i - \mathbf{b}\right)$, for all i.

PCA (SVD)

1. Let $\mathbf{b} = \frac{1}{n}\sum_i x_i$ be the mean vector **x.** Translate the origin to the center of gravity, *data center.*
2. Calculate the singular centered values of data, $\tilde{\mathbf{X}} = \mathbf{U}\Sigma\mathbf{V}^T$.
3. Compute the variances by squaring the singular values. Since $\sum_i (x_i - \mathbf{b})(x_i - \mathbf{b})^T = \mathrm{U}\Sigma\mathbf{V}^T\mathbf{V}\Sigma\mathbf{U}^T = \mathbf{U}\Sigma^2\mathbf{U}^T$ and considering that VΛVT = K, U contains the eigenvector of X. The diagonal values in matrix Σ are the *singular values* (the square roots of the *eigenvalues* of $\mathbf{XX}^T$).
4. Compute $\mathbf{s}_i = \mathbf{U}^T(\mathbf{x}_i - \mathbf{b})$, for all i.

4.3 Independent component analysis

ICA extracts the components that are not only decorrelated but also independent. It considers the computation of higher order moments (3rd and 4th moment) and is suitable for signals that have no more than one Gaussian component. The algorithm is briefly described in the figure bellow:

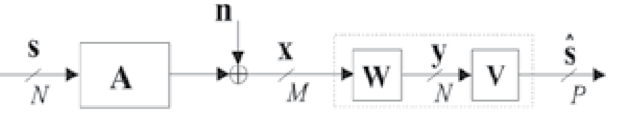


Fig. 9. ICA model - BSS extraction of P signals

ICA extracts the signal sources by applying the matrix inverse:

$$\mathbf{s} = \mathbf{A}^{-1}\mathbf{x} \tag{2}$$

Two of the most representative ICA algorithms reported in the literature are: i) JADE (joint approximate diagonalization of eigen-matrices) developed by J. F. Cardoso and Antoine Souloumiac (1993), and ii) Fast-ICA, developed by Hyvärinen (1999); it is based on a fixed-point iteration scheme maximizing non-Gaussianity as a measure of statistical independence. The idea of ICA is to extract the vector sources, **s,** with *q* components, from the recorded vector **x**, including *p* channels:

$$\mathbf{x} = \mathbf{A}\mathbf{s} + \mathbf{n} \tag{3}$$

A is the mixing matrix, **n** represents the additive noise. The following assumptions must be met in order to apply ICA:

1. **A** has linear independent columns (satisfied for real signals usually)
2. **x** contains independent variables
3. **n** and **x** are independent**.**

Under these assumptions the mixing matrix can be estimated and the sources are extracted:

$$\mathbf{s} \approx \hat{\mathbf{s}} = \hat{\mathbf{A}}^{-1}\mathbf{x} \tag{4}$$

ICA (JADE)

It is the most applied ICA algorithm and uses the fourth-order cumulants to compute the kurtosis. The steps of the algorithm are:

1. Initialization (data whitening):

$$\hat{\mathbf{W}} = diag\left(\left(\lambda_1 - \hat{\sigma}^2\right)^{-1/2}, \cdots, \left(\lambda q - \hat{\sigma}^2\right)^{-1/2}, 0, \cdots, 0\right)\mathbf{V}^T,$$

   with $\hat{\mathbf{y}} = \hat{\mathbf{W}}\mathbf{x}$ and,

$$\hat{\sigma}^2 = \frac{1}{p-q} \cdot \sum_{j=p+1}^{q} \lambda_j,$$

   with $q < p$.

2. Computation of the Kurtosis for $\hat{\mathbf{y}}$; the set of the fourth-order cumulants, $\left\{Q_i^y\right\}$, is obtained.
3. Optimize an orthogonal contrast: the matrix V has to be estimated so that the contrast function is minimized:

$$\varphi^{JADE} = \sum_{ijkl \neq iikl} Q_{ijkl}^y = \sum_i off\left(\mathbf{V}^T \mathbf{Q}_i^y \mathbf{V}\right)$$

   where $off(\mathbf{A})$ are the nondiagonal elements:

$$off(\mathbf{A}) = \sum_{i \neq j} a_{ij}$$

   The matrix **V** is computed using the Jacobian.

4. Mixing matrix estimation:

$$\hat{\mathbf{A}} = \mathbf{W}^T \mathbf{V}$$

5. The extraction of the independent components:

$$\mathbf{s} \approx \hat{\mathbf{s}} = \mathbf{V}^T \mathbf{y} = \mathbf{V}^T \mathbf{W} \mathbf{x}$$

ICA (FastICA)

The FastICA (a fast, batch type algorithm for performing ICA) learning rule finds a direction, i.e. a unit vector **w**, such that the projection $\mathbf{w}^T\mathbf{x}$ maximizes the nongaussianity. Nongaussianity is here measured by the approximation of negentropy $\boldsymbol{J(\mathbf{w}^T\mathbf{x})}$. Recall that the variance of $\mathbf{w}^T\mathbf{x}$ must be here constrained to unity; for whitened data this is equivalent to constraining the norm of **w** to be unity. The FastICA is based on a fixed-point iteration scheme for finding a maximum of the nongaussianity of $\mathbf{w}^T\mathbf{x}$. It can be also derived as an approximative Newton iteration [9]. Let us denote by g the derivative of the nonquadratic function G used in definition of negentropy. The following choices of G have been proved very useful: $G_1(u) = 1/a_1 \log\cosh(a_1 u)$ or $G_2(u) = -\exp(-u^2/2)$; the derivatives of G functions are $g_1(u) = \tanh(a_1 u)$, and $g_2(u) = u \exp(-u^2/2)$, where $1 \le a_1 \le 2$ (usually $a_1 = 1$).

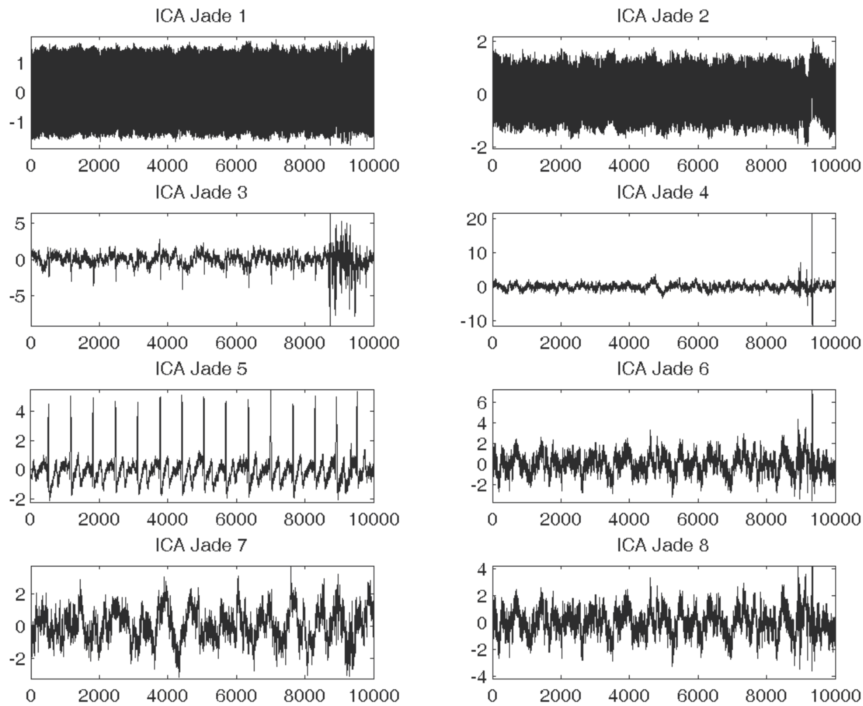


Fig. 10. Results obtained when applying the ICA-JADE method (the real signals are shown in Fig. 7.a). Note that the fECG is not visible in the extracted components.

The steps of the algorithm are:

1. *Data whitening*; the whitened matrix is estimated by:

$$\hat{\mathbf{W}} = diag\left(\left(\lambda_1 - \hat{\sigma}^2\right)^{-1/2}, \cdots, \left(\lambda_q - \hat{\sigma}^2\right)^{-1/2}, 0, \cdots, 0\right)\mathbf{V}^T ,$$

   where $\hat{\mathbf{y}} = \hat{\mathbf{W}}\mathbf{x}$, and

$$\hat{\sigma}^2 = \frac{1}{p-q} \sum_{j=p+1}^{q} \lambda_j$$

   with $q < p$. Whitening is always accomplished by principal component analysis.

2. Choose an initial (e.g. random) weight vector $\mathbf{w}$.
3. Let $\mathbf{w}^+ = E\left\{\mathbf{x}g\left(\mathbf{w}^T\mathbf{x}\right)\right\} - E\left\{g'\left(\mathbf{w}^T\mathbf{x}\right)\right\}\mathbf{w}$
4. Let $\mathbf{w} = \frac{\mathbf{w}^+}{\left\|\mathbf{w}^+\right\|}$.
5. If not converged, go back to step 3.

The one-unit algorithm described above (a "unit" refers to a computational unit, eventually an artificial neuron, having a weight vector **w** that the neuron is able to update by a learning rule) can be extended, to obtain the whole ICA transformation, $\mathbf{s} = \mathbf{W}^T\mathbf{x}$. To prevent different neurons from converging to the same maxima, the outputs $\mathbf{w}_1^T\mathbf{x},\cdots,\mathbf{w}_n^T\mathbf{x}$ are decorrelated after every iteration. A simple way to accomplish this is a deflation scheme based on a Gram-Schmidt-like decorrelation: whenever p independent components are estimated (p vectors $\mathbf{w}_1,\ldots,\mathbf{w}_p$), the one-unit fixed-point algorithm for $\mathbf{w}_{p+1}$ is applied, and after each iteration step the projections of the previously estimated p vectors are subtracted from $\mathbf{w}_{p+1}$; $\mathbf{w}_{p+1}$ is then renormalized:

$$\mathbf{w}_{p+1} = \mathbf{w}_{p+1} - \sum_{j=1}^{p} \mathbf{w}_j \mathbf{w}_j^T \mathbf{w}_{p+1} \ , \ \mathbf{w}_{p+1} = \frac{\mathbf{w}_{p+1}}{\left\| \mathbf{w}_{p+1} \right\|}$$

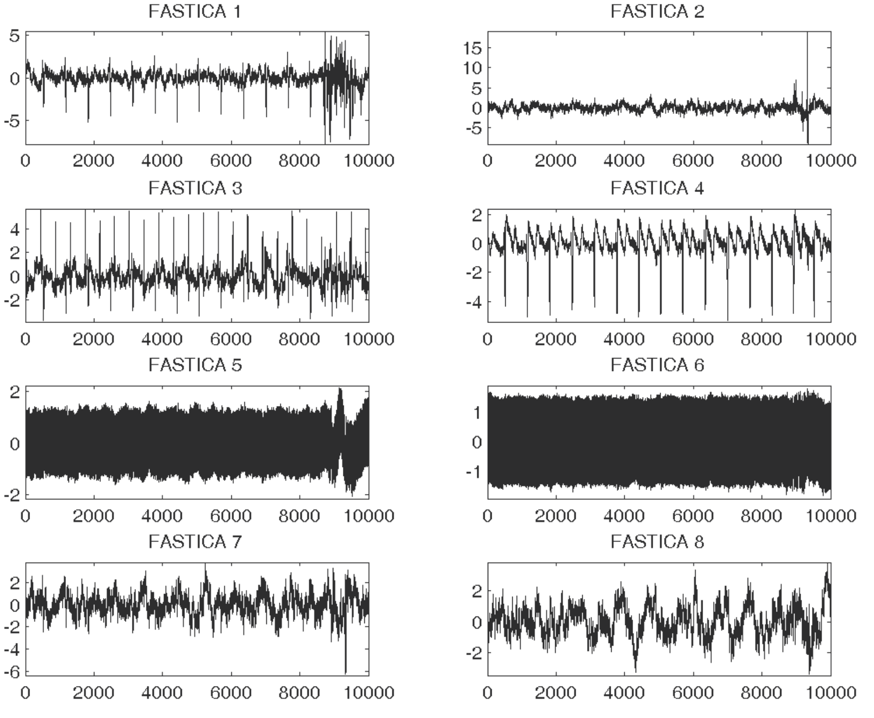


Fig. 11. Results obtained when applying the ICA-FastICA method (the real signals are shown in Fig. 6.a). Note the clear extracted fECG in the 2nd ICA component.

The above decorrelation scheme is suitable for the separation of the independent components. Sometimes it is more convenient to estimate all the independent components simultaneously, and use a symmetric decorrelation. This can be accomplished by the following transformation:

$$\mathbf{W} = \mathbf{W}\left(\mathbf{W}^T\mathbf{W}\right)^{-1/2}$$

where $\mathbf{W} = \left(\mathbf{w}_1,\cdots,\mathbf{w}_n\right)$.

5. Discussions and conclusions

The recent evolution in the sensors development, communications and information technology yields a lot of challenges for the researchers interested in contributing to low cost, long-term, fetal (tele)monitoring. A lot of recording techniques and signal processing methods are available, and the communication strategy offers also a lot of options, making the development of telemedicine systems a bit difficult. Among the fetal extraction methods, the event synchronous canceller method proves to be a useful tool, preserving the morphology of the fetal ECG. In addition the extraction of fECG and EHG from abdominal recordings can be enhanced by ESC application and data fusion of multichannel recordings.

6. Acknowledgement

The study was supported by the National University Research Council of Romania (CNCSIS) under the national research grant PN_II_ID_PCE ID_1723/2009. The authors would like to thank to Dragos Taralunga, PhD Student, to Dr. Camelia Dutescu, and to Ing. Ana Maria Ilincai, for their efforts to record the abdominal signals.

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7

Prenatal Telemedicine: A New System for Conventional and Computerized Telecardiotocography and Tele-Ultrasonography

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Italy

1. Introduction

Telemedicine is the delivery of health care and the exchange of health-care information across distances using both information technology and telecommunications. More simply, Telemedicine is medicine at distance. It encompasses the whole range of medical activities including diagnosis, treatment and prevention of disease, continuing education of health-care providers and consumers and research. Telemedicine should always aim to support health workers providing care as close to the patients as possible. This means information resources should be provided to all levels starting at primary care and clinical Telemedicine should be used where possible to prevent referrals to district or tertiary hospitals and support care at the more local level. Used in this way, Telemedicine can strengthen care at the primary care and district level (Viegas, 1998; Barrett & Brecht, 1998). Prenatal

Telemedicine is a branch of Telemedicine, born from the combination and application of healthcare instrumentation, informatics and telecommunication technologies to prenatal care. It aims to extend medical expertise to pregnant women who cannot access to specific prenatal clinical services, either because of logistical difficulties and emergencies. In the field of the prenatal care, the most widespread applications of Telemedicine are Telecardiotocography and Tele-Ultrasonography. This chapter will illustrate the state-of-art of these two applications and then will focus on the organization and activity of the first and unique Prenatal Telemedicine network in Italy, based on a system called TOCOMAT.

2. The origins of cardiotocography

The era of modern obstetrics started in 1821 with the discovery of auscultation of fetal heart by Jacques Alexandre Lejumeau Visconte of Kergaradec. His observation was a kind of revolution, since, for the first time, the presence of the living child in utero became perceptible. It passed from the situation of the fetus as an 'object' to the one of the fetus as a 'subject'. During the next thirty years, or so, everything within the field of obstetrical auscultation was ready to be discovered and described, i.e. the description of the obstetrical stethoscope, the determination of the mean fetal heart rate frequency, the recognition of its general lack of relationship with the maternal heart rate, and its usefulness for the diagnosis of fetal life or death, the existence of twin pregnancy, and fetal presentation and position. Until the second half of the 20th century, nothing new was been added and the assessment of the fetal condition depended on very limited means: the growth of the uterus and its contents, the movements of the fetus perceived by the mother and the listening of the fetal heart beat with a stethoscope. Sudden absence of fetal movements in the second half of pregnancy was, at that time, a serious diagnostic problem. Usually one had to wait for some weeks in order to observe if the uterus would grow before the decision could be reached to induce labour. The sign of Spalding at X-ray examination, showing overlapping of the fetal skull bones like roof tiles as a result of advanced maceration of the fetal tissues, was one of the few helpful objective diagnostic signs of fetal demise. This recurrent dilemma, whether or not the fetus was died in utero, formed the major impulse for the development of cardiotocography. Initially fetal abdominal electrocardiography and phonocardiotocography were pursued, but failed, primarily due to technical problems. It was only when the fetal heart beat could be rather easily detected by means of ultrasound or through the application of direct electrocardiography, that cardiotocography became popular as the method to monitor the condition of the fetus (Sureau, 1994). Currently, the majority of obstetric decisions to assist delivery of the baby by artificial means (caesarean section, forceps or vacuum extraction) for suspected fetal distress, relies on information gathered through the application of cardiotocography. It is the obstetrician's reassurance that when the fetal heart rate (FHR) pattern is normal there is nearly 100% certainty that the fetus is in a good condition, which has made cardiotocography so attractive and has induced its widespread use. This development is very understandable considering the dependence on indirect signals from the fetus and the problems concerning the very limited means to monitor the condition of the fetus prior to the introduction of cardiotocography. Nowadays, cardiotocography is the most common method of monitoring fetal well being, both before and during labour. Cardiotocography during pregnancy, together with ultrasonography, fetal biophysical profile evaluation and Doppler-velocimetry of the maternal-fetal vascular district, not only allows to diagnose the fetal distress, but also to confirm the fetal wellbeing and to obtain an early diagnosis of any fetal state deterioration. The aim is to carry out well-timed obstetric interventions to reduce both fetal morbility and mortality.

3. Conventional and computerized cardiotocography

Cardiotocography is the simultaneous recording of fetal heart rate and uterine contractions using two separated transducers placed on the maternal abdominal wall. The fetal heart rate is recorded using an abdominal Doppler ultrasound transducer, while uterine contractions are estimated using an abdominal wall pressure sensor. This technique is used during the third trimester of pregnancy, especially near term, and during labour, to monitor the fetus and to early diagnose any change of its condition due to a deterioration of the status of oxygenation. Traditionally, cardiotocographic trace is interpreted in a visual manner, but with high intra- and interobserver variability. The computerised analysis, if compared with the visual reading, allows a more objective interpretation since is based on predefined criteria, provides further parameters, such as short-term variability and approximate entropy, more specifically related to fetal hypoxia, and seems to be associated with less time spent in testing and with a reduction in the number of additional examinations to be performed for the fetal well-being evaluation. Moreover, the computerised analysis allows the repeatability of the results obtained from different centres. Practically, all pregnant women at high risk undergo electronic fetal monitoring in the last half of pregnancy, with a frequency ranging from daily to weekly. Usually, intensive antepartum fetal surveillance is requested in pregnancies where there is a high risk of antepartum fetal death, as a result of either maternal conditions (i.e. hypertension, diabetes) or pregnancy-related conditions (i.e. decreased fetal movements, oligohydramnios) (Di Renzo et al., 1994; Van Geijn, 1996).

4. The Italian experience with the TOCOMAT system

The use of the cardiotocographic recording in pregnant women at high risk often requires them to travel, which is particularly stressful for patients who live far from suitably equipped health centres. For this reason, Telemedicine has been used in cardiotocography to avoid the referral too much pregnant women to clinics or hospitals and to reduce long hospitalization for high-risk patients. An early description of a long-distance cardiotocographic transmission, in 1983, referred to the use of telemetry applied to cardiotocographic recording. Subsequently, computerized networks for the remote transmission and analysis of cardiotocographic traces have been described. Campania is one of Italian regions with a high birth rate. In the last few years, an increasing number of pregnant women, both at high risk and at apparent low risk, have crowded health centres to undergo cardiotocographic monitoring. Because adequately equipped health centres are often located far from patients' homes, pregnant women, who need intensive cardiotocographic monitoring, are forced to travel long distances or to undergo to long hospitalization. Moreover, health workers increasingly request the computerized analysis of cardiotocographic traces because, based on literature 's evidences, it is more accurate and objective than the traditional visual analysis and shows a better correlation with fetal health. In spite of this growing demand, the number of computerized systems for cardiotocographic interpretation available in Campania is very low, due to their high cost and to the need of adequately trained personnel. On these grounds, the first Italian system for antepartum

Telecardiotocography, called TOCOMAT, began in 1998 at the Prenatal Care Unit of the Department of Obstetrical-Gynaecological and Urological Science and Reproductive Medicine of the University Federico II of Naples, with the main aim of extending specialized medical expertise to pregnant women who are at high risk requiring antepartum electronic fetal monitoring and who live far from adequately equipped health centres (Di Lieto et al., 2001). At the beginning, the activity of the network was cofinanced by the University Federico II of Naples and the Campania Region. Subsequently, the activity of the TOCOMAT system has been included in several projects and then financed by the Campania Region (project NEUROMATIC, 2000; project CYBERFETUS, 2000) and the European Union (European Project of Telemedicine, 2003) (Di Lieto et al., 2002; Di Lieto et al., 2003; Ippolito et al., 2003; Romano et al., 2006; Ferrario et al., 2009).

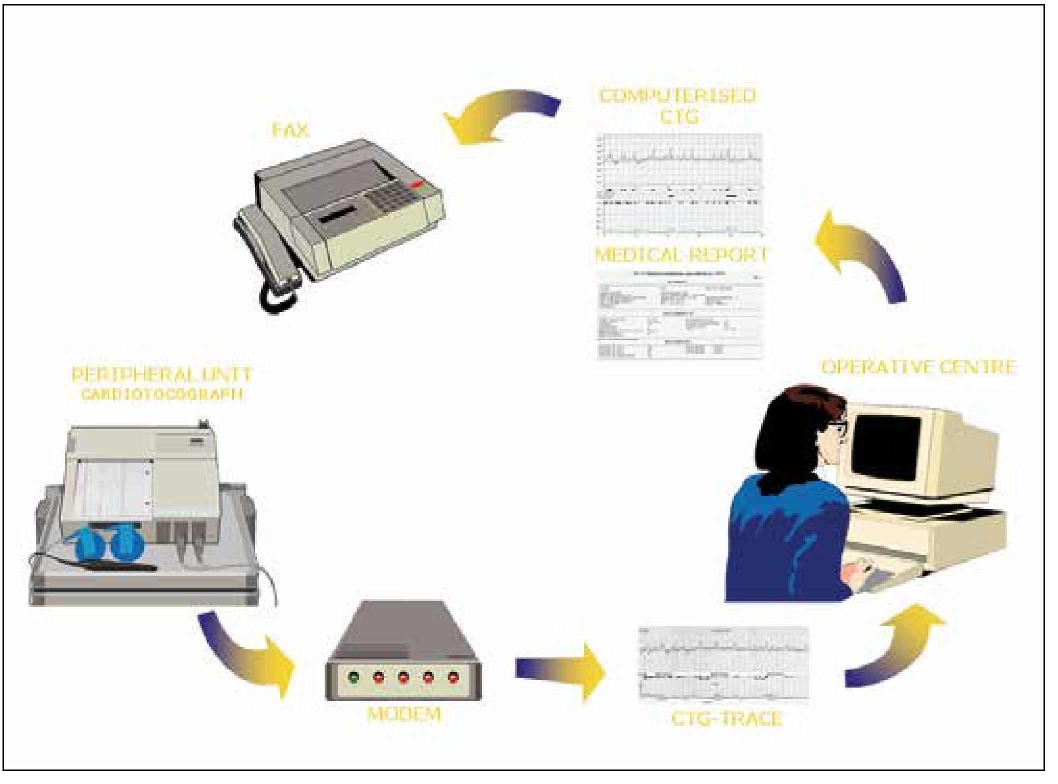

Fig. 1. The organization of the first version of the TOCOMAT system.

The system has been also included into the EUROTOCOMAT project (2004), based on a scientific cooperation between the University Federico II of Naples and the Semmelweis University of Budapest (Hungary) (Di Lieto et al., 2008). In its first version, the TOCOMAT network connected nine peripheral units located in small hospitals and consulting rooms in Campania. The network operations centre is located in Naples, the regional capital, at the University Federico II.
From 2004, two remote units, located at the Department of Obstetrics and Gynaecology of the Semmelweis University of Budapest (Hungary) and at the Hospital of Tripoli (Greece) have also been working with the Operation Centre.

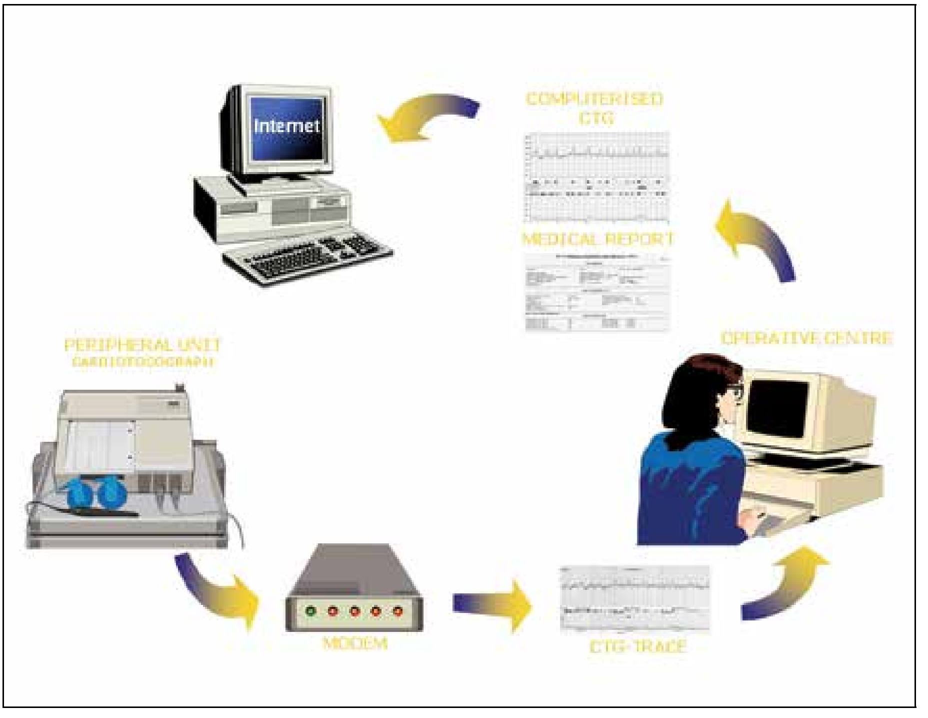

Fig. 2. The first updating of the TOCOMAT system (2005). The medical report is transmitted by e-mail to the remote unit.

Fig. 3. The TOCOMAT system in Europe.

Peripheral units are equipped with a traditional cardiotocograph able to transmit via modem both fetal heart rate traces and data about patients to the Operation Centre. Transmission takes 40-60 seconds.

Fig. 4. The cardiotocograph used at the remote units.

At the Operation Centre, data are received, displayed and stored in a system called OB TraceVue (Philips Medical Systems) and then analysed by the 2CTG system, a software which provides the computerized analysis of the traces. Within few minutes, the computerized trace, together with the analysis and medical reports, is sent back to the peripheral unit by fax or by e-mail. Until December 2009, 3194 patients have been monitored with the TOCOMAT system, and about 10000 traces have been recorded and analysed. Admissions were efficiently planned, as a consequence of a continuous interaction between peripheral units and the Operation Centre.

Fig. 5. The University Operation Centre.

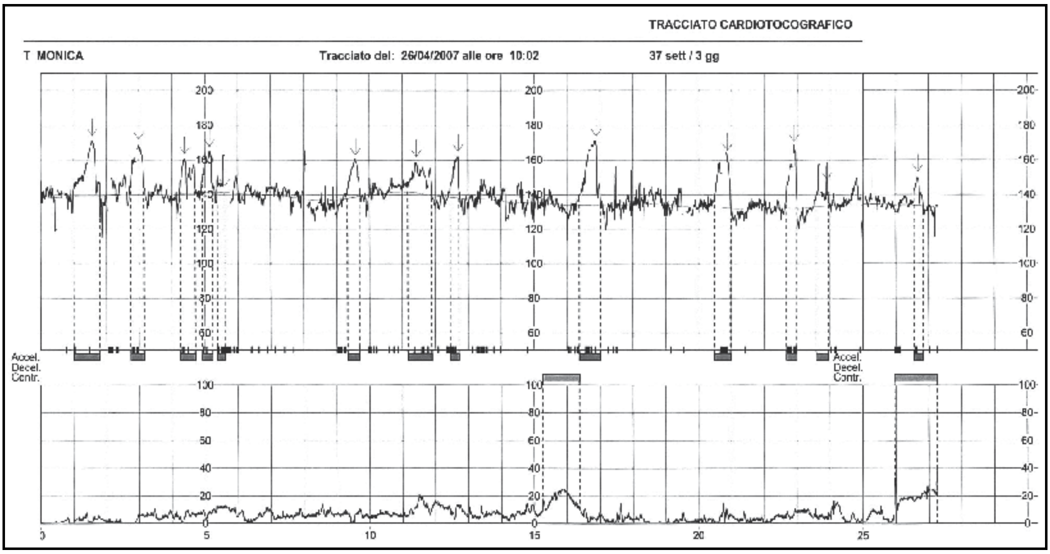

Fig. 6. A cardiotocographic trace elaborated by the 2CTG system at the Operation Centre.

TRACCIATO CARDIOTOCOGRAFICO

T MONICA
Num. registrazione: 9312
Cognome coniugata:
Indirizzo:
Ultima mestruazione: 07/08/2006
Numero gravidanza: 1

Eseguito il: 26/04/2007 alle: 10:02
Data di nascita: 10/11/1977
Tel:
Gestazione: 37 set / 3 gg
Parita:

Durata: 27 minuti
Codice paziente: 020420071016
Correzione ecografica:

Analisi automatica del CTG

	Totali	/Ora
FCF basale Media (FCFB bpm)	136.50	
Rapporto grandi / piccole accelerazioni	---	
Numero decelerazioni > 20 bpm per 30 sec o > 10 bpm per 60 sec	0.00	---
Numero movimenti (marker)	0.00	---
Numero grandi accelerazioni > 15 bpm per 15 sec	13.00	---
Numero piccole accelerazioni > 10 bpm e < 15 bpm per 15 sec	0.00	---
Numero contrazioni	2.00	---

Analisi automatica parametri Frequenza Cardiaca Fetale (FCF)

	Media	Mediana	Interquantile 25%	Interquantile 75%
FCF basale (FCFB bpm)	136.50	136.51	133.77	139.51
Variabilità breve periodo (STV msec)	7.26	6.13	5.67	9.04
Variabilità lungo periodo (LTI msec)	23.82	25.73	22.78	26.63
Ampiezza della variabilità (Delta msec)	45.22	41.00	35.70	55.87
Interval index (II)	0.79	0.77	0.66	0.87
Entropia approssimata (ApEn)	1.45	1.33	1.29	1.64
Contributo spettrale bassa frequenza (LF)	76.74	78.92	68.05	83.61
Contributo spettrale media frequenza (MF)	13.21	11.60	9.59	18.31
Contributo spettrale alta frequenza (HF)	10.05	9.48	6.80	13.64
LF/(HF+MF)	2.26	1.85	0.00	3.94

Qualità del segnale CTG: 5 Percentuale tracciato analizzato: 54% Operatore: ID cardiotocografo:
Note: DH 3702 EPISODI DI SINCOPE RICORRENTE
Campo utente 1: Campo utente 2:

Fig. 7. The report of the computerized analysis of the cardiotocographic trace.

5. Some technical and scientific results obtained with the TOCOMAT system

5.1 Agreement in cardiotocogram interpretation between the 2CTG computerized system and experienced and inexperienced observers involved in the TOCOMAT network

As previously indicated, computerized cardiotocography could overcome some of the limits of the conventional visual reading of cardiotocographic traces. It is based on predefined criteria, and therefore provides a reproducible and objective reading and allows repeatability of the results obtained in different centres. In a study performed (Di Lieto et al., 2003), as a part of the research activities related to the TOCOMAT network, we evaluated the agreement in the interpretation of traces between the 2CTG computerised system and experienced and inexperienced observers involved in the Telecardiotocography project. 150 antepartum traces were randomly chosen from the 457 recorded during the first working year of the TOCOMAT system. The traces were analysed to assess the statistical agreement between the observers and the computer about the interpretation of some parameters, detectable by both visual and computerized analysis. The expert were two operators of the Operation Centre; the midwives working at the remote units were included in the study as inexperienced observers. We found good agreement among the observers and between the observers and the computer for some parameters (fetal heart rate baseline, assessment of accelerations) whose evaluation seems to be not more accurate of the computerised analysis. On the contrary, we found lack of agreement among the observers and between the observers and the computer in the evaluation of the fetal heart rate variability, probably because the computerised analysis gives exact values, overcoming the interobserver poor reproducibility. The disagreement between experienced and inexperienced observers could also be influenced by the different degree of professional experience. Finally, the experience of the observers resulted crucial in the evaluation and definition of fetal heart rate decelerations. In conclusion, we demonstrated that the use of a computerised system provides exact values for most cardiotocographic parameters; the experts of the Operation Centre, however, should rely both on clinical features and on the computerized interpretation to make decision about the management. Therefore, the use of a computerized system for the analysis of cardiotocographic traces obtains a decrease in the intra- and interobserver variability also in our prenatal Telemedicine system.

5.2 Level of satisfaction of operators and patients

After the first four years of experience with the TOCOMAT system, we evaluated the acquisition of specific skills and the satisfaction of the operators working at the remote units (one doctor at each unit) (Di Lieto et al., 2006). We asked them to answer two questionnaires. The first one, submitted twice a year, was a test about the interpretation of a cardiotocographic trace. The second one, submitted once a year, concerned the job satisfaction of the operators.

A similar questionnaire was also mailed to the monitored patients after delivery, to test their compliance and satisfaction. At the beginning, the operators were afraid of losing their professional independence because of their involvement in the project. They also doubted that the trace displayed at the Operation Centre after transmission would be identical to the trace recorded at the peripheral unit. However, their answers showed that they gradually overcame their scepticism during the course of the project. From the beginning of the project, they had positive opinions about the usefulness of computerized cardiotocography

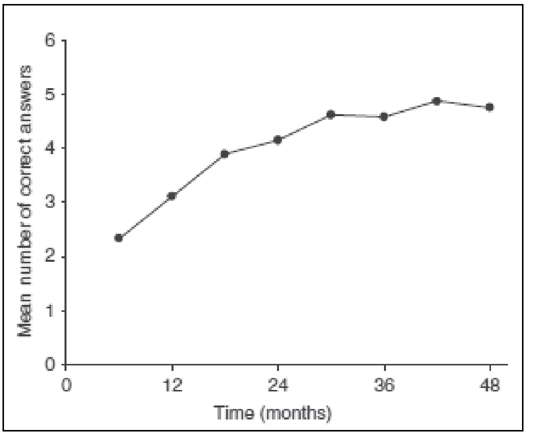

Fig. 8. Mean score of the questionnaire evaluating the acquisition of specific skills.

Question	1st year (n=8)	2nd year (n=8)	3rd year (n=8)	4th year (n=9)
1 Do you think the organization of a telecardiotocography network is useful to improve the management of pregnant women at risk?	50	63	75	89
2 Do you think the computerized interpretation of the traces is really useful to support your clinical decision?	63	63	88	100
3 Do you think you could lose your own professional independence because of your involvement in the telecardiotocography project?	75	63	25	11
4 Do you think the trace displayed at the operations centre is effectively identical to that recorded at the peripheral unit?	25	75	100	100
5 Do you think the interaction with the experts of the operations centre is useful as an experience of continuous distance training?	13	38	63	78

The percentage answering 'yes' is shown.

Fig. 9. Results of the operators' questionnaire.

Question	Percentage of 'yes'
1 Did you regularly receive fetal monitoring at the remote unit involved in the telecardiotocography project?	89
2 Was the transfer to the remote unit stressful for you or your family?	7
3 Did you feel reassured by the fact that the trace was also interpreted by the experts and the computerized systems of the university operations centre?	83
4 Did you wait too long for the results of the computerized analysis performed at the operations centre?	18
5 Did your trust in your own doctor diminish as a consequence of your participation in the telecardiotocography project?	11

Fig. 10. Results of the patients' questionnaire (n = 1098).

in the management of high-risk pregnancies. Finally, they expressed an increasing appreciation of the project as a method of continuous education. As regards the patients, the answers to the questionnaires showed a moderate level of satisfaction. They appreciated the organization of the Telecardiotocography system and felt reassured by the interaction between their own consultant doctors, the operators working at peripheral units and the Operation Centre.

5.3 Efficiency of the TOCOMAT system and cost study

Reviewing the first years of experience with telemonitoring of patients with high-risk pregnancies using the TOCOMAT system, we demonstrated as a high number of patients at high risk underwent computerized cardiotocographic monitoring in their own environment and were hospitalized only when necessary (Ippolito et al., 2003). Admissions were efficiently planned, as a consequence of a continuous interaction between peripheral units and the Operation Centre. The neonatal outcome overall was good. An increase number of preterm births and of caesarean sections are frequently cited as collateral effects associated with the widespread adoption of cardiotocographic recording. However, in spite of the substantial number of cases, mainly high risk patients, we found a caesarean rate of 49%, in comparison to the rate observed in Campania which is 61%. Telecardiotocography allowed the decentralization of prenatal surveillance, with a gradual decentralization of obstetric surveillance and subsequent improvement in the quality of life for mothers and newborns.

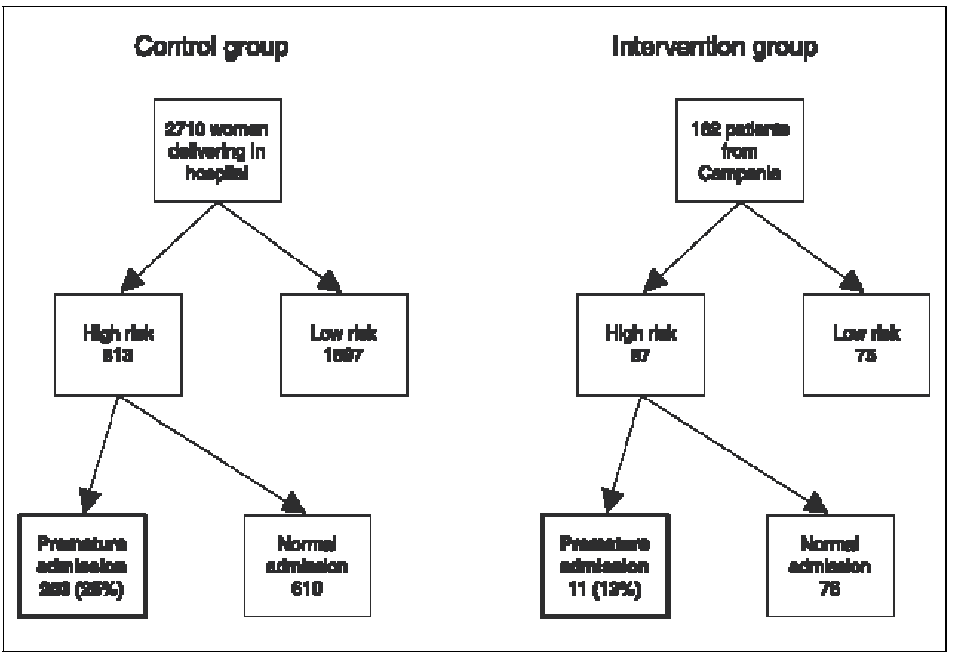

Fig. 11. Cost study design.

To make a cost study of the TOCOMAT network, we compared the hospital costs of high-risk patients monitored with the system during the year 2000 with those of control group, i.e. high-risk patients hospitalized and delivered at the University Federico II of Naples.
Costs were calculated for the equipment and the working of the Operation Centre and of five peripheral units. Hospital costs were calculated basing on the length of hospitalization and the resources used. In the control group, 25% of the women were hospitalized prematurely.

	Cost (€)
Allowance for depreciation of the equipment[a]	11,620
Equipment maintenance[b]	3,254
Cost of electricity[c]	120
Cost of medical personnel[d]	50,355
Total annual cost	*65,349*

[a]The cost of the server was €46,486 and it was amortized over four years.
[b]The annual maintenance charge was 7% of the total cost of the server.
[c]The server required 360 W.
[d]The CTG monitoring needed one physician for 1560 hours per year, at an hourly remuneration of €32.28.

Fig. 12. Annual cost of cardiotocographic recording at the Operation Centre.

	Cost (€)
Allowance for depreciation of the equipment[a]	2066
Equipment maintenance[b]	578
Cost of electricity[c]	8
Cost of telephone line	2820
Cost of modem	52
Annual cost of medical personnel[d]	50,355
Total annual cost	55,879

[a]The total cost of the peripheral unit was €8263, which was amortized over four years.
[b]The annual maintenance charge was 7% of the total cost of the peripheral unit.
[c]The peripheral unit required 25 W.

Fig. 13. Annual cost of a remote unit.

	Cost (€)
Cost of the operations centre	65,349
Cost of the five peripheral units	279,395
Cost of modem[a]	52
Total annual cost	*344,796*

[a]This modem is located at the operations centre, to receive information from the peripheral units and to send them the medical report and the trace analysed by the computerized system; this cost has to be calculated, because the cost considered in Table 1 refers to an autonomous unit, not included in a telemedicine network, so it does not need the modem.

Fig. 14. Total annual cost of the Telemedicine project.

In the case study group, a lower proportion of the women were hospitalized prematurely (13%). If we apply the same effect of monitoring to the control group, then a smaller number of patients would have been hospitalized prematurely, with a notional saving, which is purely indicative, of about € 358.00,00.
In conclusion, the organization of the TOCOMAT system for the computerized recording of fetal heart rate traces increases the efficiency of the service provided to the patients. Such a system involves a rationalization of the costs of prenatal surveillance, as there is a decrease in the probability that high-risk pregnant women will be unnecessarily hospitalized and in the length of hospitalization. Moreover, it allows peripheral units, although located far from the University Operation Centre and provided with modest resources, to use computerized analysis at very low costs.

6. Technologies

The organization of the TOCOMAT network was made possible by the availability of technologies capable of transferring data from the remote units to the Operation Centre in short time and without constraints due to the distance. Information can be stored and transmitted as either analogue or digital information. Analogue information uses a continuously varying signal. Digital information reduced everything to a series of discrete numerical values which in the computer are represented as a series of 1's and 0's. Examples of analogue technologies are broadcast radio and television, traditional telephone, gramophone records, audio cassette players and, in health's field, X-ray machines and ECGs. Examples of digital technology are computers, audio CDs, digital television, digital mobile telephone and, in health's field, CT scanning and MRI scanning. It is generally possible to convert information from analogue to digital and vice versa. A computer modem is an example: it is a device which connects a computer (digital) to the telephone network (analogue). The modem converts the digital computer signal into an analogue signal for transmission and then reverses the process at the receiving computer. Data transfer from the remote unit to the Operation Centre in the TOCOMAT network is based on this principle. Telecommunication technologies are moving towards digital signals because: audio, video, graphics and other data can be all converted into digital signals and then transmitted through the same digital network (i.e. multimedia capability); digital information can be transmitted more accurately, analogue information always degrades more the further it is sent; digital signals can be transmitted at extraordinarily fast rates; digital signals can be switched and routed more cheaply and flexibly than analogue signals. The technologies involved in Telemedicine can be divided into two main groups, those that are involved in the transmission and receiving of the information (i.e. running the network), and those which represent end-user devices able to generate and present the information (i.e. computers, televisions, telephones.). Generally, the end-user only needs to understand how using the end-device and confirm that the network support the service. Details of the networking technology are generally irrelevant. For instance, it is not necessary for an internet user to know the details about internet's functions, but he has only to know if telephone line can carry sufficient bandwidth to the Internet Service Provider.

6.1 Transmission technologies

Wires and cabling

Digital signals are sent as streams of electrical impulses. The existing telephone networks are generally built around copper wires and co-axial cables. The amount of information which can be carried (bandwidth) depends on the type of cable or wire. The major factors for district health facilities are the connection of the local exchange to the country's telecommunications backbone and the quality of the connection from the health facility to the exchange. The potential bandwidth of the connection to the exchange falls rapidly with distance. Most computer networks within a health facility (local area network or LAN) are connected with co-axial cable.

Fibreoptic cable

Fibreoptic cable is very fine set of glass fibres which carry digital signals as pulses of light. Fibreoptic cable has revolutionized telecommunications because it is able to carry enormous volumes of information. It is also not subject to electrical interference. The initial roll-out is expensive and its main use is in providing the telecommunications backbone which links all country's telephone exchanges.

Radio-based technologies

This technology uses radio waves to send information through the air. The fixed equipment required is a transmitter and a receiver. Radio frequencies are regulated in each country with frequency bands, reserved for various purposes. It may be used for radio broadcast or point-to-point telephony as in the mobile phone network. Its range varies with frequency and the power of the transmitter and there are often areas of poor reception if the radio waves are blocked by mountains or buildings. Its advantages are mobility and the independence from wires and cabling. Its disadvantages are low bandwidth and lack of reliability.

Microwave links

Microwaves can be used to send digital information in a similar way as radio. It is of a higher frequency than a radio and is totally dependent on line of sight from transmitter to receiver. It is usually used on a point-to-point basis over distances up to 50 kilometres. Quite high bandwidths can be achieved.

Satellite technology

Satellites are able to receive radio signals from earth and then transmit them back. The device is a satellite transponder. The geographic area covered by the satellite signal is known as the satellite's footprint. Most communications satellites are in geostationary orbit over 40.000 kilometres above the equator and have footprints covering very large regions. The equipment required to transmit a signal to a satellite in geostationary orbit is expensive. The equipment required to receive the signal from the satellite is much less expensive. For this reason, satellite technology is often used to broadcast signals, e.g. television or as a means of "trunking" an aggregated signal between telecommunications hubs. Satellite charges have been falling as their numbers and overall capacity have increased. There are initiatives under way to use satellites in lower orbits. For example, the Iridium network plans to use 66 satellites orbiting at 780 kilometres to provide a mobile phone and the network covering the whole world. The lower orbit means that hand held phones will be powerful enough to both transmit and receive signals.

6.2 Networks

Local Area Network (LAN)

A LAN is used to connect digital devices, such as personal computers and mainframe computers, over a localized area such as a building or campus of a hospital, university or factory. LANs are normally installed and maintained by the organization and are essentially a small private computer network. Distances covered are small, 1-2 kilometres at the most, and this allows high data transmission rates. LANs are used to share information throughout an organization. In a hospital they are often used to access a Patient Master Index, medical record tracking, appointment booking systems and clinical test results. In some workplaces, they are used to streamline and control workflows. Any organization with two or more computers will generally have them networked.

Wide Area Networks (W AN)

A wide area network is a network which covers a greater geographic area than a LAN. Generally, the dispersed sites are linked by lines leased from the telephone companies. Because of the distance involved, WANs have lower transmission rates than a LAN. Banks, for instance, run WAN s connecting their bank branches to their central databases. Credit card companies run WANs which cover the entire globe. In health's field, a typical WAN connect the LANs of all the hospitals in a city or region.

Public Switched Telephone Network (PSTN)

This is the analogue telephone network which is the largest network absolute. It can be used to carry voice and, by using a modem, data as well. It consists in a large number of carriers whose networks are interconnected. Telecommunications companies are continually developing and offering an expanding range of value-added communication services beyond the basic telephone service. For district hospitals, ISDN (integrated services digital network) services are the most relevant additional service. An ISDN connection is required for video-conferencing and also for high bandwidth access to the Internet.

Private Automatic Branch Exchange (PABX)

Many organizations have a PABX to automatically switch calls between telephone extensions in an organization, and to and from the public telephone network.

Internet

The Internet is a global network of computer networks. Individual computers or entire networks connect to the Internet via a gateway which converts the information to the required format (TCP/IP) and routes the information. The backbone of the Internet is run by the telecommunications companies. Individuals normally connect their computer using a modem and phone line via an Internet Service Provider. The Internet services include e-mail, file transfer protocol, and access to the World Wide Web.

6.3 End-user equipment

Telephone

A number of added services are possible. Multi-point audio conferencing involves three or more telephones dialing into a bridge which gets the multiple feeds in and relays the appropriate signal out. This is often useful for administrative meetings or educational sessions. Voice-based interactive information services provide prerecorded information to a caller by allowing them to navigate through menu choices by dialing individual digits.

Facsimile (Fax)

Fax is a device which electronically transmits documents and reproduces them at the other end over phone lines. It is possible to have a device which operates as both a fax and a phone as required. Because of their cheapness fax devices are widespread in most organizations.

Video-conferencing

Video-conferencing is similar to a telephone call except that there is a video picture together with audio. The equipment for video-conferencing consists of a video camera and microphone, a 'TV', and a codec at each end with an ISDN connection. Cost varies with the quality, size and sophistication of the system. There are a large range of add-ons such as a document camera, electronic white board and slide projection equipment which can be included in the package. The video and audio signal are sent to the codec (a specialized computer) which performs analogue/digital conversion and then compresses the signal. The compressed signal is sent over an ISDN line to the other destination where another codec decompresses the signal and converts it to audio and video for viewing on the TV monitor. The minimum bandwidth for video-conferencing is 128 kilobits per second. At this bandwidth a compression ratio of 600: 1 is required. The resulting picture is adequate for interpersonal communication; however, there is some degradation of picture quality and when there is a lot of movement the picture degrades further for a number of frames. A higher quality can be
achieved by using a higher bandwidth such as 256 or 384 kilobits per second. Video-conferencing using an ISDN connection is analogous to using the telephone. The other parties' number is dialed and the call is automatically connected when the call is answered. At the end of the call the parties hang up. The advantages of video-conferencing as opposed to the telephone are that people form a better rapport and communicate better when can see each other. A doctor can take a better medical history from the patient and physical signs and symptoms can be visually demonstrated or inspected. This also applies to administrative meetings.

Television

Television is not an interactive media but is suitable for passive education. It is usually delivered by terrestrial broadcasts, satellite broadcast, or videotapes. Public TV is a major influence and educator of the general public and is important in health promotion and preventive health strategies.

Radio

Like television, radio broadcasts are not interactive (except talkback radio) but can have a major role in health promotion and preventive health strategies.

Computers

Computers are capable of storing, processing and presenting a lot of information in a variety of formats. They are extremely flexible and can be programmed to do virtually any information processing task. PCs (personal computers) are commonly placed on workers' desktops and their main uses, relevant to health facilities, are word processing, spreadsheets, database services, data analysis, e- mail communication and Internet access. There are many peripheral devices which can be used with computers. Printers are the most common peripheral devices. A scanner is a device which scans and digitizes pictures. In health's field, they can be used to digitize X-rays. CD ROMs (compact disc -read only memory) are able to store over 600 megabytes of data on one disc which is sufficient to store the entire Encyclopaedia Britannica. The CD ROM reader is quite a cheap peripheral device. Sound card and speakers are required for audio output from the computer. A modem is required to connect a computer to other computers including the Internet using telephone lines.

6.4 Internet services

Internet is a system of interconnected networks which spans the globe. Most businesses, universities and other organizations, as well as many individuals, are able to access and use Internet. It has been estimated that the number of users is greater than 250 million but such estimates are always out of date owing to the phenomenal growth of use. An individual user connects via an Internet Service Provider using a computer, a modem, and an ordinary telephone line. Organizations generally have their own computers operating through a LAN and connect the LAN to the Internet via a single computer which operates as a gateway for the others. For rural and remote users the existence of a reasonably priced local Internet Service Provider may be a limiting factor as long-distance phone charges may make it financially impractical if there is no local Internet Service Provider.

E-mail (Electronic Mail)

E-mail is a system whereby computer users send electronic messages to each other over computer networks. The messages can be stored, read and printed by receiver. Internet uses an e-mail addressing system organized on a world-wide basis. E-mail messages are delivered electronically and an e-mail from one country to another will take only a matter of minutes to arrive. The cost of e-mail is encompassed as part of the Internet connection charge and so the marginal cost approaches zero. E-mail has great potential in health to allow health workers to communicate and keep in touch with each other.

The World Wide Web (WWW)

The WWW is a system organized on a world-wide basis whereby resources on remote computers are downloaded and made available to users of the WWW. Most commonly the user downloads a "page" from the remote computer. This page may contain text, graphics, animations, audio, video, and forms. The downloaded page will contain words or pictures known as hyperlinks which when clicked on with the computer mouse result in another WWW page being downloaded (from the same or a different computer). In this way, the WWW forms a "web" of interlinked pages spanning the globe. The massive amount of material linked by the WWW is a problem in itself. Much of it is advertising and promotional material and there are no controls on quality. Nevertheless it is an extremely cheap method of publishing and sharing information. There is an increasing amount of high quality health-related resources on the WWW.

7. Limits of the conventional Telemedicine and new perspectives

Currently the main applications of Telemedicine fall within the conventional Telemedicine, which consists of connecting two different locations using a wired connection. This type of connection means that the conventional Telemedicine is not suitable for mobility, flexibility and portability. These three aspects of conventional Telemedicine encourage the use of wireless connections. When the Telemedicine equipment become mobile, flexible and portable, the chances of delivering a health consultation increase and are especially useful in case of emergencies. In all cases of emergency, disaster areas and in places where the ratio between patients and doctors is very high, the use and benefit of flexible and mobile

equipment is substantial. Conventional Telemedicine currently uses PSTN (Public Switched Telephone Network, analogical) and ISDN (Integrated Service Digital Network, digital) connections to transmit data and allow the acquisition and remote transmission of data in real time. Therefore, if the patient or the doctor does not have available the proper equipment, it remains the problem of displacement and cost of this. So, despite the impressive performance of conventional Telemedicine, there is still much work to do to make Telemedicine available for a larger number of users.
The main problem with conventional Telemedicine is its reliance on "wired" connections. These connections depend on the big telecommunications companies and are therefore extremely expensive. In addition, they exclude the mobility or portability of Telemedicine equipments, precluding the use of Telemedicine service based on the location of the patient and, therefore, limiting their use to health care institutions that already have such systems. Wireless Telemedicine is a form of Telemedicine that can be supplied through a wireless network. It involves the use of wireless telecommunication technologies connected to the Internet, in order to allow that teleconsultation happen in any geographical region covered by a wireless network. In this way, some critical problems of conventional Telemedicine, like immobility, lack of flexibility and portability, can be overcome. Another advantage of wireless Telemedicine systems is the lower cost compared to a conventional's one, since a wired connection between the Telemedicine system and the Internet is not required. A further potential of wireless Telemedicine systems is represented by the different types of equipment. The software and hardware for wireless systems are clearly more accessible, especially for facilities with fewer economic resources. In fact, most kits require a simple

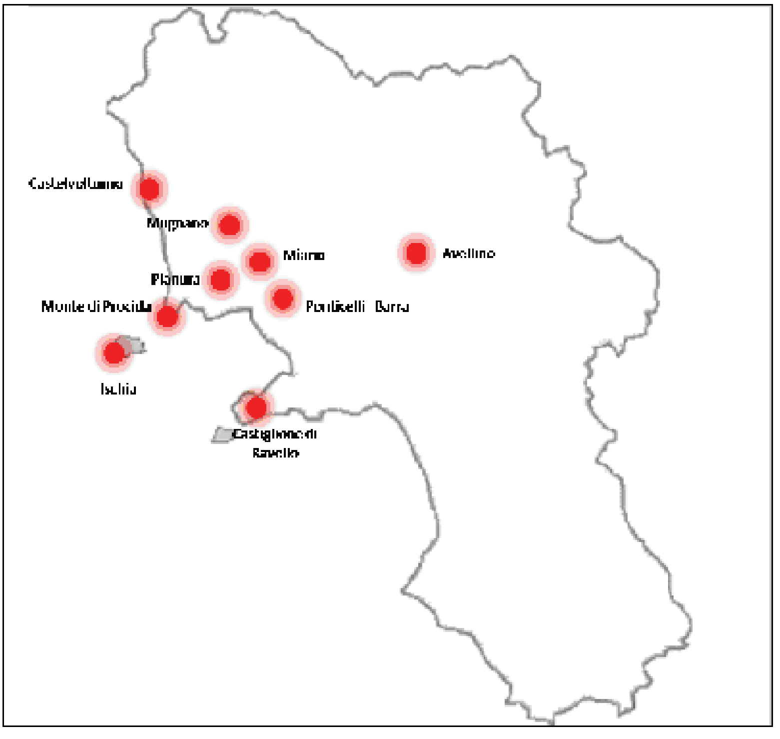

Fig. 15. Remote units of the new TOCOMAT network in Campania.

wireless connection, a laptop or tablet computer, a digital camera, some simple devices and sometimes a camera and a microphone.

8. The new TOCOMAT system

The availability of new technologies for the organization of wireless Telemedicine networks represents the ground of the recent updating of the TOCOMAT system, in order to allow intensive cardiotocographic monitoring of fetuses at risk independently from the mother and doctor location. In this way, the remaining space limitations related to the Prenatal Telemedicine network can be overcome.

8.1 The network

The remote units

In the new network, each remote unit is equipped with a last generation, small, user-friendly cardiotocograph (Corometrics 170, General Electrics).

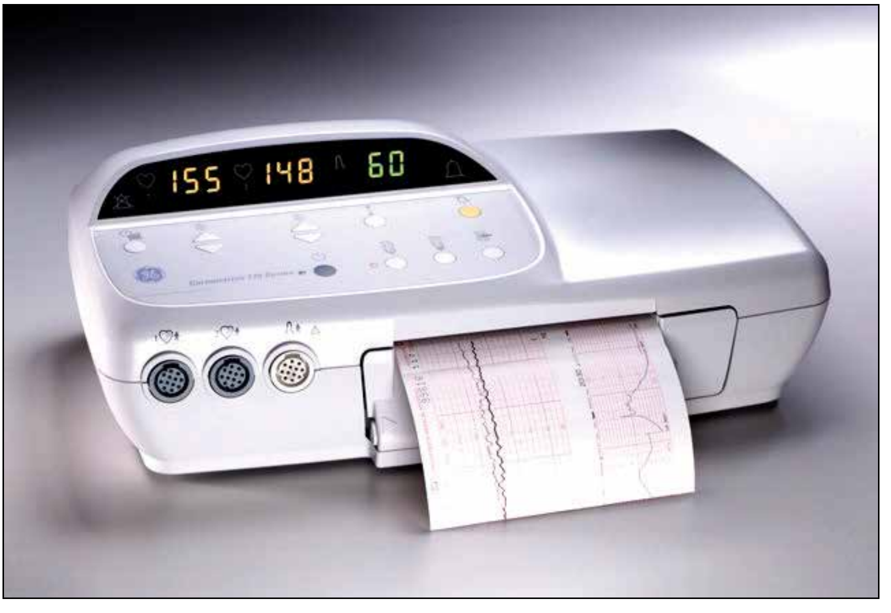

Fig. 16. The fetal monitor used at the remote units included in the new TOCOMAT network.

This equipment has a weight of about 3.6 kg and is able to transmit the cardiotocographic traces and the data related to the patient and her pregnancy to a T-Mobile MDA GPRS Smart Phone using a Bluetooth wireless port.

The Smart Phone is equipped with the software TRIUM Application (TRIUM, München, Germany), which allows receiving all signals coming from the cardiotocograph and sending them in real time to the Operation Centre. Moreover, the Smart Phone receives via e-mail the medical report and the report of the computerized analysis from the Operation Centre. This new system does not use a traditional telephone line for data transmission. So, it overcomes the considerable space limit of the old system, and could allow trace recording and transmission also of patients at home.

Fig. 17. A Smart Phone is used for the data transmission in the new TOCOMAT network.

The Operation Centre

The Operation Centre, located at the Prenatal Care Unit of the University Federico II of Naples, is equipped with the new system TRIUM CTG Online. It was born from the cooperation between the engineers of the General Electrics and the creators of the 2CTG (SEA, Monza, Italy) software for the computerized analysis of cardiotocographic recordings. The system has been expressly developed to receive, display and store cardiotocographic traces and patients' data recorded by the remote units and to send them to the 2CTG2-Trium option software for the computerized analysis.

Trium CTG Online

Trium files are located into a shared folder on the hard disk of the 2CTG workstation, whose path will be available to the 2CTG software user. The database structure of the 2CTG uses an external identification field to univocally distinguish between different patients coming from other software devices. In order to allow that exams concerning the same patient can be stored together and to avoid data redundancy, the Trium software generates and exports a unique key for each patient. When loading a new exam, the 2CTG reads this ID and searches for a corresponding instance in the current database. If the patient already exists in the database, then the new exam will be imported and associated to that patient.
Data concerning the cardiotocographic exam are stored in the Trium analyze file, composed by a series of formatted lines corresponding to each acquired sample. In each line, the 2CTG extracts the values corresponding to: time in seconds of the sample; fetal heart rate (FHR); tocodynamometry; fetal movement profile (FMP); signal quality (SQ). FHR is expressed as a floating point number corresponding to the value in beats per minute (bpm) in the range [0-300] bpm with resolution of 0.25 bpm. In the same way, the tocodynamometry is represented as the real toco value in the range [0-127] with a resolution of 0.5. FMP is a

single character which is coded as following: 0 = no movement registered, 1 = movement registered. Only the first ASCII character composing the SQ string is interpreted, following the rule: SQ = 2 means good quality (green in the 2CTG representation); SQ in (0, 1) means insufficient quality (red in the 2CTG representation). In order to store and analyze recording in its common internal representation, the 2CTG requires that tracings are sampled at a frequency of 2 Hz, that corresponds to a time lag between two contiguous samples of 0.5 seconds. The data file provided by Trium has a sampling frequency of 4 Hz. Therefore 2CTG decimates the time series coming from the Trium system during the import procedure.

2CTG Trium option

This software was born from an update on the 2CTG version 2, in order to allow the computerized analysis of the traces recorded at the remote units of the TOCOMAT network and received by the Trium CTG Online. The software computes a set of standard parameters related to the morphology of the signal (baseline, large and small accelerations, decelerations and contractions) and to the time domain characteristics of the FHR (FHR mean over a minute, FHR standard deviation, Delta FHR, Short term variability (STV), Long term irregularity (LTI), Interval Index (II). Moreover, it is able to compute frequency domain indices and regularity /non linear parameters. In particular, among the regularity and nonlinear parameters, the Approximate Entropy (ApEn) and the Spectral Analysis are included in the standard clinical version. The time and frequency domain indices can be evaluated only with the computerized analysis of the traces and are more precisely related to the fetal oxygenation status.

Medical report

Within few minutes, the trace displayed by the computerized system, the medical report and the report of the computerized analysis are sent back to the remote unit via e-mail.

Fig. 18. Actual organization of the updated TOCOMAT network for Telecardiotocography.

8.2 First results with the new system

Starting the activity of the new TOCOMAT system, we equipped six of the remote units included in the network with last generation monitors and Smart Phones. One of these units has been used for home monitoring. During the first six months of activity with the updated version of the TOCOMAT system, 112 patients (age 26±6 [SD] years, parity 0.63±1.2 [SD]) with pregnancies at high risk received cardiotocographic monitoring. 25 of these patients have been monitored at home. The most common reason for cardiotocographic monitoring was preterm labour. In total, we recorded 185 traces. 8 of the 185 recorded traces (4.3%) were repeated because of technical problems or inadequacy. Excluding them, we analyzed 177 traces of good quality. The personnel involved in the activity of the remote units was the same employed in the previous system. It just received a short training to use the new equipment. The home monitoring unit employed a midwife who performed the cardiotocographic recording at patients' home. The updating of the system did not require any change in the activity of the Operation Centre, because the way of display, analyze and store the traces was the same as the previous version.

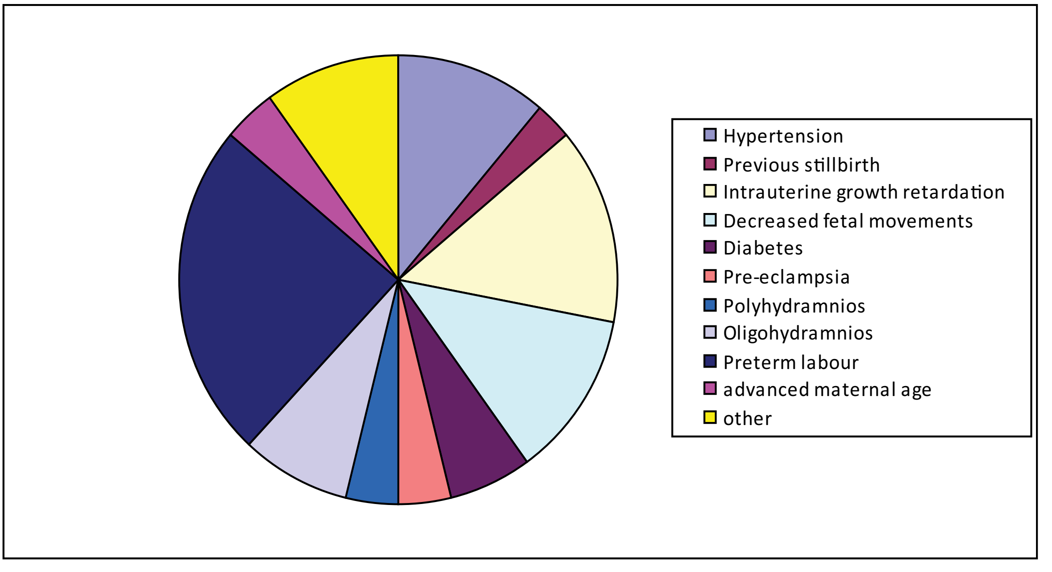

Fig. 19. Reasons for cardiotocographic monitoring with the new TOCOMAT network.

The new organization of the TOCOMAT system, with the introduction of the Bluetooth and the GPRS technology, adds an important added value to cardiotocographic monitoring at distance. As a matter of fact, it becomes independent from any space limit and allows to record the traces and perform the computerized analysis everywhere, including the patients' home. During the year 2009, we recorded 1231 traces from 640 patients using the old TOCOMAT system. During the first year of activity with the new system, we expect to monitor at least 250 patients using six remote units. Moreover, we expect to use the remote units mainly for remote home monitoring of patients at high risk. This system could improve the quality of life of pregnant women at high risk and allow the development of a wide network able to extend computerized telecardiotocography to geographic area lacking of this kind of service.

9. Tele-Ultrasonography

Tele-Ultrasonography is an application of Telemedicine to ultrasound scan. Several systems of Tele-Ultrasonography has been developed and described all over the world. Current ultrasound technologies provide high resolution images and are relatively reliable. Therefore, they are becoming important in daily medicine from routine examinations to emergency situations. However, the main drawback is that ultrasound scanning requires a high skilled operator for both probe positioning on the patient's skin and for image interpretation. Furthermore, an examination requires good hand to eye coordination in order to integrate over time and space the information made up on the patient and the acquired 2D ultrasound image. Tele-Ultrasonography applications can rely on three types of scenarios (Vieyres et al., 2003). In the first scenario, ultrasound image data are captured, stored and forwarded for further expert advice. In this case, the examination is performed by a clinical expert standing next to the patient; ultrasound data are acquired and sent to data base station and processed to reconstruct a 3D representation of anatomical regions of interest. In the second scenario, ultrasound data are transmitted in almost real time between the capture site and the expert site via a videoconference link. This mode requires a high bandwidth, at list three ISDN lines, through which the distant operator performed the ultrasound scan under visual control of the expert. These two scenarios can be classified as telemedical protocols during which only local physician can interact physically on the real ultrasound probe positioning and, therefore, on the quality of the acquired ultrasound images. In the third scenario, the examination is remotely controlled partly or fully by the expert. The main advantage of this scenario is that it does not need the presence of skilled expert on the patient site. One of the first Tele-Ultrasonography project, called TERESA, was born from space research, to propose a solution to bring astronauts and remotely located patients on ground quality ultrasound examinations despite the lack of a specialist. The project has been based on the concept of a tele-operated probe holder system integrated in a tele-ultrasonograpy chain. The chain was composed of an expert station, a patient station and a communication link. The expert station is where the specialist controls the remote probe holder system using a fictive probe and analyses in real time the image sent from the patient site. The patient station is from where a tele-operate robot is set on the chosen anatomical patient area; a general application ultrasound probe is held by the robotic system and connected to a standard ultrasound device. The communication link allows to transfer data and ultrasound images from one site to another using ISDN lines. The results of the TERESA project have been extended to a project on mobile Tele-Ultrasonography called OTELO, whose improvements focused on: the robotic design to better satisfy the user need; the communication link to bring medical ultrasound examination to anyone anywhere, using ISDN communication links but also fixed and mobile satellite link, or 3G mobile; the image quality, by developing specific compression techniques; the graphic, using interface and the input device at the expert centre to bring the best control system of the remote device and also to offer the best rendering on the distant environment including the interaction between the robot and the patient (Courreges et al., 2005). In the field of Prenatal Medicine, obstetric ultrasound is now an indispensable tool for the assessment of fetal anomalies and wellbeing (Chan, 2007). When a fetal anomaly is suspected, accurate diagnosis is essential before management options can be discussed with the parents. The families require accurate, unequivocal information and need high standard of compassionate, professional care during these times of crisis. Referral to tertiary unit with a multidisciplinary team of specialists, such as maternal fetal medicine subspecialists, neonatologists, pediatric cardiologists, neonatal surgeons, geneticists and genetic counselors, is usually indicated. Tertiary fetal diagnostic centers are scarce, and most are situated in capital cities. Telemedicine provides a means of bridging the healthcare gap between the country and the city, as well as improving access to medical education and enhancing the quality of care. In view of the sensitivities in dealing with possible anomalies

in the fetus, and the significance of obtaining all information about a fetus during the ultrasound examination, it is highly recommended that real-time video transmission be used for tele-ultrasonography consultations. The clinician can direct the sonographers at the remote site to obtain all the information needed via a video-conferencing link. The specialist can interpret the findings and then assist in the counseling women and families on subsequent management. One barrier for Telemedicine is that the operational costs are often substantial if high bandwidths are required. The transmission of medical images involves high volumes of data. In general, the transmission of still images does not pose major problems as a slight delay in trasnsmission is usually acceptable. The transmission of real-time moving ultrasound images, however, represents a technical challenge. The high cost of the transmission, in these cases, may inhibit the introduction of such services to remote areas, which are, actually, those most in need. Under the above considerations, the use of portable ultrasound machines for remote consultation has been investigated. This can enable ultrasound consultation to be carried out at really remote sites, where dial-up access to the Internet may suffice. Another ultrasound technique, three-dimensional imaging, is especially suited as a Telemedicine application, as the whole volume of ultrasound data can be acquired in a single sweep and transmitted online for subsequent interpretation. The remote expert can then cut and review any plane of data as required. The availability of technologies able to allow the distance transmission of such data could really improve the potentiality of Telemedicine. M-Health is an emerging concept. It is defined as "mobile computing, medical sensor, and communications technologies for healthcare" and represents the evolution of e-health systems from traditional desktop "Telemedicine" platforms to wireless and mobile configurations. Current and emerging developments in wireless communications integrated with developments in pervasive and wearable technologies will have a radical impact on future healthcare delivery systems. One of the new areas of advanced mobile healthcare applications that has not been explored and investigated in detail is the wireless tele-ultrasonography system.
All these considerations formed the basis for a further upgrading of the TOCOMAT system, aimed to carry out remote tele-ultrasonography consultations.

10. Tele-Ultrasonography in the TOCOMAT system

Historically, images and clinical data management has been thought as a tool for radiologists and it is based on a system consisting of a PACS. PACS means Picture Archiving and Communication System and consists of a hardware and software for archiving, transmitting and showing diagnostic digital images. A PACS system usually consists of archive part, used to manage data and images, and a visualization part, which presents diagnostic image on monitors at very high resolution, where it's possible, to make diagnoses. Recently, with the evolution of networking technology, more and more PACS systems are moving to web-based architecture, giving a simple access to images via the use of Internet browsers, without installation of any application. Obviously, the network technology draws the line at the quantity of data that can be transmitted between different sites due to the limit in bandwidth. The fetal Tele-Ultrasonography system developed at the University Federico II of Naples, as a part of the TOCOMAT networks, is based on the GE ViewPoint system. It is configured as a Mini-PACS system, able to manage ultrasound images, needed in obstetrical and gynecological patient management for maternity department. Technical limits that can be faced on using a complete PACS system are not present here, because the mean size of data files, containing ultrasound images, is very low and absolutely smaller than radiological images for which PACS systems are created. Plus, GE ViewPoint gives to the physician a complete reporting solution in order to create a full specific case history of the patients, independently by the site where the patients have been examined (main hospital, remote hospital, patient's home, patient's bed, etc.). The Tele-Ultrasonography application of the TOCOMAT system consists of two workstations able to share ultrasound clinical data and images via Internet to the hospital network using a secure connection via VPN.We can configure two different modalities to connect the scanners to the hospital:

- The interface between ultrasound devices and the archiving system can be performed in a transparent way to the operator, which should only activate the Internet connection and the VPN access to the hospital network using a remote connectivity device; this device will be able to send images directly to the remote server (Solution 1)
- Using a connectivity device which can directly connect to internet and access to the VPN i.e. a PC (Solution 2)

In the solution 2, the connection between PC (a laptop) and the ultrasound scanner can be physical or wireless; the PC will have to be connected to the hospital network via VPN and must share this connection with the scanner. This configuration will give the operator a reviewing workstation (installed or visible via the laptop which is sending the images) which will let him check the correct archiving and it gives the possibility to make reports and comments.

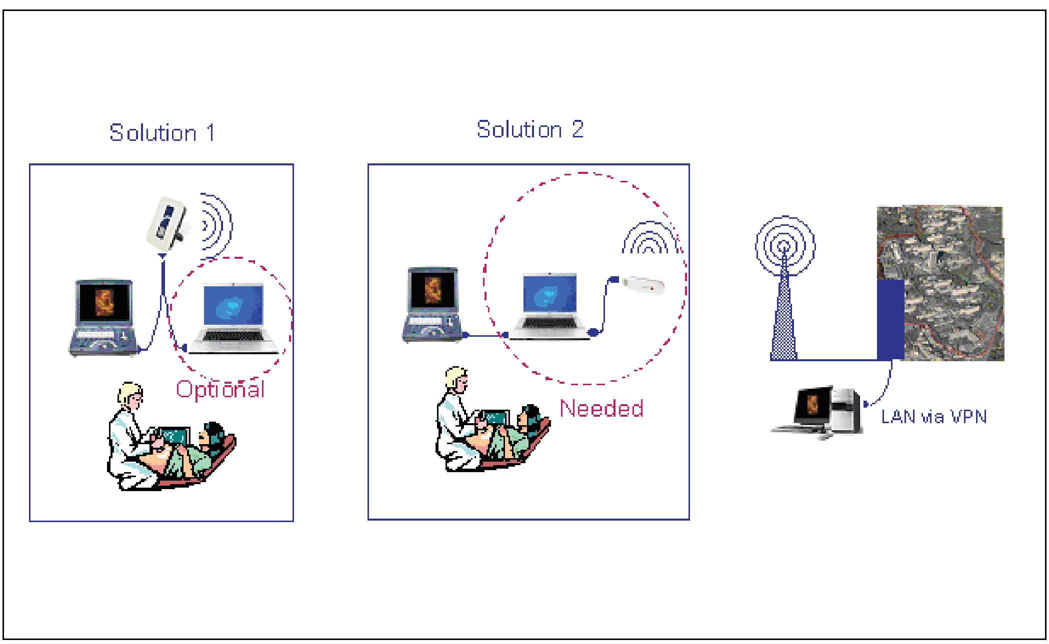

Fig. 20. Two different solutions to connect the ultrasound scanners to the hospital.

Now in the TOCOMAT project we adopted the solution 2, but soon the solution 1 will be supported in terms of feasibility and reliability. Here the workflow is shown:

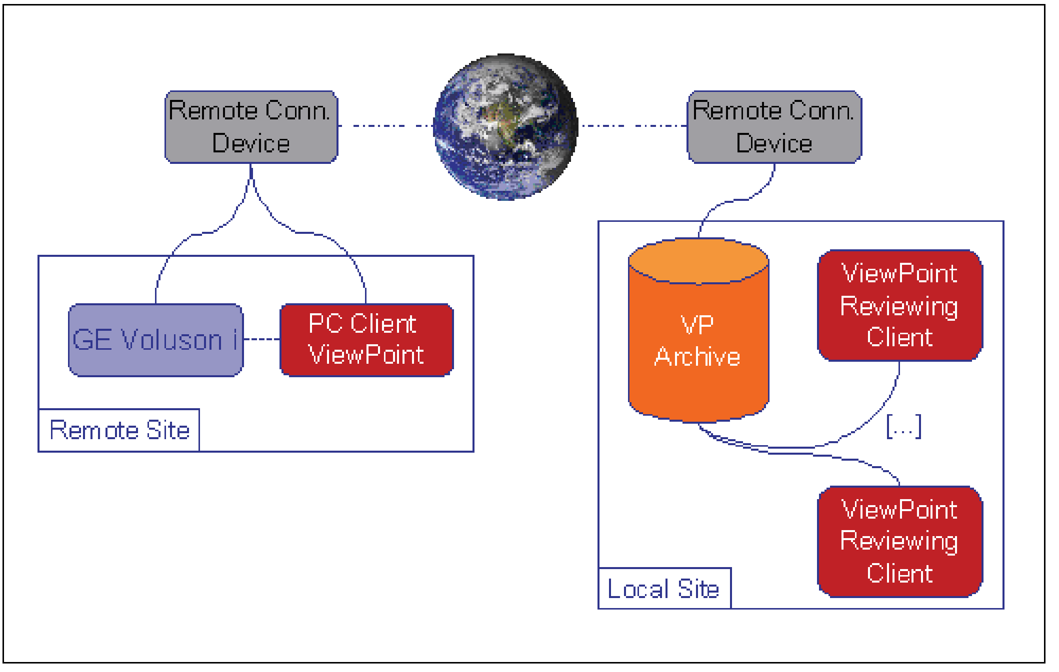

Fig. 21. The workflow of the new TOCOMAT network for Tele-Ultrasonography.

Wireless networking is clearly presented as the milestone of this project. It has been implemented via GPRS / UMTS / Satellite and connects the two main blocks: local site (Main Hospital) and remote site (Remote Hospital, Patient's home, etc.). More than one remote site could be implemented, as far as more than one local site. This gives the operators the possibility to have simultaneous access to the same data, in order to give second opinions and suggestions to operators on site. The ultrasound scanner included into the network is a portable last-generation scanner (GE Voluson-i) able to transmit the scans to the Operation Centre through a T-Mobile MDA GPRS Smart Phone using a Bluetooth wireless port. The availability of a portable scanner allows to perform the examination independently from the location of the remote unit.

Fig. 22. Organization of the new TOCOMAT network for Tele-Ultrasonography.

10.1 Preliminary results with the TOCOMAT system for Tele-Ultrasonography

During the first six month of activity with the updated version of the TOCOMAT system (January-June 2010), we recruited 135 patients referred to five of the nine remote units included into the network in Campania. The examinations have been performed by an operator located at the remote unit and then the images have been transmitted to the Operation Centre and evaluated by two expert specialists. The major indications for referral were: detailed assessment for high-risk patients (25%); isolated fetal anomalies (24%); evaluation of markers for anomalies (20%); assessment of growth restriction or fetal wellbeing in the third trimester (21%); complex fetal problems such as twin complications or multiple fetal anomalies (10%).

Fig. 23. A 3D fetal scan obtained and transmitted with the TOCOMAT network.

After the scanning at the remote unit, 22% of the patients were referred to the Operation Centre of the TOCOMAT system, in order to be submitted to deeper examinations needed to confirm the diagnosis. This means that 78% of the patients avoided to move from their living place to perform ultrasound examination. Overall, the consultation resulted in some modifications of the clinical diagnosis in 41% of the cases. 72% of the patients have been delivered. All major anomalies and diagnoses have been confirmed. These preliminary results show that fetal Tele-ultrasonography is technically feasible and welcomed by the clinicians and patients involved. It contributes to diagnosis and management and seems to be an effective strategy for bridging the healthcare gap between periphery and centre.

11. Legal and ethical aspects of Telemedicine

The development and use of new technology or new applications of existing technology have legal and ethical implications that arise subsequent from the of such technology. Often, these legal and ethical implications themselves are not new but their context may be new or changed. Such may be the case in Telemedicine, in which the use of technology to provide and support healthcare when distance separate the participants alters the context in which healthcare services are provided (Blair et al., 1998). The main legal issues raised by Telemedicine are licensing, medical malpractice and standard of care. Licensing is one of the most confounding issues, because it depends on the laws of each region and state, particularly when a cross-state Telemedicine network is organized. A national Telemedicine licensing scheme would be desirable. Medical malpractice refers to professional misconduct that includes an unreasonable lack of skill or failure to execute professional or fiduciary duties that are owed to a patient. Such misconduct could include, for example, negligence in providing or failing to provide treatment, failure to obtain a patient's informed consent to treatment, or improper disclosure of confidential or private medical information. Two of the most vexing questions concerning malpractice in Telemedicine are exposure to malpractice liability, when Telemedicine practice transcend jurisdictional lines, and whether a Telemedicine encounter suffices to establish the requisite "professional-patient" relationship on which any finding of liability must rest (Herscha, 1996). To compel a health professional to answer in court for alleged malpractice, a court must have personal jurisdiction over the health professional. Such jurisdiction may be difficult to establish based on a Telemedicine encounter in which the consulting or treating health professional was physically located in one state and the patient in another at the time of the encounter. Clearly, those physicians who have frequent Telemedicine contacts in other states should expect to be subject to those states' jurisdiction in malpractice cases. Exposure to liability also depends on whether a Telemedicine encounter is sufficient to establish a professional relationship between the professional being sued for negligence and the patient claiming damages. The existence of a professional-patient relationship establishes the professional's duty to exercise reasonable care in treating his patient. Lack of a professional-patient relationship precludes such a duty and also liability for negligence. Such a relationship may be established by the referral of a patient to a consulting physician, a formal consultation between two or more physicians regarding a patient, or a contractual relationship between a physician and a hospital under which the physician is on-call to provide consultative or supervisory services to other physicians regarding their patients. Standard of care are essentially criteria against which a clinician's conduct pertaining to patient care is measured. Standards of care are used in medical malpractice negligence lawsuits to gauge whether a clinician charged with negligence conformed his or her conduct to the legal fiction of how a reasonable and prudent physician would act under the same or similar sets of circumstances. There is no clarity with respect of the standards of care in Telemedicine practice. This is not surprising because the widespread use of communications technology to provide or support healthcare over distances is relatively new, and there has been little opportunity for the development of standards of care. As regards the ethical issued arisen by Telemedicine, they are centered around maintaining traditional aspects of medical practice (Blair et al., 1998). The main issues are: health professional-patient relationship; confidentiality and privacy; consent to treatment. If physical separation and distance between patients and caregivers retards the development of the patients' trust in the caregiver, the traditional relationship may suffer noticeably. It is therefore important to examine ways in which patient trust can be preserved in a Telemedicine encounter. Change in the professional-patient relationship because of Telemedicine practice depends, in part, on how encounters are designed. For instance, consider a case in which a primary physician and patient in one location consult with another distant physician. Although two physician-patient relationships then exists between the patient and the presenting physician and between the patient and the consulting physician, the primary relationship typically resides between the presenting physician and the patient. As the patient's primary physician, the presenting physician may have long-term relationship with the patient, and therefore the patient would justifiably expect greater obligation within that relationship. Medical and health professionals can enhance the relationship with patients of remote sites by focusing on empathic medical practice, improving their listening skills, interpreting and using body language effectively, becoming attuned to other nonverbal communication and creating an office environment that visually enhances communication and intimacy between the patient and consultant. Respect for patient privacy and confidentiality is essential to the long-term health of the professional-patient relationship. These are also important issues in the Telemedicine setting, because they can potentially be breached in any of several ways: during the Telemedicine encounter; during transmission of information; when patient records and information regarding the encounter are stores either electronically or on paper. Ideally, the presenter should indicate to the consultant the presence of all persons who are on- or off-camera and vice-versa, and the presence of such external parties would be kept to a minimum. Certain technical safeguards, such as encryption, can be used to help ensure that data obtained without authorization are neither translatable nor linked to identifiable patients. Using passwords and key cards to access patient records may also reduce threats to confidentiality. Informed consent is one of the cornerstones of responsible medical practice and applies equally to Telemedicine practice. Patients always should be informed of and understand the risks and benefits of all treatments and agree to those treatments before those treatments are applied. Insofar as Telemedicine is one of an array of options involved in the medical encounter, informed consent to use Telemedicine during the medical encounter may be necessary. To establish a high level of informed consent for Telemedicine, the document should include certain information relevant to the patient's decision to use this type of encounter, including how Telemedicine works; who will be present during the examination; known or potential risks to privacy and confidentiality of patient information; and the consequences of refusal, including delays in treatment due to the complications of scheduling a hospital visit.

12. Telemedicine in rural areas and in the developing world: future perspectives of the TOCOMAT system

Telemedicine aims at equal access to medical expertise irrespective of the geographical location of the person in need. So, patients can get access to medical expertise that may not be available at the patients' site. In this way, Telemedicine changes conventional medical practice and enables patients to access medical service via telecommunication. Telemedicine thus establishes a new kind of relationship between smaller hospitals and larger ones, and between patients and hospitals generally. Patients and subordinate hospitals may benefit from the resources of large hospitals, via teleconsultation, telediagnosis and telemonitoring. This is particularly beneficial for patients living in rural areas, where the healthcare system is less well developed than in cities. The growing number of Telemedicine networks covering rural areas all over the world confirms the great potential of Telemedicine to help unbalanced and underdeveloped health Wootton, 2008). An example of rural Telemedicine is the Chinese one (Wang & Gu, 2009). China is the largest developing country in the world in terms of both population and area, and 70% of its people live in rural areas. There are serious disparities in medical resources between rural areas and cities. Only 20% of China's medical resources are available to the 900 million rural population. Telemedicine has a great potential to help unbalanced and underdeveloped health. Telemedicine in China began in the mid-1980s and the early Chinese Telemedicine activities were mostly based on store-and-forward technologies such as telegraph and email. Real time Telemedicine was not used initially as the telecommunication infrastructure required was no available. In recent years, Telemedicine in China has developed quickly with the rapid growth of telecommunication networks. Now, China has three major Telemedicine networks that allow people living in rural areas to enjoy low-cost Telemedicine services and have a better quality of life. Another example of rural Telemedicine is the purpose of a rural Telemedicine network in South Africa using store and forward Voice-over-IP (VoIP) (Scholl et al., 2009). The advantage of such a system is that it is accessible from devices similar to traditional telephones, and thus can be used by those that lack computer skills. VoIP services can also be developed relatively cheaply using open source software, and can be deployed without fixed infrastructure or support from providers. In this way, some barriers to introducing information telecommunication technology solutions in rural areas, such as cost, poor infrastructures and lack of computer skills among the staff, could be overcome. Also the developing world can beneficiate from the applications of Telemedicine for educational and clinical purposes (Wootton, 2008). The developing world contains some 5400 million people in 127 countries. Suppose that one in every 10 people sees a healthcare professional each year, and that in one in 100 of these interactions, the healthcare professional concerned would like to seek a second opinion. Then there would be some 5 million referrals to be dealt with each year. Since the present Telemedicine networks collectively are servicing about 5000 referrals per year, at most, this suggests that only 0.1% of the potential demand is being met. Low-cost Telemedicine in the developing world is feasible, clinically useful, sustainable and scaleable. However, Telemedicine is not yet being used on a significant scale. The right strategy to obtain a widespread diffusion of Telemedicine in the developing world appears to be to build intra-country Telemedicine networks as soon as practicable. By developing a Telemedicine network under the control of the appropriate Ministry of Health, there can be no question about perceived loss of control. That is, we need Telemedicine networks that rely largely on within-country resources. Such Telemedicine networks might need to begin with support from outside the country, but they should become independent of outside resources as quickly as possible. These are the grounds of the programmed extension of the TOCOMAT network to the rural areas of Kenya and Senegal, called TELEAFRICARE. In Kenya, basic primary care is provided at primary healthcare centres and dispensaries. They are run and managed by nurses and provide outpatient services for simple ailments. Primary care facilities are often under-staffed, under-equipped and have limited medicines. Those patients who cannot be managed by the nurse are referred to the health centres. Sub-district, district and provincial hospitals provide secondary care. Sub-district hospitals are similar to health centres with the addition of a surgery unit for caesarean sections and other procedures. District hospitals usually provide comprehensive medical and surgical services. Provincial hospitals provide specialised care including intensive care, life support and specialist consultations. Third level care is provided at the General Hospitals Moi and Kenyatta, both located in Nairobi. In Kenya, there is on average one doctor per 500 people in Nairobi, but only one per 160.000 in rural Turkana district. Nairobi has three times the national average of hospital beds, but people in the rural areas, that represent the majority of the population, are not so well provided for. Health facilities are often located in urban areas, far away from rural populations most in need, or are not accessible to large numbers of the population via public transportation. In Senegal, the organizational structure of the national healthcare system is divided in three levels: Regional Hospitals, District Health Centres, Health Posts. The District Health Centres offer some few operational facilities and have about 1 to 2 medical doctors and 15 to 20 people staff. The Health Posts have about 4 to 5 health workers, but there is no medical doctor working. Under each health post, there are numerous health points with 1 or 2 health agents and a midwife. In addition, the country has two university hospitals. Also in Senegal people living in rural areas doesn't have easy access to care facilities owing to the extreme distances and environmental conditions. For 80.5% of the households, the health post is the only accessible health facility in a average distance of 4.3 km and an average travel time of 30 minutes. The next health centre is an average distance of 23.5 km, the next hospital is more than 30 km far. After analysing all this information, we concluded for a project aimed to the improvement of the woman care as a whole, that is Prenatal Care, delivery and labour management, by using tools allowing interventions at the various levels of healthcare in Kenya and Senegal and promoting the awareness of local communities to play their key role to obtain a real change in their health conditions. First of all, basing on the evidence that the high rate of maternal and perinatal mortality, recorded in these countries, above all regards the rural areas, is especially related to a difficult access to health facilities, we imagined to improve the care using Telemedicine. The intervention of the TOCOMAT-TELEAFRICARE system on the African reality materializes not only with an implementation of the health resources immediately reachable by the rural population, but also with an improvement of the level of healthcare offered by the central hospitals connected with the telematic network.

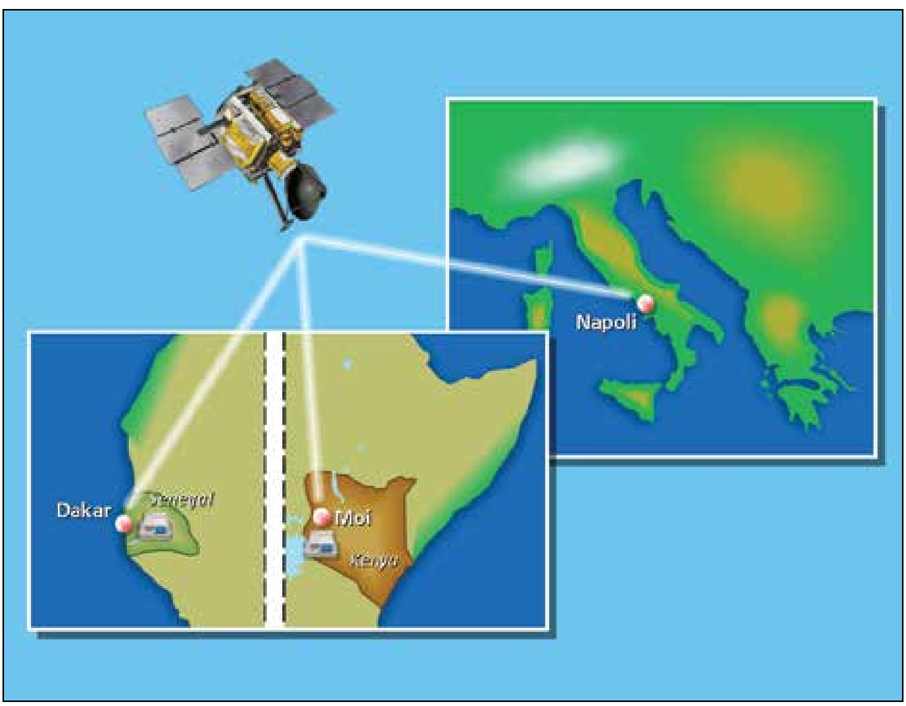

Fig. 24. The TOCOMAT network in Africa.

In this way, the project adapts to the needs and the context of the local communities and proposes an easy and feasible solution for some of the above explained critical situations. The TOCOMAT-TELEAFRICARE system could allow the wide diffusion of cardiotocography in the rural areas of Kenya and Senegal, that lack in this kind of service, and, moreover, could extend to these areas the innovation of computerized cardiotocography, for a more appropriate assessment of the real conditions of high risk fetuses. Another tool offered by the TOCOMAT-TELEAFRICARE system to reach the aim of introducing specific diagnostic innovations is represented by Tele-Ultrasonography. Women coming from the rural areas could have access to ultrasonography without moving to higher level hospitals. In this way, a wide number of patients could be submitted to this exam, with the chance to have a better management.

The TOCOMAT network is addressed not only to rural areas and peripheral health facilities, but also to the central hospitals. These will become the key points for the delivery of the Telemedicine service, because they will be the sites of the Operation Centres of the network. They will provide the organization and management of the activities connected with Telemedicine and will be the responsible for their operative application. Also in this case, Telemedicine could aid operators through teleconsulting and a continuous interaction with the European partners. African caregivers should reach self-sufficiency also through a basic and advanced training activity promoted by the European partners, not only to transfer the technological know-how, but also to share with the African partners the clinical protocols needed to improve the quality of healthcare provided in their own structures. The aim is to contribute to the diffusion of right procedures for the management of both physiological and pathological conditions before and during pregnancy, during delivery and labour and in the early neonatal care. During the last century, major advances in medical technology have led to a substantial improvement in healthcare. This has come at a cost; the healthcare technology has become complex and expensive which, in turn, has led to a very wide disparity in health resources between those who have the financial resources to benefit from the advanced medical technology and those that do not. The ultimate outcome of this situation is that the majority of the world population does not have access to advanced medical technology and advanced healthcare. The extension of the TOCOMAT-TELEAFRICARE network to some African countries is aimed at find a solution to this disparity in the field of prenatal medicine. But the recent availability of wireless technology and cloud computing could obtain a further improvement of this situation in the future (Meir & Rubinsky, 2009). The key concept is that the computational part (hardware and software) is at a central facility, now called "cloud computing" which does the data processing and provides the most advanced computational service, at any time, to an unlimited number of users, connected through telecommunication to the central processing facility. The devices at the user site have limited or no data processing facility and are used primarily to transfer the raw data to the central processing facility and to display the processed data. The remote devices become a dumb terminal for a central computational facility. This removes the cost and limitations of the computation, manipulation and interpretation of data from the vicinity of the patient and uses instead a central and effectively unlimited computational facility. In the vicinity of the patient only the component that directly interact with the patient and which acquire or use the raw data are needed. This is different from conventional Telemedicine in which the data processing is still done in the vicinity of the patient and the processes images, for example, are sent on. In the concept of cloud computing, the majority of the processing is done at the central facility that can be at a completely different geographical location than the patient. The central facility serves a large number of remote users and the telecommunication is used to transfer the raw or minimally processed data to this central processing. If applied to the TOCOMAT network, this technology could obtain a decrease in the costs and allow a more simple recording, transmission and analysis of data, thus further promoting the diffusion of Telemedicine in the developing world.

13. Conclusions

In conclusion, the TOCOMAT system, with its recent updating, could contribute to improve the quality of the healthcare given to pregnant women at high risk living far from adequately equipped health centres. It allows to perform intensive computerized cardiotocographic monitoring of fetuses at risk even at patient's home. Moreover, it allows performing distance ultrasonography, in order to avoid the referral of a too high number of patients to centres of third level. The extension of the system to Kenya and Senegal could contribute to the diffusion of a right way to manage the pregnancies at risk, without bearing high costs. The technological innovation could further simplify the organization of the TOCOMAT system. For example, the use of an ultrasound scan connected with a central computer though a cloud computing system could reduce the cost of imaging by orders of magnitude and remove the requirement of having a highly trained imaging expert at the patient site (Meir & Rubinsky, 2009).

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Part 3

Further Selected Medical Applications

8

Computer Aided Diagnosis of Glandular Tumours for Internet-Based Telemedicine

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1. Introduction

In developing countries and isolated islands, lack of medical staff is a major problem. When a person feels unwell, he or she usually attends hospital and is assessed by a clinician and given a provisional diagnosis. When the clinician suspects cancer, a pathological diagnosis is required. This requires a pathologist, but pathologists are badly off and scarce in many countries. Since pathological diagnosis represents a subjective assessment by each pathologist, several pathologists must examine the same specimen and collate the results for accurate diagnosis, and each pathological diagnosis accordingly requires a substantial amount of time. A diagnosis support system using objective and quantitative approaches would thus be extremely useful. Moreover, the use of the Internet for diagnosis is expected to alleviate the problem of access to medical professionals in developing countries and isolated islands. Glandular cancers, such as those of the stomach, colon, prostate, and breast, are common, and we have therefore focused on these cancers in developing a computer aided diagnosis system using the Internet.

In the field of medical image engineering, automatic and quantitative diagnosis systems have previously been studied by many researchers. Most such research has aimed at the development of diagnosis support systems addressing the lack of pathologists. A representative system is the pre-screening system for uterine cytodiagnosis that is currently in use. The pathologist must still perform many image processing steps to use these diagnosis systems. In research for tumour imaging, human input is still required for detection of the region of breast cancer, for identifying the glomeruli in the kidney; and so on. Although the types of tumour involved increase year by year, most research centres on tumours of the lung, colon, prostate, and ovaries, with few studies examining gastric tumours.

Well-differentiated glandular cancer and adenoma differ from each other, and the classification of these tumours has recently been discussed by pathologists. However, no adequate automatic diagnosis systems for glandular tumours are available for such studies as described above, and pathologists have been eagerly awaiting a system for glandular tumours. Morphological classification of colorectal microscopic images has been reported as a recent diagnosis support system. This method allows features of tumours to be obtained from the whole image, but has a low rate of correct classification for images with a relatively large background region. With the aim of formulating an Internet-based diagnosis system,

we first created an automatic diagnosis system for glandular cancer. In the second stage of our research, we will integrate the Internet-based diagnosis system.
In this chapter we explain our computer-aided diagnosis system for glandular tumours based on morphological features of the cytoplasm and nucleus. In this system, glandular tumours are classified into malignant tumours or adenoma, using numerical features obtained from the morphological assessments of pathologists. For numerical conversion of morphological features, manual extraction of regions of interest (ROIs) was performed, with pre-processing selection of colour components comprising image, contrast enhancement, binarisation using the Laplacian histogram and discriminant methods. In the pre-processing stage, each tumour was classified in terms of its glandular structure and nucleus. From the regions selected, many morphological and texture were identified, and using the obtained features, glandular tumours were classified by the discriminant method with the stepwise method. A small number of features were selected for diagnosis by the stepwise method. Finally, tumours were classified into various categories: non-neoplastic, gastric adenoma, and gastric cancer, using the obtained numerical features.

2. System summary

In this section we summarise the Internet-based diagnosis system, which allows doctors to obtain diagnostic results anytime, anywhere. Figure 1 shows the essential components of the system. First, we upload a glandular image to the system using the internet. After some processing, the system displays the uploaded image and the diagnosis. This upload window will be created using Perl. Recently, Java and PHP have been recognised as useful internet languages, and C language can also create diagnostic programs. Since the diagnosis system has to perform a large amount of processing, Perl cannot deliver sufficient computing speed. Figure 2 shows the algorithm used by the diagnosis system. One need only upload the lesion image, and the diagnosis system analyses the severity of the lesion. Since this algorithm is essential for this system, it may be very useful in future systems.

Fig. 1. Internet-based diagnosis system

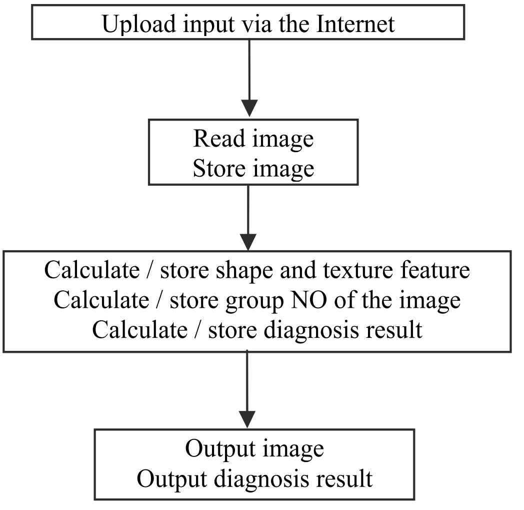


Fig. 2. Algorithm of the internet-based diagnosis system

3. Severity grading of glandular tumours

Pathologists classify glandular tumours into several categories as shown in Table 1, based on morphological features of the nucleus and cytoplasm as shown in Figure 3. Group 1 includes normal tissue and obviously benign lesions, and group 5 corresponds to frank malignancy. Group 2 to 4 are borderline cases between benign tissue and malignant tumor. Classification of group 2 to 4 is difficult, even when tissue samples are analysed by pathologists. We classify gastrointestinal glandular tumours into group 1, group 3, and group 5. As an example we show a typical case of classification of colon tumour according to morphological features of the nucleus and cytoplasm. The original images are classified into the correct category by the pathologist.

Group 1	Normal tissue and benign lesion
Group 2	Benign lesion with aberrant tissue
Group 3	Boundary case between benign and malignant tumor
Group 4	Tissue at increased risk for cancer
Group 5	Complete cancer

Table 1. Severity classification of gastric biopsy specimens

The severity of the tumour is decided by the shape of glands and the distribution of typically shaped glands. Although histological images can provide only 2D information about gland structure, pathologists need information on 3D structure. Pathologists mentally construct the 3D structure from the 2D shape and thereby determine the severity of the tumour. Figure 3 shows one examples of the relationship between 2D shape and 3D structure of glands. Many structures with a similar 2D appearance have different structures in 3D. Thus substantial experience is required for pathological diagnosis. In this research, statistical processing is used to recognise various 3D patterns.

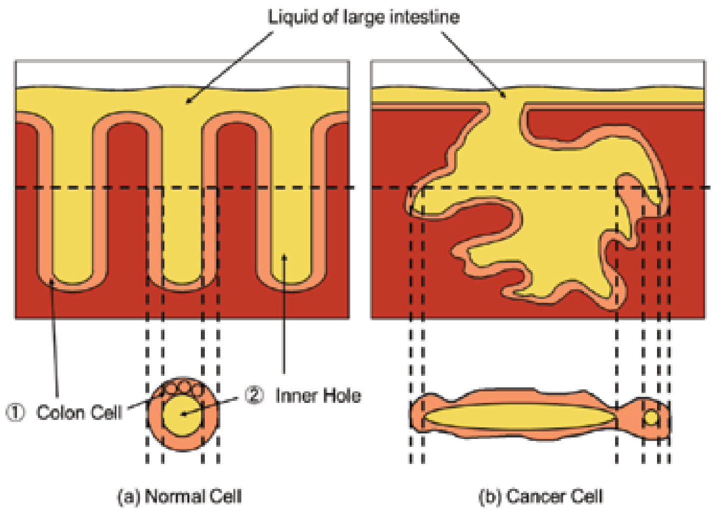


Fig. 3. Relation between 2D shape and 3D structure of glands

4. Methodology

4.1 Region extraction

In this study we used original 2240x1680 pixel images with a 24-bit bitmap file format. As shown in Figure 4, rectangular regions containing glands are manually removed from the original image, and are used as the input images. The entire gland must be visible in these images.

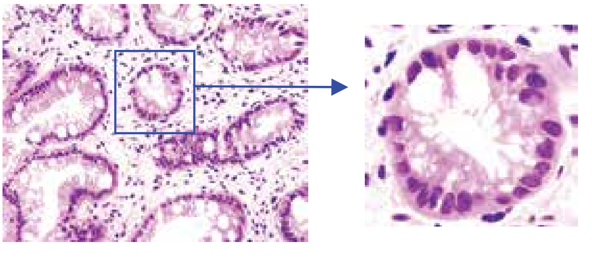


Fig. 4. Original image and extracted gland image

First of procedure in this research we precisely extracted the nuclear regions and the glandular regions for computation of morphological features. Figure 5 shows the flowchart of the region extraction method for nuclear and glandular regions. A different binarisation method was used for these two types of region extraction: strong contrast between the nucleus and cytoplasm is better for binarisation for nuclear region extraction while strong contrast between the gland and background is preferred for binarisation for gland region extraction. In this study we used the red component of the RGB image for nuclear region extraction, and the green component image for glandular region extraction. The dotted line in Figure 5 shows that the nuclear regions are extracted from the extracted gland regions. In the automatic diagnosis system the discrimination of tumour severity was performed by the features computed from the extracted nuclear and gland shapes.

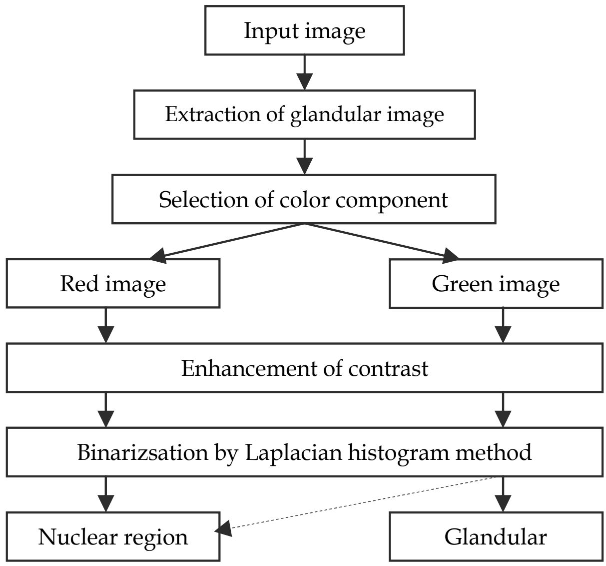


Fig. 5. Flowchart of region extraction method for nuclei and glands

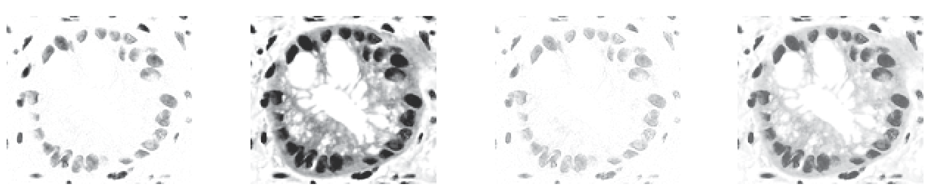
4.2 Pre-processing

4.2.1 Selection of colour components for pre-processing

Since the nuclei and glands are different colours in the images and these colours also vary slightly according to the staining protocol, it is difficult to extract the shape of nuclei and glands from colour images. We therefore converted the colour image into a greyscale image. There are various methods for doing this; one using one component in the RGB image and one converting the RGB basis into the YIQ basis. We used the second method, which is well known, using the Y component of the image in the YIQ basis. We show the conversion equation from the RGB basis to the YIQ basis below.

$$\begin{bmatrix} Y \\ I \\ Q \end{bmatrix} = \begin{bmatrix} 0.299 & 0.587 & 0.144 \\ 0.596 & -0.274 & -0.322 \\ 0.211 & -0.522 & 0.331 \end{bmatrix} \begin{bmatrix} R \\ G \\ B \end{bmatrix} \tag{1}$$

Figure 6 shows the obtained colour components of a glandular image represented in greyscale. In this instance, the R component image in the RGB basis is suitable for extraction of the nuclear region and the G component image is suitable for extraction of the glandular region. Moreover, the Y component image in the YIQ basis is suitable for computation of textural features within the glandular region.



(a) R component (b) G component (c) B component (d) Y component

Fig. 6. Colour components of glandular image

4.2.2 γ compensation

We performed γ compensation in order to optimise the results of binarisation. When the input pixel density is X and output pixel density is Y, the equation for γ compensation is shown below.

$$Y = \left(\frac{X}{255}\right)^{\frac{1}{\gamma}} \times 255 \tag{2}$$

In the above equation, γ indicates the parameter of the equation, and we use γ=5 for the nuclear region extraction and γ=3 for the glandular region extraction.

4.3 Binarisation

4.3.1 Binarisation by fixed threshold

A binarisation method is useful when we try to extract an object shape. Here we explain the fundamental approach. Binarisation converts an intensity image into a two-level black and white image, using one threshold for the whole image. In the intensity image each pixel has a value of 8 bits, which is from 0 to 255. Below is a fundamental equation of binarisation in which $f(x,y)$ indicates an intensity value of (x,y) coordinates in an image, $g(x,y)$ refers to the output value after binarisation, and a T means the threshold value.

$$g(x,y) = \begin{cases} 0 & f(x,y) \le T \\ 255 & f(x,y) > T \end{cases} \tag{3}$$

Since an object region such as a nuclear or gland region has a lower intensity than a background region, object regions have an intensity of 0 and background regions have intensity of 255 after binarisation. Therefore we can select the object region after binarisation, and easily analyse morphological features from the selected object. The selection of threshold value is important in the binarisation because the shape of the object can change according to the selected threshold. In this research we used the Laplacian histogram method and discriminant method.

4.3.1 Binarisation by the discriminant method

Here we explain binarisation with the discriminant method. In this method the optimal threshold is determined by searching for the maximal interclass variance after the intensity histogram $h(k)$ is constructed from an image and is converted into two classes.

First, an intensity value is set as k. We define the following equation as an index for goodness of binarisation, in which $\eta(k)$ is the degree of separation used in the discriminant method, $\sigma_B^2(k)$ is the interclass variance, and σ_T^2 is the whole variance.

$$\eta(k) = \frac{\sigma_B^{\,2}(k)}{\sigma_T^{\,2}} \tag{4}$$

$\sigma_B^2(k)$ and σ_T^2 are computed in the next equation.

$$\sigma_B^{\,2}(k) = \frac{\{\mu_T \cdot \omega(k) - \mu(k)\}^2}{\omega(k)\{1-\omega(k)\}} \tag{5}$$

$$\sigma_T{}^2 = \sum_{l=0}^{L-1} (l - \mu_T)^2 p(l) \tag{6}$$

When an occurrence probability is $p(l)$ using intensity l, the whole level is L (L=255 in this research), intensity histogram is $h(l)$, and the total pixel number is N, the whole average value μ_T is shown in the next equation.

$$p(l) = \frac{h(l)}{N} = \frac{h(l)}{\sum_{l=0}^{L-1} h(l)} \quad \left(p(l) \geq 0, \sum_{l=0}^{L-1} p(l) = 1 \right) \tag{7}$$

$$\mu_T = \sum_{l=0}^{L-1} l p(l) \tag{8}$$

Moreover $\omega(k)$ and $\mu(k)$ are defined by the occurrence probability $p(l)$.

$$\omega(k) = \sum_{l=0}^{L-1} p(l) = \omega(k-1) + p(k) \tag{9}$$

$$\mu(k) = \sum_{l=0}^{L-1} l p(l) = \mu(k-1) + k p(k) \tag{10}$$

Since $\sigma_T{}^2$ is constant regardless of k value, the degree of selection $\eta(k)$ between classes becomes maximal when the value of $\sigma_B{}^2(k)$ becomes maximal. $\sigma_B{}^2(k)$ is computed by changing the value of k from 0 to L-1 in series, and an optimal k value is obtained. We perform the binarisation of a greyscale image using the obtained k value. We can objectively and automatically obtain an optimal threshold in this manner.

4.3.1 Laplacian histogram method

A problem arises when determining the threshold by the discriminant method: the obtained threshold shifts a little toward the intensity of a larger area when the ratio of the object area to background area is large. However, it is hoped that the intensity histogram for the discriminant method has a ratio of object area to background area of almost 1.

The Laplacian histogram method is one solution for this problem. In this method the range of the histogram is limited to the regions adjacent to an object and background using the Laplacian value of an input image. In the images we used, the regions adjacent to an object and background have a large absolute Laplacian value of each pixel. We use the following equation for computing the Laplacian value for all pixels within an image and construct the histogram using only pixels with a Laplacian value greater than a certain threshold.

$$\begin{aligned} \nabla^2 f(x,y) &= \frac{\partial^2 f(x,y)}{\partial x^2} + \frac{\partial^2 f(x,y)}{\partial y^2} \\ &= f(x,y-1) + f(x,y+1) + f(x-1,y) + f(x+1,y) - 4f(x,y) \end{aligned} \tag{11}$$

In this study we selected only the pixels within the top 20% of all computed Laplacian values.

4.4 Post-processing

The two-level image obtained by the Laplacian histogram and discriminant method has the following noise considerations.

1. Salt-and-pepper noise in the background
2. White space in the object region

For the first type of noise a median filter is effective, and a filter operator of 3x3 is used in this study. For the second type an area combination by closing processing is effective.

In the G component image after labelling processing for the two-level image, we select the largest area as the glandular region and eliminate other regions as noise in the image. For the white space in the gland we obtain the area and leave the largest area as the glandular cavity and eliminate any other white space.

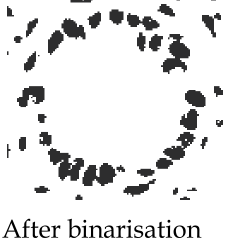
In the two-level image of the R component we select the regions within the gland as nuclear and eliminate the regions external to the gland as noise. In other words, the nuclear region is determined after extraction of the glandular region.

Figure 7 shows the result of post-processing for the G component image. Figure 7(a) shows an image after binarisation of the G component image and Figure 7(b) shows the image obtained after post-processing. Figure 8 shows the result of post-processing for the R component image. Figure 8(a) shows the image after binarisation of R component image and Figure 8(b) shows an obtained image after post-processing.

(a) After binarisation

(b) After post-processing

Fig. 7. Glandular image



(a) After binarisation

(b) After post-processing

Fig. 8. Nuclear image

The median filter outputs the median value of intensity magnitude as intensity value of reference pixel after the pixel values within the masked region are permutated according to the intensity magnitude. This filter is suitable for elimination of salt-and-pepper noise in an image. For the filtering in this study we use a filter operator (mask operator) of 3x3 pixels. As the closing processing, several shrinkage treatments are performed after several expanding processing procedures.

4.6 Morphological feature extraction
4.6.1 Features of area
The area of an object region is expressed by the number of pixels within the connected components. In this study we define the area as shown in Figure 9 and Table 2. Four types of area are computed as shown below.
1. The nuclear area: the sum of the areas of all nuclei within a gland
2. The cytoplasmic area: the area of A in Figure 9
3. The glandular cavity area: the area of B+C in Figure 9
4. The glandular area: the area of A+B+C in Figure 9

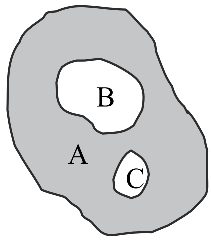


Fig. 9. Definitions of various areas

Cytoplasm	Hole	Gland
A	B+C	A+B+C

Table 2. The definitions of various areas

4.6.2 Features of length
The perimeter of an object region is expressed using the number of contour pixels obtained by contour tracing. The distance between obliquely lining pixels is multiplied by a weight of $\sqrt{2}$. Three features as shown below are computed as the features of length.
1. Perimeters of the gland and glandular cavity
2. Feret's diameter: the length of the diagonal line of the minimal rectangle surrounding a gland

4.6.3 Features of chord and axis
The five features computed as features of chord and axes are as follows.
1. The longest segment: the length of the maximal segment in the gland and the length of A in the horizontal direction as shown in Figure 10.
2. The maximal section: the length of the longest segment among segments in all directions and the length of B as shown in Figure 10.
3. The average number of chords comprising the gland in the horizontal axis and in the vertical axis
4. The average length of the vertical segment; the average length of the segment vertical to the maximal segment and the length of C as shown in Fig.10.

4.6.4 Features of equivalent shape
One feature of equivalent shape is defined as the length of the short axis in the ellipse which has the same area of the gland and half of the maximal segment. In this definition we obtain the following equation using the letters *a* and *b* in Fig.11.

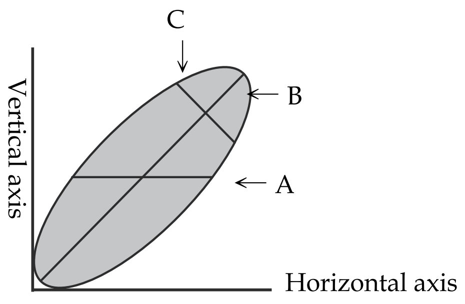


Fig. 10. Definition of chord and axis features of the object

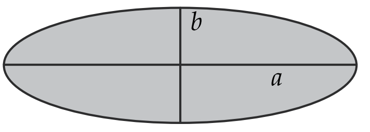


Fig. 11. The definition of equivalent oval

$$\begin{aligned} \text{particle area} &= \pi ab \\ \text{maximal segment} &= 2a \end{aligned} \tag{12}$$

The short axis of the equivalent ellipse is computed by the next equation.

$$2b = \frac{4 \times \pi ab}{\pi \times 2a} \tag{13}$$

4.6.5 Other features of equivalent shape

1. The short axis and long axis of the ellipse: the length of the short axis and long axis of the ellipse which has the same area and the same perimeter.
2. The ellipticity: the ratio of the long axis length to the short axis length. The ratio increases as the long axis length of the equivalent ellipse increases, and the ratio becomes 1 as the shape of equivalent ellipse approximates a circle.
3. The side ratio of rectangle: the ratio of the long axis length to short axis length in the equivalent rectangle. The side ratio of the rectangle increases as the rectangle becomes longer and thinner, and the ratio becomes 1 as the rectangle approximates a quadrate.

4.6.6 Features of morphology

1. The inertia moment: this feature shows the distribution of pixels to the centre of inertia.
2. The stretching factor: the ratio of maximal segment of the gland to the average vertical segment. The factor increases as the gland becomes larger and thinner.
3. The degree of dispersion: the ratio of the gland area to the minimal rectangle including a gland. The value ranges from 0 to 1, and becomes 1 as the gland shape approximates a rectangle.
4. Heywood diameter: the ratio of gland perimeter to circle perimeter with the same area as the gland. Heywood diameter becomes 1 as the shape of the object approximates a circle.
5. The hydraulic radius: the ratio of area to perimeter in a gland.

6. Waddel disk radius: the radius of a circle with the same area as the gland.
7. Nuclear to cytoplasmic ratio: this index is used by pathologists in actual diagnosis.

4.7 Textural feature extraction

4.7.1 Textural feature extraction

Essentially, the aim of our system is to diagnose gastric tumours using morphological features of the glands, cytoplasm, and nucleus. However, with increasing tumor grade it is difficult to separate the individual nuclei. Therefore we use the following textural features within the cytoplasm instead of computing the morphological features of individual nuclei. We determine textural features by intensity histogram, difference statistics, and co-occurrence matrix.

1. Intensity histogram

In an image the normalized histogram *p(l)* is characterized by the following equation, using the intensity level L (L=256) and the intensity histogram *h(l)* ($0 \leq l \leq L$-1).

$$p(l) = \frac{h(l)}{\sum_{l=0}^{L-1} h(l)} \tag{14}$$

The above normalized histogram indicates a probability distribution of intensity. By treating the intensity histogram as the probability distribution, the computed result does not depend on the area of region. We use seven scalar values computed by the probability distribution *p(l)* as features in the intensity histogram. The equations for these features are shown below.

$$\mathrm{MEN} = \sum_{l=0}^{L-1} l p(l) \tag{14}$$

$$\mathrm{CNT} = \sum_{l=0}^{L-1} l^2 p(l) \tag{15}$$

$$\mathrm{VAR} = \sum_{l=0}^{L-1} (l - \mathrm{MEN})^2 p(l) \tag{16}$$

$$\mathrm{SKW} = \frac{1}{\mathrm{VAR}^3} \left\{ \sum_{l=0}^{L-1} (l - \mathrm{MEN})^3 p(l) \right\}^2 \tag{17}$$

$$\mathrm{KRT} = \frac{1}{\mathrm{VAR}^2} \sum_{l=0}^{L-1} (l - \mathrm{MEN})^4 p(l) \tag{18}$$

$$\mathrm{EGY} = \sum_{l=0}^{L-1} p^2(l) \tag{19}$$

$$\mathrm{EPY} = -\sum_{l=0}^{L-1} p(l) \log p(l) \tag{20}$$

In the above equation, MEN means the average of the intensity values of all the pixels in an image. CNT indicates contrast and is the second moment around the origin. CNT becomes large when the histogram distribution slants to the strong intensity side. VAR means variance and is the second moment around the variance or the average. VAR becomes large when the number of pixels with values far from the average is large. SKW means skewness and is large when the histogram shape is distorted from the normal distribution. KRT means kurtorsis and shows a degree of concentration ("peakedness") compared with the normal distribution. EGY indicates energy and the angular second moment. EGY is large when the histogram distribution focuses on the pixels with a particular intensity. EPY means entropy and has a large value when the pixels within the reference region have different intensities.

2. Difference statistics

We construct a histogram with frequencies with the intensity difference l between pixels at the positional relation of $\delta=(r, \theta)$ within a reference region, as shown in Figure 12. Like the intensity histogram, the intensity probability $p_\delta(l)$ is constructed from the frequency of the histogram. The seven above-mentioned scalar features are computed by replacing $p(l)$ by $p_\delta(l)$. In this study MEN, EGY, EPY, and VAR are selected by the after-mentioned test.

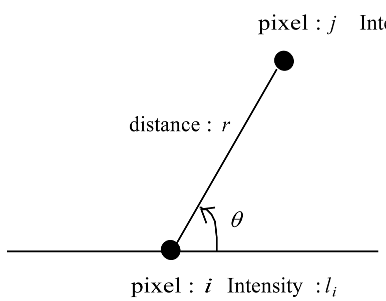


Fig. 12. The positional relationship of a pixel pair

3. Co-occurrence matrix

Like the difference statistics, the co-occurrence matrix is the method that quantifies the relationship between pixels at the positional relationship of $\delta=(r, \theta)$. When the reference pixel is i and has an intensity of l_i, the pixel j is separately placed at distance of δ and has an intensity of l_j, and the probability is defined by $P_\delta(l_i, l_j)$. The matrix obtained by $P_\delta(l_i, l_j)$ is called a co-occurence matrix. When the intensity level is L, the co-occurence matrix has a size of LxL. Figure 13 shows an example of a co-occurrence matrix. Figure 13(1) shows part of an image and each small square represents a pixel within the image. The numbers in the squares in Figure 13(a) represents the intensity values in each pixel. Figure 13(b) shows a co-occurence matrix when the distance r=1 and the angle θ=0°, and Figure 13(c) shows a co-occurence matrix when the distance r=1 and the angle θ=90°.

We use 13 textural features obtained from the co-occurrence matrix. Before computation of these textural features, we define $P_x(l_i)$, $P_y(l_j)$, $P_{x-y}(k)$, $P_{x+y}(k)$, μ_x, μ_y, σ_x^2, σ_y^2, HX, HY, HXY1, and HXY2 as follows.

$$P_x(l_i) = \sum_{l_i=0}^{L-1} P_\delta(l_i, l_j) \tag{21}$$

0	0	1	1	1	2
3	0	0	1	1	1
3	0	2	2	1	1
3	3	3	3	2	3
0	0	2	2	2	0
1	0	0	2	2	1

(a). Object image

$$\text{Intensity}\quad \begin{array}{c|c} & 0\quad 1\quad 2\quad 3 \\ \hline \begin{array}{c}0\\1\\2\\3\end{array} & \begin{pmatrix} 4 & 2 & 3 & 0 \\ 1 & 5 & 1 & 0 \\ 1 & 2 & 4 & 1 \\ 2 & 0 & 1 & 3 \end{pmatrix} \end{array}$$

(b). $p_\delta(l_i, l_j)$ （$\delta = (1, 0°)$）

$$\text{Intensity}\quad \begin{array}{c|c} & 0\quad 1\quad 2\quad 3 \\ \hline \begin{array}{c}0\\1\\2\\3\end{array} & \begin{pmatrix} 3 & 2 & 1 & 2 \\ 1 & 4 & 2 & 1 \\ 1 & 1 & 2 & 2 \\ 3 & 0 & 2 & 2 \end{pmatrix} \end{array}$$

(c). $p_\delta(l_i, l_j)$ （$\delta = (1, 90°)$）

Fig. 13. Example of a co-occurrence matrix

$$P_y(l_j) = \sum_{l_i=0}^{L-1} P_\delta(l_i, l_j) \tag{22}$$

$$P_{x-y}(k) = \sum_{l_i=0}^{L-1}\sum_{l_j=0}^{L-1} P_\delta(l_i, l_j) \quad (0 \le k = \left| l_i - l_j \right| \le L-1) \tag{23}$$

$$P_{x+y}(k) = \sum_{l_i=0}^{L-1}\sum_{l_j=0}^{L-1} P_\delta(l_i, l_j) \quad (0 \le k = l_i + l_j \le 2L\text{-}2) \tag{24}$$

$$\mu_x = \sum_{l_i=0}^{L-1} l_i P_x(l_i) \tag{25}$$

$$\mu_y = \sum_{l_j=0}^{L-1} l_j P_y(l_j) \tag{26}$$

$$\sigma_x{}^2 = \sum_{l_i=0}^{L-1} (l_i - \mu_x)^2 P_x(l_i) \tag{27}$$

$$\sigma_y{}^2 = \sum_{l_j=0}^{L-1} (l_j - \mu_y)^2 P_y(l_j) \tag{28}$$

By using the above definitions, the textural features are computed as shown in the next equations.

$$\text{ASM} = \sum_{l_i=0}^{L-1}\sum_{l_j=0}^{L-1} \left\{ P_\delta(l_i, l_j) \right\}^2 \tag{28}$$

$$\text{CNT} = \sum_{k=0}^{L-1} k^2 P_{x-y}(k) \tag{29}$$

$$\mathrm{CRR} = \frac{\sum_{l_i=0}^{L-1}\sum_{l_j=0}^{L-1} l_i l_j P_\delta(l_i,l_j) - \mu_x\mu_y}{\sigma_x\sigma_y} \tag{30}$$

$$\mathrm{VAR} = \sum_{l_i=0}^{L-1}\sum_{l_j=0}^{L-1} (l_i - \mu_x)^2 P_\delta(l_i,l_j) \tag{31}$$

$$\mathrm{IDM} = \sum_{l_i=0}^{L-1}\sum_{l_j=0}^{L-1} \frac{1}{1+(l_i-l_j)^2} P_\delta(l_i,l_j) \tag{32}$$

$$\mathrm{SAV} = \sum_{k=0}^{2L-2} kP_{x+y}(k) \tag{33}$$

$$\mathrm{SVR} = \sum_{k=0}^{2L-2} (k-\mathrm{SAV})^2 P_{x+y}(k) \tag{34}$$

$$\mathrm{SEP} = -\sum_{k=0}^{2L-2} P_{x+y}(k)\log\left\{P_{x+y}(k)\right\} \tag{35}$$

$$\mathrm{EPY} = -\sum_{l_i=0}^{L-1}\sum_{l_j=0}^{L-1} P_\delta(l_i,l_j)\log\left\{P_\delta(l_i,l_j)\right\} \tag{36}$$

$$\mathrm{DVR} = \sum_{k=0}^{L-1}\left\{k - \sum_{k=0}^{L-1} kP_{x-y}(k)\right\}^2 P_{x-y}(k) \tag{37}$$

$$\mathrm{DEP} = -\sum_{k=0}^{L-1} P_{x-y}(k)\log\left\{P_{x-y}(k)\right\} \tag{38}$$

$$\mathrm{IM1} = \frac{\mathrm{EPY} - \mathrm{HXY1}}{\max\left\{\mathrm{HX},\mathrm{HY}\right\}} \tag{39}$$

$$\mathrm{IM2} = \left[1 - \exp\left\{-2\left(\mathrm{HXY2} - \mathrm{EPY}\right)\right\}\right]^{1/2} \tag{40}$$

$$HXY = -\sum_{l_i=0}^{L-1}\sum_{l_j=0}^{L-1} P_\delta(l_i,l_j)\log\{P_\delta(l_i,l_j)\} \tag{41}$$

$$HX = -\sum_{l_i=0}^{L-1} P_x(l_i)\log\{P_x(l_i)\} \tag{42}$$

$$HY = -\sum_{l_j=0}^{L-1} P_y(l_j)\log\{P_y(l_j)\} \tag{43}$$

$$HXY1 = -\sum_{l_i=0}^{L-1}\sum_{l_j=0}^{L-1} P_\delta(l_i,l_j)\log\{P_x(l_i)P_y(l_j)\} \tag{44}$$

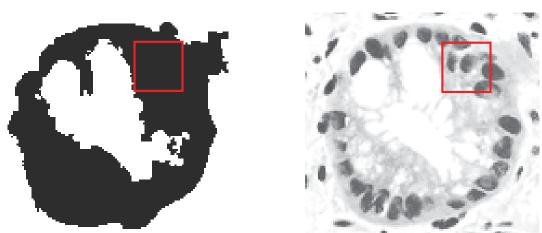
$$HXY2 = -\sum_{l_i=0}^{L-1}\sum_{l_j=0}^{L-1} P_x(l_i)P_y(l_j)\log\{P_x(l_i)P_y(l_j)\} \tag{45}$$

Since the above features are mathematically defined by the co-occurrence matrix, it is difficult to explain their physical meanings.

In our study a small square of 16x16 pixels is clipped from the tumour region for textural analysis. We compute the textural features with respect to this small region. For the analysis of nuclear distribution, an area near the gland base is desirable. We use the next procedure for clipping the small regions.

1. A raster scan is performed using a small square with 16x16 pixels within a two-level image of the gland region.
2. The raster scan is finished when all the intensity values are 0 in the small region.
3. The textural analysis is performed by Y component image with the coordinates that are obtained at the end of the scan.

Figure 14 shows the clipped 16x16-pixel region. Figure 14(a) shows a small square obtained by raster scanning and Figure 14(b) shows the Y component image superimposed on the specified small region.



(a) Binarized image (b) Y image

Fig. 14. The small region obtained for the computation of textural features

4.8 Principal component analysis

The principal component analysis is performed to reduce the number of dimensions after the computation of shape and textural features. When variables are x_i (i=1 to n) and coefficients are a_i (i=1 to n), the principal component Z is defined by the next equation.

$$Z = a_1 \cdot x_1 + a_2 \cdot x_2 + \cdots + a_n \cdot x_n \tag{46}$$

For the principal component, the coefficients a_i are obtained under the next condition.

$$a_1^2 + a_2^2 + \cdots + a_n^2 = 1 \tag{47}$$

The coefficients are obtained by the eigenvalues λ_i of the coefficient correlation matrix. The contribution rate of the obtained principal component is computed by the following equation. In this study the principal components are selected so that the cumulative contribution rate becomes about 90%.

$$\text{contribution rate} = \frac{\lambda_i}{p} \times 100\ [\%] \tag{48}$$

4.9 Discriminant method

The discriminant method is performed for classifying the cases into three classes (non-neoplastic, adenoma, and adenocarcinoma) after the shape and textural features and the principal component score are computed. The procedure of discrimination is shown below.

Step 1. F test for homoscedasticity
Step 2. t-test for average difference
Step 3. Stepwise method
Step 4. Discriminant method

In step 1 all 54 features are tested to determine whether each feature has similar variance in each tumour. In step 2 all the features are tested to determine whether they have similar averages in each tumour. Homoscedasticity must be tested because the method by which the t test is conducted varies depending on whether homoscedasticity is present or not. When a feature des not have average difference, the feature is removed from among the candidates for classification. In step 3 the features for step 4 are selected. In step 4 pattern classification is performed by the discriminant method.

5. Results and discussion

The tumour image information used in our system is shown in Table 3. For computation of shape features we used images with 896x672 pixels, which was reduced at a ratio of 40% of the original image. For computation of textural features we used images with 444x336 pixels, reduced at a ratio of 40% of the original image.

Tumor	Number of images	Number of glands
Not malignant	8	28
Gastric adenoma	19	84
Gastric cancer	6	46

Table 3. Number of images corresponding to each category

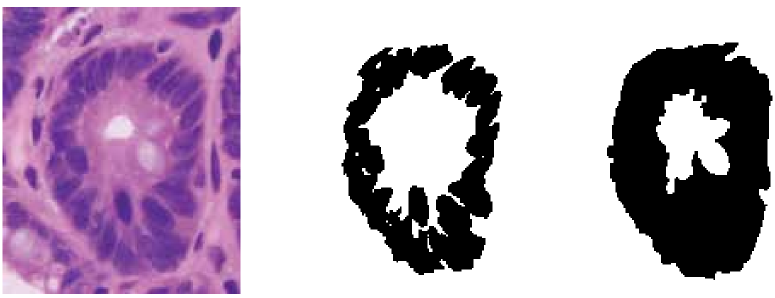
5.1 Pre-processing and Post-processing

The region extraction results for nuclei and glands are shown in Figures 15 and 16. Figures are photographed at the same magnitude. In these figures, (a) is the original image including a gland, (b) is the extracted nuclear region, and (c) is the extracted gland (cytoplasm) region.

Using the threshold determined by the Laplacian histogram and discriminant method, the nuclear and glandular regions were precisely extracted for most of the images. Although the nuclear region was precisely extracted for all the images, extraction was less precise for glandular regions. Figure 17 shows one of the unsuccessful attempts. The reason for the lack of success is that the boundary between the background and gland is not clear.

(a) Non-neoplastic tissue (b) Nuclear image (c) Glandular image

Fig. 15. Extraction results for non-neoplastic tissue



(a) Gastric adenoma (b) Nuclear image (c) Glandular image

Fig. 16. Extraction results for gastric adenoma

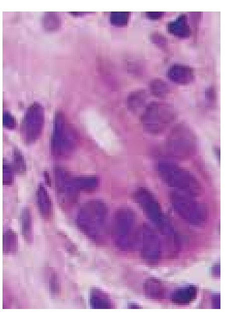


Fig. 17. Image for which extraction of the gland region was unsuccessful

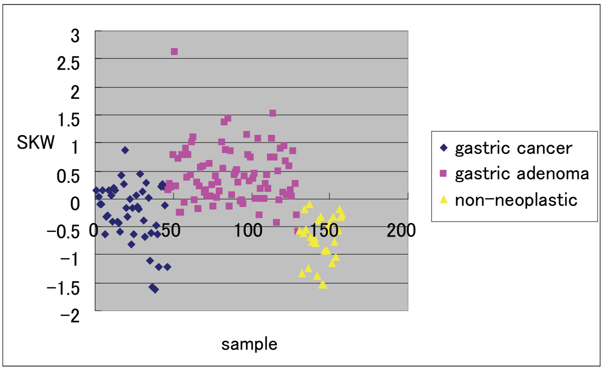
5.2 Textural features

We selected 14 textural features among all the candidate features by the principal component analysis and discriminant methods. The following parameters were derived from difference statistics and co-occurrence matrix at the computation of these textural features.

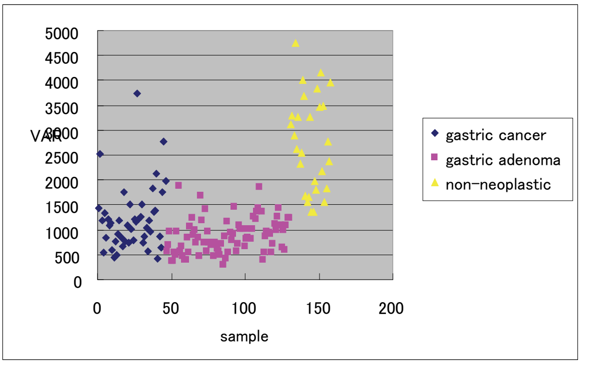
The results of the computed textural features are shown in Figure 18. Figure 18 (a) shows the values of SKW obtained from the intensity histogram and figure (b) shows those of VAR. In both figures blue plots show cancer cases, pink plots indicate adenoma cases, and yellow plots show the non-neoplastic cases. Values of SKW for cancer and non-neoplastic lesions are similar, and those of cancer and adenoma are similar. For example, when we classify all cases into 3 classes, we first classify them into 2 classes according to Figure 18(a); one being cancer and non-neoplastic lesions and the other adenoma. Next we classify the class of cancer and non-neoplastic lesions into the class of cancer and the class of non-neoplastic lesions. In this way we can classify all cases into 3 classes.

Features	invariables	value
Gray-Level Difference Matrix	distance : r	4
	angle : θ	0°
co-occurrence matrix	distance : r	4
	angle : θ	0°

Table 4. Parameters for computation of difference statistics and co-occurrence matrix



(a) SKW (density histogram)



(b) VAR (density histogram)

Fig. 18. Results of computed textural features

5.3 Principal component analysis

In this study we computed 40 shape features and 14 textural features for discrimination of tumor severity. The relationship between factor loading and each principal component is shown in Figure 19. The vertical axis indicates factor loading and the horizontal axis shows the number of principal components. In this study we selected the principal components with an eigenvalue of more than 1. Consequently, the 1st to the 9th principal components were selected, and the cumulative contribution rate was 91%.

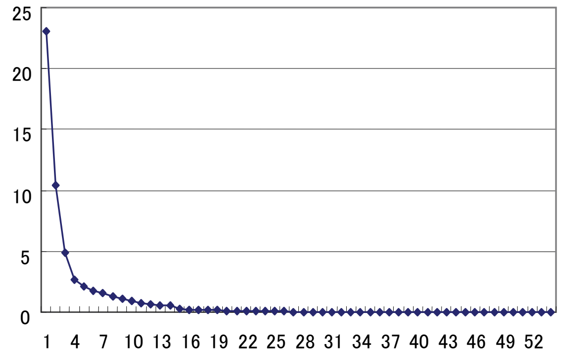


Fig. 19. Factor loading of each principal component

5.4 Stepwise method

In the previous section, 40 shape features and 14 textural features were computed and then selected by principal component analysis. However, some features revealed a strong correlation with each other or did not contribute towards discrimination. In this situation the features used for the discriminant analysis are selected by the stepwise method. The following seven features among the 54 features were selected by the stepwise method.

1. AVE in the intensity histogram
2. VAR in the intensity histogram
3. EPY in the co-occurrence matrix
4. Nuclear to cytoplasmic ratio
5. Stretching factor
6. The average number of chords in glands in the horizontal axis
7. SKW in the intensity histogram

5.5 Discriminant analysis

5.5.1 Discriminant analysis by principal component score

The Table 5 shows the result of pattern classification using eight principal components without the third principal component. “Actual tumour category” in this Table means the classification according to the pathologist and “assigned tumour category” means the classification according to the computer analysis.

According to the computer analysis, the correct classification rate was 88% and the incorrect classification rate was 12%. Further, both the false negative rate and false positive rate were about 6%.

5.5.2 Discriminant analysis by shape features and textural features

Table 6 shows the results by shape features and textural features using seven features that obtained by stepwise method. “Actual tumour category” in this Table means the classification according to the pathologist and “assigned tumour category” means the classification according to the computer analysis.

		Assigned tumour		
		Gastric cancer	Gastric adenoma	Not malignant
Actual tumour	Gastric cancer	37 (80%)	6 (13%)	3 (7%)
	Gastric adenoma	9 (11%)	75 (89%)	0 (0%)
	Not malignant	1 (4%)	0 (0%)	27 (96%)

Table 5. Result of discriminant analysis using principal components score

		Assigned tumour		
		Gastric cancer	Gastric adenoma	Not malignant
Actual tumour	Gastric cancer	38 (82%)	4 (9%)	4 (9%)
	Gastric adenoma	6 (7%)	78 (93%)	0 (0%)
	Not malignant	1 (4%)	0 (0%)	27 (96%)

Table 6. Result of discriminant analysis using features

According to this method, the correct classification rate was 91% and incorrect classification rate was about 9%. Further, both the false negative rate and false positive rate were about 5%.

5.5.3 Glandular images that were unsuccessfully classified

Here we consider the glandular images that were unsuccessfully classified. In tumour diagnosis in particular, it is important to reduce the false negative rate. Representative images that were unsuccessfully classified are shown below.

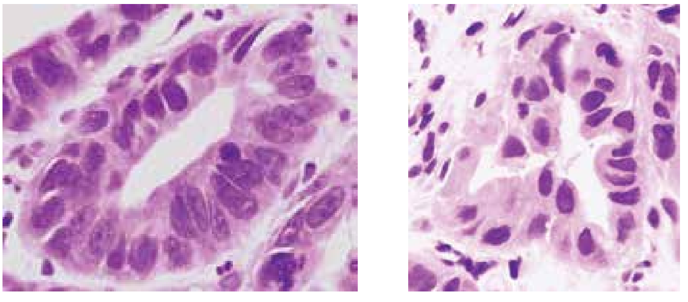


Fig. 20. Glandular images that were misclassified

The above images have glands that appear to suggest cancer, but they were classified as non-neoplastic. The reason for the misclassification is that the gland in the left image has low apytia and is similar to glands seen in non-neoplastic tissue. The gland in the right image also has low apytia and is not enlarged.

5.5.4 Diagnosis by weighting combination

In the previous section each glandular image was diagnosed by the discriminant method. But in the actual hospital setting, pathologists formulate a diagnosis only by looking at the shape and distribution of all glands. Here we propose a more comprehensive diagnosis method by averaging the classification score of each gland. Gastric cancer would score 3; gastric adenoma, 2; and non-neoplastic lesions, 1, as shown in Table 7.

tumor	weight
Gastric cancer	3
Gastric adenoma	2
Not malignant	1

Table 7. Scores for cancer, adenoma, and non-neoplastic lesions

Table 8 shows the diagnosis results of all the cases, obtained by computing an average of all glandular scores in the original image. This table shows that the correct diagnosis rate was 91% and the wrong diagnosis rate about 9% by this method. Moreover, the false negative rate was 0% and the false positive rate was about 9%.

		assigned tumor		
		Gastric cancer	Gastric adenoma	Not malignant
actual tumor	Gastric cancer	7 (88%)	1 (13%)	0 (0%)
	Gastric adenoma	2 (11%)	17 (89%)	0 (0%)
	Not malignant	0 (0%)	0 (0%)	7 (100%)

Table 8. Classification of gastric tumours using severity score

6. Conclusion

This chapter deals with computer-aided diagnosis of glandular tumours for internet-based telemedicine. In many countries including Japan, the scarcity of pathologists is one of the problems in medical diagnosis, and this Internet-based diagnosis system goes some way toward addressing this issue. In this chapter we have reported a diagnosis system for glandular tumours such as those of the stomach, colon, prostate, and breast. Here we explain the diagnosis system with a central focus on gastric tumour.

First, we discussed the difference between shape features and textural features of non-neoplastic lesions, adenoma, and cancer, and perform numerical conversion of atypism and anisocytosis. We created a system for extracting the nuclei and glands and tested this method in gastric tumours. As the result the system using binarisation of the red and green components of a tumour image can extract a region with an arbitrary density when the region is surrounded by a relatively clear boundary. Next, we computed 40 shape features and 14 textural features and determined the score of principal component analysis. The discriminant result reached 88% with eight principal components, and 91% with seven selected features. Moreover, when we performed weighting based on the discriminated gland and classified the original image into three categories of severity, the discriminant ratio reached 91% by the principal component method and 94% by the selected features method. Our proposed system therefore appears valid for the diagnosis of gastric tumours.

With this method, we must remove each gland region from the original image. In future work, we will focus on a method of automatically extracting each gland. In higher grade cases most of the glands are unformed, and creation of an automatic gland shape extraction algorithm is a difficult problem facing Internet-based diagnosis systems.

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9

Development and Introduction of the Telemedical System into the Blood Transfusion Practice

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1. Introduction

The blood transfusion service is a distributed service. Blood products are delivered from the central blood bank to the final consumer – local hospitals. Before a blood transfusion is given, obligatory pre-transfusion tests are performed at the hospital laboratories for confirmation of the donor/patient compatibility. They are normally performed by specially trained personnel. Normally, these agglutination-based compatibility tests have straightforward results, enabling easy diagnostic decisions of the local staff. In approx 1-5% of tests, various serological difficulties and ambiguities occur (Rozman & Domanovic, 2006). In these cases, transfusion is delayed and an expert opinion is needed for the resolution of test results. In such cases, patient's blood samples are sent to the reference transfusion laboratory to a qualified immunohaematology expert by a courier. The expert performs additional tests and interprets them. The consultation between the expert and local technician is then performed by telephone or fax. Notably, this method is error prone procedure with a poor safety, quality and traceability performance, resulting in a time consuming and expensive operation.

In case of Slovenia, transfusion service is provided by two central national transfusion centres with reference laboratories and 9 hospital transfusion departments with their transfusion laboratories. Transfusion centres are expert centres coordinating all transfusion actions on national level. They are responsible for blood collection, testing, production of blood components and performing pre-transfusion tests. Hospital transfusion departments with their transfusion laboratories are responsible for blood collecting and pre-transfusion testing (Bricl et al., 2010). On the average, transfusion service of Slovenia handles 400 transfusion cases per day (Rozman & Domanovic, 2006). Since it is impossible to predict when transfusion services are required, it is necessary to provide transfusion experts 24/7 in all hospitals depending on transfusion service. Therefore an adequate number of experts are required. It is difficult to satisfy these demands due to lack of the qualified experts and lack of funds. Furthermore, in smaller hospitals only a few transfusions per day occur. In these hospitals transfusion expertise is provided without dedicated personnel by expanding a set of assignments of other on duty doctors. These doctors attended additional transfusion medicine training course. They are able to solve straightforward cases occurring during their shift, when dedicated transfusion specialist is not present. But these doctors solve relatively small amount of transfusion cases and an obvious problem is lack of practical experience of these *multipurpose* doctors.

The core problem, addressed by our telemedical system is the remote readout and interpretation of the agglutination tests, performed prior each blood transfusion (pre-transfusion tests), following the EU Directive 2002/98/EC that introduced quality management and haemovigilance into the practice of the current blood supply (Faber, 2004). The ability to perform remote readout and interpretation of pre-transfusion tests solved the problem of the delayed pre-transfusion procedure in cases of ambiguous cases which required attendance of reference laboratories. Another problem addressed by the system is provision of remote immunohaemathology expertise to laboratories with insufficient personnel resources. Furthermore, the law requires issue of a signed document as a result of the pre-transfusion test. Since the telemedical system does not transmit signed paper documents, our system had to provide legally sound documents. To provide documents, legally equivalent to their signed paper counterparts, a digital signature infrastructure was introduced into the system.

2. Existing solutions

Regarding the mode of operation, two main models of telemedical systems for exchange of expertise between health care experts exist. These models are "store-and-forward" model and "real-time" model.

Store-and-forward telemedical system approach is asynchronous interaction. A query can be transmitted by the referrer and then answered by a specialist at later time. It is used in various forms and on various fields of medicine (Harnett, 2006). Many authors report successful store-and-forward telemedical implementations using common e-mail service (Bonnardot & Rainis, 2009; Wotton, et al., 2010). Telemedical solutions using e-mail as baseline technology platform are relatively easy to implement, since most of the infrastructure already exists, therefore investment into equipment is relatively low. These solutions use existing widespread applications for e-mail exchange. These applications and underlying communication protocols are mature and are relatively reliable. More advanced solutions use different PACS systems as their baseline technology platform. Store-and-forward service is capable of transmitting diagnostic data that can be digitalized or is already created in digital form. The most common store-and-forward applications using e-mail service are tele-ECG and still image transfer for dermatology or wound care. System using PACS are mainly tele-radiology systems (Bahaadinbeigy, et al., 2010).

On the other hand in cases where immediate response is required, real-time telemedical systems are used. They provide real-time communication between communicating parties, providing consulting side with immediate consultant expertise. Using the real-time system, it is possible to provide expert tele-presence. Expert consultant can interactively guide the consulting personnel through the patient treatment procedure. The majority of real-time telemedical systems transmit voice, and video image of the communicating parties. Several studies have shown, that it is important for the in communication participating persons to see each other, since a lot of information is exchanged through visual communication. Videoconferencing real-time approach can also be used to transmit diagnostic images of patients, their conditions and other objects. Several reported real-time telemedical systems are built using of the shelf videoconferencing equipment. Addition to relatively standard videoconference communication is transmission of other patient diagnostic data such as

real-time ECG. The most common real-time telemedical application areas employing videoconferencing are education, wound care and psychiatry (Bahaadinbeigy, et al., 2010).
Comparing both widely used approaches of telemedical systems, store-and-forward model of telemedical service provides better accuracy and traceability, compared to real-time systems. Better accuracy is provided because the consultant does not have to work under constant pressure of swift decisions since he/she can take time to handle the cases. Better traceability is provided because the model by its definition provides track of performed actions. Data is exchanged in a condensed form. Data exchanged usually consists of diagnostic data, patient health record data and refined question to the consultant, awaiting refined response. On the other hand the real-time system provides its users with quick resolution of their problems. It enables additional data exchange through real-time interaction on specific topics needed to resolve the problem (Wootton 2006).
Regardless of many telemedical systems in existence no publication about the telemedical system, other than ours, supporting the blood transfusion was found.

3. Our solution

Our system enables remote interpretation of pre-transfusion tests performed on gel-cards. Considering advantages of both store-and-forward and real-time approach a hybrid telemedical system was developed using store-and-forward as base mode of operation with possibility to switch to real-time mode when necessary. In real-time mode audio/video communication between its users is offered. A special device Gelscope was developed to capture images of gel-cards.
Our system follows high level of security, user identification and data protection requirements. The result of the system usage is prompt exchange of immunohaematology expertise in form of legally valid electronic document containing the pre-transfusion test readout, interpretation and diagnose.

4. Background: pre-transfusion serological testing

Our telemedical system is based on the pre-transfusion serological testing consisting of ABO blood grouping, cross matching, antibody detection and specification (direct and indirect antiglobulin tests) (Lapierre et al., 1990; Langston et al., 1999). These tests are based on the detection of red cell antigen-antibody reactions, resulting in the agglutination of red blood cells. Although several agglutination methods exist, the micro-tube gel method with the DiaMed® gel-cards is probably the most widely used. Gel-cards are plastic cards with 6 embedded micro-tubes, filled with a mixture of sephadex gel, buffer and reagent. For each pre-transfusion test a different combination of the reagents is used in the gel-card test tubes. Figure Fig. 1 depicts the image of commonly used serological test ABO Rh gel-card with agglutinates fixed, ready for the readout and interpretation. During the test a suspension of red blood cells or a mixture of the red blood cells and diagnostic antibodies is centrifuged through the gel under standardized conditions. If no agglutination occurs, the red blood cells penetrate the gel and sediment at the bottom of these micro-tubes (negative result). In cases when agglutination occurs, agglutinates are trapped on the surface of the gel (positive result).
The readout and interpretation of the test is performed by visual interpretation of the agglutination pattern in six micro-tubes. It consists of two steps. In the first step, the

strength of agglutination is determined for each of the six micro-tubes, ranging from 0 to 4+. Typical agglutination patterns ranging from 0 to 4+ are shown on Figure Fig. 2. An ambiguous agglutination pattern is also shown and is marked by (?). In the second step of the pre-transfusion test interpretation, the result is interpreted based on the agglutination pattern in six micro-tubes. By capturing the image of the gel-card, it is possible to electronically capture the result of the pre-transfusion test.

The gel test method of pre-transfusion serological testing, when performed by standardized procedures, yields sensitive, specific and reproducible results. The final visual read out and interpretation of the gel-card represents the most important step affecting the accuracy of the medical diagnosis (Lapierre et al., 1990; Langston et al., 1999). It requires engagement of highly qualified and experienced personnel. In addition, access to the patient's medical history is required during the diagnostic procedure for an accurate diagnostic decision.

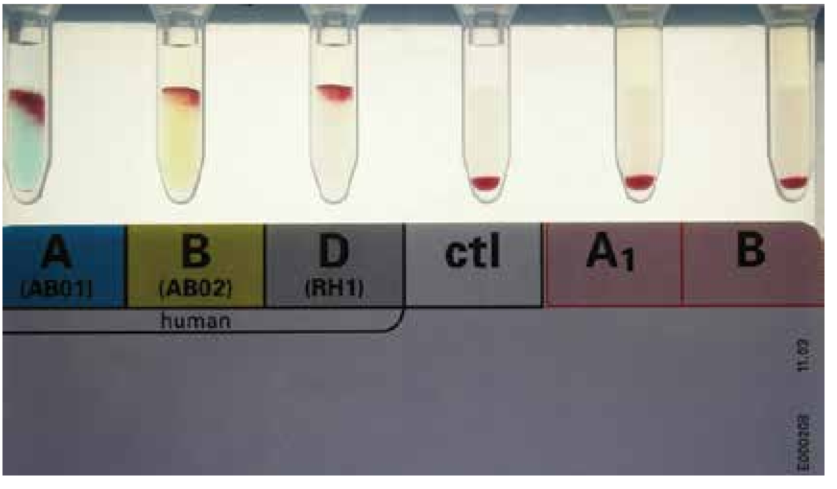

Fig. 1. ABO Rh gel-card after centrifugation with agglutinates trapped in the gel. The image is obtained from the working telemedical system.

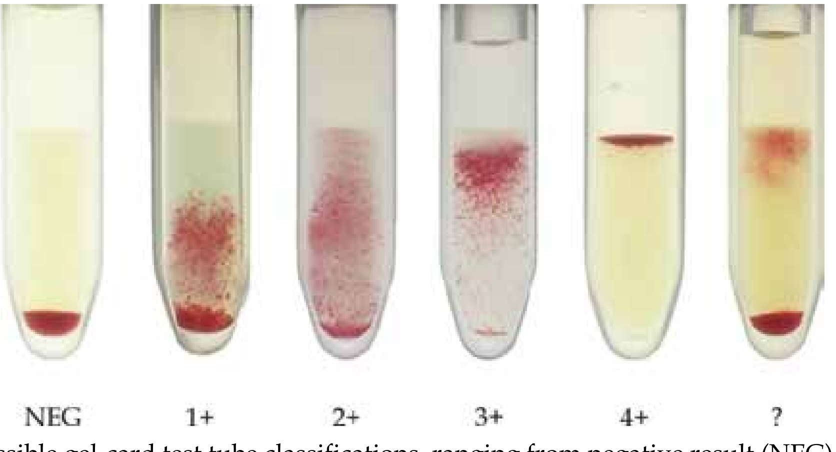

Fig. 2. Possible gel-card test tube classifications, ranging from negative result (NEG) to positive result (4+). Ambiguous test tube is marked with question mark (?).

5. User requirements acquisition

As already mentioned, the blood transfusion service of Slovenia is provided by 2 large blood transfusion centres and 9 hospital-associated transfusion departments with laboratories, which supply hospitals with blood products and obligatory pre-transfusion serological testing. Provisioning of these services in Slovenia requires 24 hours per day, 7 days per week availability of at least one immunohaematology expert in each institution (Rozman & Domanovic, 2006). To rationalize these needs, several requirements for the telemedical system for a remote read-out and interpretation of pre-transfusion tests were identified. Prospective users of the telemedical system were involved into the system design from its beginning. At the start it was not possible to generate detailed system specification; therefore the process of developing the telemedical system was iterative. In the first iteration use case scenarios of the system were discussed with prospective system users – immunohaematology experts and technicians from transfusion laboratories. Based on discussed use case scenarios high level user requirements of the system were obtained. These user requirements were used to create detailed set of technical specifications, based on which a prototype system demonstrating the basic functionality was build. The prototype system was then evaluated by the prospective users who provided refined user requirements set. Refined user requirements were then used in another iteration of the development cycle. The whole procedure was then repeated until the system was in the production ready state.

Current condensed set of high level user requirements of the telemedical system is as follows. The telemedical system should provide (Meza, et al., 2007):

- capturing of high resolution images of DiaMed® gel-cards;
- transmission and archiving of the captured gel-card images;
- magnification of the gel-card images for detailed observation of agglutinates;
- 24-hour availability of expertise from the reference laboratory to the remote hospital laboratories;
- a store-and-forward telemedical model for non-urgent transfusion cases;
- exchange of corresponding medical data of patients and blood donors;
- permanent on-line connection to the national data bases of blood donors and patients for the provision of the transfusion and anamnestic data;
- real-time interaction between the technician in the local hospital laboratory and the expert in the reference laboratory in urgent cases;
- audio and visual communication between its users;
- complete traceability of all procedures;
- scalable system design;
- notification of users via SMS;
- reliable, safe, secure and encrypted data transmissions.

Since users of the telemedical system were involved into the system design, they adopted the system as their project, which helped to the system success. Common problems did not deter them from using it. According to the authors (Broens, et al., 2007) technical problems are among the main barriers for successful telemedical system implementations. Involvement of users of the system into the system's development also lead to quick resolution of technical problems, since they were quickly identified, and thoroughly described to the development team.

Use case scenario, describing the system usage is presented in the next section.

6. Use case scenario – system usage workflow

The system usage workflow can be explained on the following use case scenario. Let us assume that in a hospital transfusion laboratory there is no immunohaematology expert present and a need for pre-transfusion testing emerges. Since no expert is present, a remote pre-transfusion test interpretation is required. Users involved into the process are divided into two roles. Users belonging to the role *consulting user* are laboratory technicians. These are users requesting the remote interpretation. Users belonging to the *consultant* role are immunohaematology experts. They are legible to issue legally valid pre-transfusion test interpretations. Technicians as well as consultants both use the terminal with the teleconsulting application. Screenshot of the teleconsulting application can be observed on Figure Fig. 5. All users must log into the application using their unique credentials. Based on the credentials the system determines user's role and rights to access different data. Roles and rights for each user are defined on the teleconsulting server. On Figure Fig. 3, a laboratory setup of the technician side is photographed.

Fig. 3. Laboratory setup of the telemedical system. Main application window can be observed on the terminal. Gelscope device is visible right next to the terminal monitor. Videoconference call is not established.

At first the laboratory technician prepares the required samples according to the protocol of the pre-transfusion testing (Langston et al., 1999). Result of sample preparation is a series of gel-cards with administered blood samples after centrifugation with agglutinates fixed in the gel of gel-cards. After gel-cards are prepared, the laboratory technician sets up a teleconsulting session by setting up a question. Teleconsulting session consists of a question and if answered of the answer to that question.

Setting up the teleconsulting question is divided into several steps. The first step is entering a blood sample number into the teleconsulting application. It is accomplished by capturing the blood sample number from the sample vial, using the barcode reader. Sample number record exists in the existing hospital information system along with patient's details, transfusion history and anamnesis. After capturing the sample number, patient's data is automatically obtained by the teleconsulting application and appended to the teleconsulting question. In the next step, the technician uses the Gelscope device to capture images of all gel-cards used in the test. For each gel-card, card type is selected and inserted into the teleconsulting application from provided dropdown menu. Users can add up to 10 gel-cards to each question. In the next step of the question setup, the case specific question is typed into the teleconsulting application. Then the available immunohaematology expert - the consultant is selected from the list of available consultants. After all question data has been entered, the technician finishes question data entry. The teleconsulting application then relays the entered data to the teleconsulting server.

All teleconsulting applications continuously pool the server for any new questions/answers. When a new question to the currently logged consultant emerges, the teleconsulting application immediately notifies the consultant about the incoming interpretation request. Notification is accomplished by displaying an alert window on the terminal and by sending an SMS to the consultant's mobile phone. Using the telemedical application, consultant reviews the question. He/she interprets the test results for each of the gel-cards and enters them into the telemedical application. After all gel-cards are interpreted, consultant determines and types the answer to the test case specific question set by the technician. After all data has been entered, the consultant can decide to digitally sign the answer. In case of digital signature the answer becomes signed document, which is legally equal to the paper document required for the blood transfusion procedure. After data has been entered into the teleconsulting application it relays it to the teleconsulting server.

Since all active teleconsulting applications pool the server for new questions/answers, a new answer to his/her question is noticed by the technician's teleconsulting application. When new question is noticed, the telemedical application immediately notifies the technician about the incoming answer by displaying an alert window on the terminal screen. It also sends an SMS message to his/her mobile phone. Technician then reviews the consultant's answer along with the question. He/she can then verify the digital signature of the document and proceeds with the transfusion procedure as if the consultant was actually present in the laboratory and has signed the paper document.

In cases, when immediate response is needed and verbal discussion is required between the technician and the consultant, users can establish a videoconference call using the telemedical application. Either user can establish a videoconference call. It is established by selecting online person from the list of users currently logged to the telemedical system. After selecting the person user wants to establish videoconference call with, the calling teleconsulting application sends videoconference request directly to the called user's teleconsulting application. Called application notifies the user about the incoming videoconference call by displaying a notification window. Called user can either accept or decline the incoming videoconference call. If accepted, a bidirectional videoconference call is established from both teleconsulting applications. Either side can then break the call after the videoconference connection is no longer needed.

Since videoconference call can be established only in a point-to-point mode, users currently in video call procedure are marked as busy in the list of for the videoconference available users and cannot be called by other users. Regardless of videoconference availability status, store-and-forward telemedical questions can still be relayed to busy users.

7. System architecture

The basic telemedical system architecture is client-server architecture. The system consists of several components, illustrated on Figure Fig 4. The first component of the system is the telemedical terminal, comprising of a personal computer, running the MS Windows XP SP3, running the telemedical application. Screenshot of the telemedical application can be observer on Figure Fig. 5. Telemedical terminal component is used at the hospital laboratories (consulting side) and at the transfusion centre (consultant side). Along with standard PC peripherals, the telemedical terminal is equipped with special propose hardware for capture of gel-card images – Gelscope device, shown on Figure Fig. 7, web camera, headphones with microphone, bar code reader, colour laser printer and VPN router. Existing hospital information system also exists in all hospital laboratories and is also shown in Figure Fig 4. Since consultant side does not need the equipment for question set up, terminals are lacking the Gelscope device and the connection to the existing hospital information system.

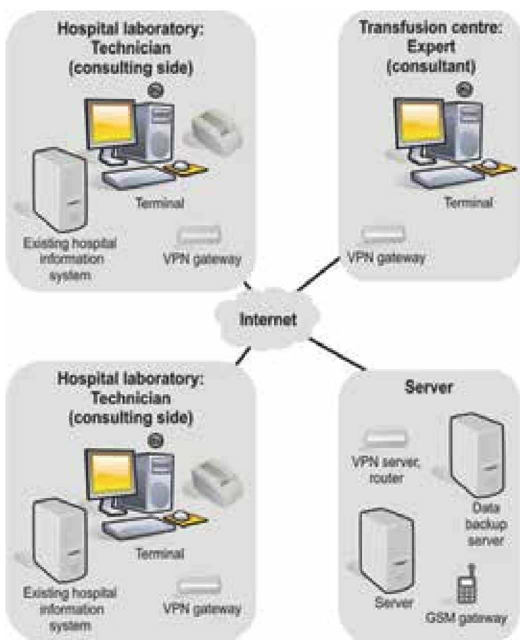

Fig 4. Teleconsulting system structure. Three terminal setups, server setup and connecting infrastructure are illustrated.

The second component is the server side of the system with main server running Debian Linux operating system, running the telemedical server application, certificate authority server application and database. The server also has GSM module attached to it and runs SMS notification application. The server side also includes VPN server – router.

All nodes of the system are securely connected through the secure virtual private network (VPN) tunnels via the public Internet established by the VPN gateways and the VPN server.

The telemedical system is integrated with the existing hospital information system through a special integration module to obtain patient basic data (name surname, birth date, and blood type), previous patient anamnesis and patient transfusion history.

Basic operation mode of the telemedical system is a store-and-forward mode. If required, users can switch to the real-time mode by establishing a videoconference call. Videoconference calls are established using the videoconference module which is a part of the telemedical application.
A digital signature infrastructure was also developed and integrated into our telemedical system. Therefore through system issued readouts, interpretations and diagnoses have the same legal value as their signed paper counterparts.

Fig. 5. Telemedical application user interface. Left shows main user interface window with a videoconference in progress; right window shows patient data obtained from existing hospital information system.

8. Telemedical system modules

8.1 Telemedical application – client

The telemedical application is the front-end of the telemedical system to its users. One of the main functionalities of the telemedical application is acquisition of the telemedical data from various sources and presentation of that data to the users. Consulting users (laboratory technicians), consultants (immunohaematology experts) as well as system administrators all use the same application. The telemedical application is running on the terminal PC. It is a client part of the telemedical system. It was developed in the Java programming language. The application user interface changes accordingly to the user level, using the system. There are several levels of users. The main difference between levels is a set of to the user allowed actions. If for example, a certain user has a role of a consulting person, than he/she is only allowed to set up questions, and he/she is not allowed to answer them. Therefore only options for setting up the question and browse them are available to that user. If user has a role of consultant, only options for answering the questions are available to that user. If user has a role of administrator, only administrative options are available to that user. Combined user roles are also possible.
The teleconsulting application screenshot is shown on Figure Fig. 5. The left window shows typical view of the telemedical application for consultant, answering the question. In the top of the window, a table with list of questions to consultant is displayed. Following below is the area where the patient basic data (name surname, birth date, blood type and medical remarks) is displayed. In the middle of the window the magnified view of the gel-card is

displayed along with gel-card image metadata. Below are question and answer entry fields. On the right side of the main teleconsulting application window a videoconference interface is shown. The top window shows incoming video stream and the bottom one is showing the outgoing stream. Below is the list of for the videoconference available users with videoconference control buttons. The right window of the Figure Fig. 5 shows screenshot of the window for display of patient data obtained from the existing hospital information system. This window is shown only on request, since there is not enough space on the monitor to simultaneously display both the main and the patient detail display window all the time.

The telemedical application communicates with the telemedical server. None of the data required for work is stored locally. All within the system existing data is obtained from the server and all newly generated data is immediately stored to the server. This enables absolute portability of the users between terminals.

There are three main modes of the common operation of the telemedical application. Not all modes are available to all users, since users have different privileges. The first mode of operation is question setup, the second one is question answering and the third one is answer review. Each mode has specific user interface. Mode switching is intuitive.

In the question setup mode, which is intended for consulting users, the application provides users with user interface for entering all question data. In this mode the application listens to the events from the attached Gelscope device. When a gel-card is inserted into the Gelscope device, it notifies the application, which commences immediate gel-card image capture. Captured gel-card images are appended to the telemedical question being set up. After a gel-card image is captured user is required to enter gel-card specific data – type of the gel-card and optionally read the gel-card serial number using the barcode reader. The gel-card images belonging to current question are shown on the ribbon as image tiles. User can select specific gel-card image for display by clicking on its tile on the ribbon. Selected gel-card can be seamlessly zoomed in or out using intuitive user interface. When image is enlarged and only a portion of the gel-card is displayed, users can pan the image view using the mouse.

In the question setup mode, the telemedical application also communicates with the existing hospital information system to obtain patient details, transfusion history and anamnesis based on the blood sample number which is read by the barcode scanner.

After all data has been entered and recipient of the question selected, the application performs data entry control and sends the data to the telemedical server.

In the question answering mode, which is intended for consultants, the telemedical application provides users with the question browser and answer entering data fields along with all question data. Using this mode of operation, users review question data and enter answers. They thoroughly examine all gel-card images and performs readout and interpretation which is entered into the provided data entry fields for each gel-card image. A patient history and anamnesis is also available. After all gel-cards are read and interpreted and patient history and anamnesis is examined, the final decision about the pre-transfusion test is made and typed into the answer field. After all data has been entered, the users can decide whether to digitally sign the answer.

In case of digital signature, the application digitally signs all question and answer data using the user's digital certificate. After the signature, neither question nor answer data can be changed without breaking the signature. After the question has been answered, the answer data is sent to the telemedical server.

In third mode of the telemedical application operation, the answer review mode, which is indented for consulting users, the application provides users with the question browser. It displays all question data entered during the question setup and in case, the question has been answered all answer data. If the answer was digitally signed, the digital signature can be verified.

Telemedical application provides its users with option to establish videoconference call with any available user of the telemedical system regardless of the current mode of the operation. In case of videoconference call audio video communication is established. Outgoing and incoming video streams are displayed in the application window.

Telemedical application is able to print question/answer data to obtain hardcopy paper documents.

The telemedical application continuously pools the telemedical server for any new questions/answers to the logged user. If a new question/answer emerges it notifies the user by displaying alert window and sending an SMS message to the logged user mobile telephone.

The telemedical application is also used to manage the users. If logged user has administrator privileges, he/she can add or change new system users, generate, register and revoke user certificates.

8.2 Existing hospital information system access module

Existing hospital information system access module is used to obtain patient data from the system and include it into the telemedical questions. It consists of two parts. The first part is a script for collecting and serving required patient data. The script is running on the existing information system. The second part is the script initiation system and data parser.

The data, obtained from the system is textual data, structured into several data fields. These are: patient details (name, surname, birth date, blood type, and medical remarks), patient transfusion history and patient anamnesis. All transfusion hospital laboratories in Slovenia use the same in-house developed information system named DATEC comprising of a UNIX running server and in FoxPRO written application. For placement of the existing information system placement within the telemedical system see Figure Fig 4. The information system DATEC was originally designed to be accessed to by its users using a terminal interface. The communication protocols, provided are telnet and FTP protocols, which were also used in our access module.

In order to gain access to patient data from the existing information hospital system DATC to the telemedical system, a special data query script to run on the information system was developed. When run, the script requests for the blood sample number which is then used to query the internal database for all patient data. Obtained data is then stored as a text file with separators used to separate distinctive data fields on the internal DATEC's file system, accessible through the FTP protocol.

When patient data is required by the telemedical application, it establishes a telnet connection to the information system. Then it starts the data query script and provides it with the sample number. After the script finishes its execution, the telemedical application breaks the telnet connection and establishes a FTP connection instead. Using the FTP connection the file containing the patient data is obtained from the DATEC's file system. The file is deleted afterwards. After the file is obtained the data is parsed into the telemedical application's data container, which is then displayed to the telemedical application's user and appended to the telemedical question. See Figure Fig. 5, right.

8.3 Gel-card image capturing device

The images of gel-cards are captured using specially for this purpose developed hardware – Gelscope, designed to be easy and simple to use. Gelscope provides standardized and repeatable capturing of images required for the correct read-out and interpretation of the pre-transfusion tests. Image capture is standardized in means of position, illumination and other optical deformations of the gel-card. The captured high resolution images (24-bit, true-colour 3.2 mega pixels) can be magnified up to 20-times without any visible degradation of the image. Hence, the observation and interpretation of the agglutinates is easy compared to the standard visual reading by the naked eye (Meza et al., 2007).

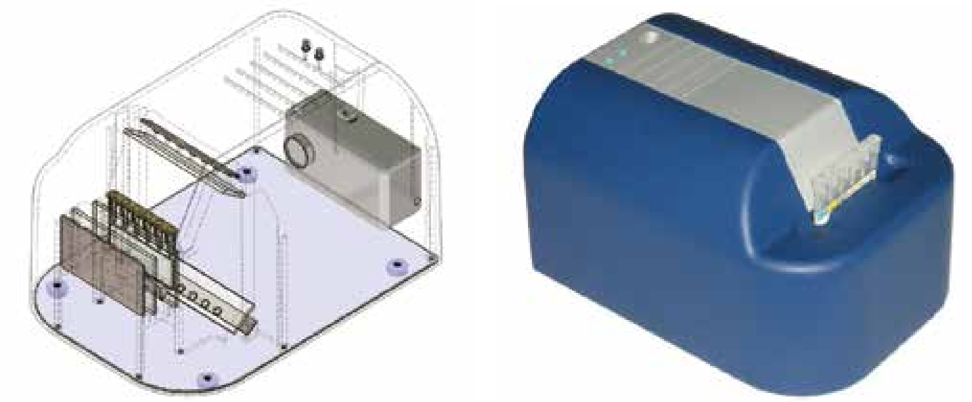

Fig. 6. Special purpose hardware for capture of gel-card images, Gelscope 32 -version 1.

To capture the image of the gel-card, it must be correctly illuminated using the white spectrum light. Due to specific requirements for gel-card image capture, the gel-cards must be illuminated from the front and from the back side to effectively illuminate all important gel-card components. They are: gel-card label and gel-card's micro tubes with their content. In our design three illuminators were used. They were made of an array of white LEDs and a light diffuser, made of white diffuser glass. The image of the gel-card is captured by the off shelf digital camera, built into the device. The setup of the illuminators, the gel-card and the camera is illustrated in Figure Fig. 8. Two illuminators are used to illuminate the front side of the gel-card and the third illuminator is used to backlight the transparent gel-card. Using this illuminator setup an efficient illumination of all gel-card components is achieved. The front illuminators must not cause any with built in camera visible reflections of the gel-card. This request is satisfied if the front illuminators illuminate the gel-card at a steep enough angle. Figure Fig. 8 depicts the worst angles of the reflections with dashed lines. It is obvious, that the gel-card, illuminator and camera locations cause no reflections to the camera lens (Meza & Kosir, 2009).

Two versions of the Gelscope device were developed. The first one named Gelscope 32 is shown on Figure Fig. 6. X-ray view of the device is also shown. During the pilot testing of the system some design flaws of the device were identified. To mention some they were: uneven gel-card illumination, deterioration of illuminators due to inappropriate heat dissipation, possibility to insert and capture the image of gel-card slightly rotated, visible visual artefacts of the Gelscope device mechanics in the captured gel-card images. These flaws were remedied in the development and production of the second version of the gel-card image capture device named Gelscope 80, shown on Figure Fig. 7. Gelscope 80 has

Fig. 7. Special purpose hardware for capture of gel-card images, Gelscope 80 - version 2.

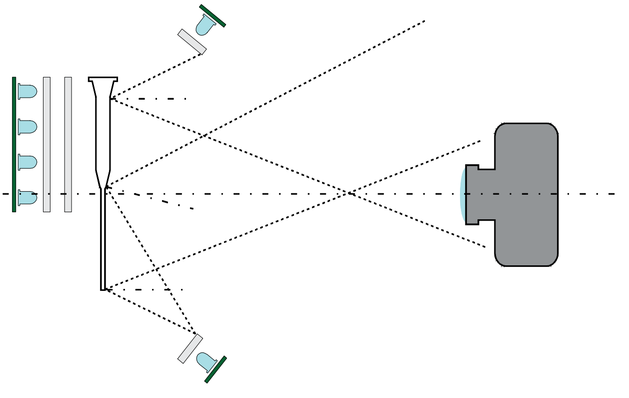

Fig. 8. Schematic display of the Gelscope device regarding illumination, gel-card and camera positions. From the left: rear illuminator, gel-card, front illuminators and camera.

further improvements to the Gelscope 32 among which are: better and more intuitive design, better quality of captured image due to higher resolution camera with better optics. Gelscope devices need individual calibration. In the Gelscope 80 the calibration data resides in its non-volatile memory, which has drastically simplified service of the telemedical terminals. In case of the Gelscope 80 device failure a service technician can simply replace the failed device with a new one without the need to enter new calibration data in the system.

8.4 Digital signature

Digital signature assures that the document was created by the known user and that it was not altered after it was signed. Our digital signature solution was implemented as combination of a digital signature module, running within the telemedical application, and a certificate authority server. Our solution is responsible for key management, digital signature of the documents and for digital signature verification. It is based on the public/private key infrastructure employing the MD5/SHA message digest algorithm and the RSA algorithm for creating and verifying the signature. The procedure of creating digital signature of the document and verifying it is illustrated on Figure Fig. 9.

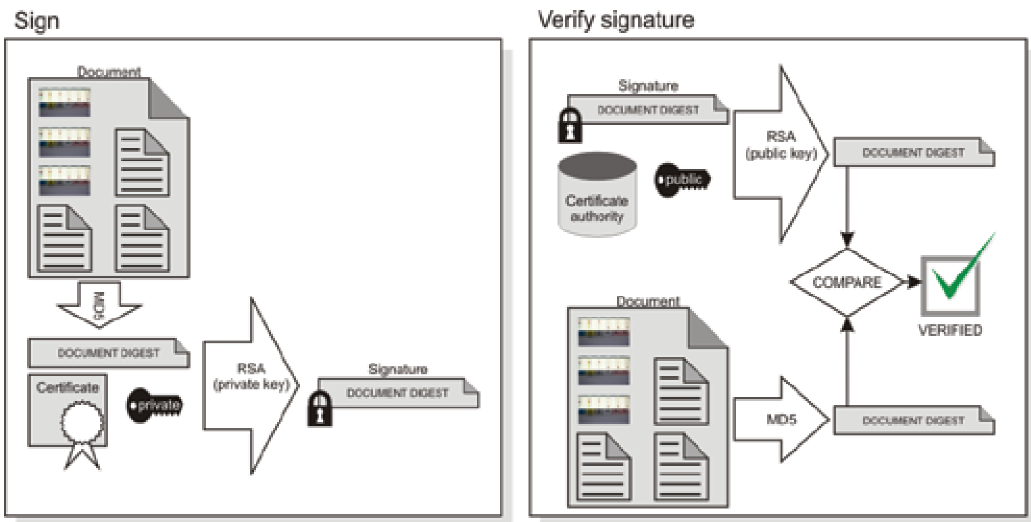

Fig. 9. Signing document with private key from certificate and verifying signature with public key obtained from certificate authority.

When signing a document, the signing user is asked to provide the telemedical application with his/hers certificate, containing the certificate serial number, user credentials and public/private key pair. After correct certificate password has been entered by the user (certificate keys are encrypted using symmetric cryptography using 3DES encryption algorithm) the private key from the key pair is obtained.

The document to be signed consists of several data objects. They are: question text, gel-card images with readout data, patient history and anamnesis, diagnosis and answer to the question. All these data objects combined represent the document to be signed. Message digest function MD5 is used to calculate 128 bit hash value of the document. Hash value of the document is then encrypted using the RSA encryption algorithm with signing user's private key. Resulting encrypted hash value can be decrypted only with user's public key, which is stored along with user's credentials on the certificate authority server.

Encrypted hash value which represents actual digital signature of the document is then attached to the document which then becomes digitally signed document. Two issues are solved this way. If anybody would change the document, the hash of the document would also change. Since only the signing user has the private key, he and only he could have used it to sign the document. This way, it is assured, that the document was not changed and that it was signed by the specific user.

Signature of the document can be verified by anybody, who has access to the user's public key, which can be obtained from the certificate authority server located at the secured location within the server of the telemedical system.

Signature verification is performed by obtaining the public key of the user claiming the signature from the certificate authority server. This key is used to decrypt the encrypted hash of the signed document. The MD5 message digest function is used to compute hash of the signed document. Decrypted and computed hash values are then compared. If they match the digital signature is valid and the document is pristine. If not, either the document was tampered with either the claiming user did not sign it.

If the digital signature matches, the artwork displayed in Figure Fig. 10 is printed on the hardcopy of the answer along with the actual digital signature string. This is a cosmetic measure, allowing quick diversification of the signed documents with verified signatures from non-signed ones.

Fig. 10. Digital signature artwork, printed on the document following the digital signature string.

8.5 Videoconference module

Videoconference module is used to establish real-time audio/video communication between users of the telemedical system. It was implemented using the JMF (Java Media Framework) framework. It is a part of the telemedical application. It consists of two major components. The first one is call control/notification component (call control). It is used to control the calls, notify the user about call status and notify the server about the user availability status changes. The other component is audio video encoding/decoding and transmission component (AVT component) which captures audio and video streams from to the terminal attached microphone and camera, encodes/decodes them and transmits them via the network. Only point to point calls are supported.

When user logs on to the telemedical system through the telemedical application, the telemedical application call control sends the terminal computer's IP address to the telemedical server. The telemedical server records the address into the database along with user details and availability status. All logged users have default status available for videoconference. Other possible videoconference user statuses are busy – a status assigned to user in ongoing videoconference call, and offline – a status of all offline users. When the telemedical application starts it runs call control component which continuously listens to the incoming videoconference calls on the special videoconference control port.

When a user in the system wants to establish a videoconference call to the other user, his/her telemedical application's call control obtains called user's terminal IP address. It then prepares the grounds for call by opening four ports for videoconference communication. These ports are incoming audio stream data and control ports and incoming video data and control ports. Then a special videoconference call message, containing callers credentials, and callers terminal IP address is sent to the called terminal's IP to videoconference control port, polled by the call control. The server is also notified about the user status change to busy. Called user is notified about the incoming videoconference call which can be either accepted or rejected. If rejected, a reject message is returned to the calling telemedical application which upon reception of the message notifies its user, closes the incoming audio video ports and notifies the server about user status change to available. If accepted, the caller's call control opens the incoming audio and video ports and returns call accepted message to the caller and notifies the server about user status

change to busy. After the connection initiation, the AVT component starts transmitting the audio stream from the terminal's microphone and the video stream from the terminal's camera to the caller's incoming data ports. When called call control receives call accepted message it also initiates AVT component to start transmitting audio and video streams to the calling telemedical application.
AVT component uses G.711 (U-law) 8 kHz codec for audio transmission. For video transmission H.263 in SQCIF resolution (128x96) codec is used. QCIF (176x144) and CIF (352x288) resolutions are also supported. RTP (Real Time Protocol) and RTCP (Real Time Control Protocol) protocols are used to transmit audio and video data streams and to control them.
When either of users in the videoconference call decides to break the connection the call control notifies other side about the break connection and both sides stop transmitting video. On that event both call controls notify the server that the user's videoconference availability has changed to available.

8.6 Server application

The server side is the core element of the telemedical system. It comprises of several components. They are main server running the telemedical application modules, database and management tools, VPN server with router, backup data storage and GSM module.
Current main server hardware is a server computer with redundant power supply (2x hot swappable + UPS) and redundant disk storage (RAID 5, hot swappable), located in a protected and clime-controlled server room at the Blood Transfusion Centre of Slovenia. The server is running Debian Linux distribution. The server side of the telemedical system consists of in Java written servlets, listening to the incoming POST and GET messages from telemedical applications – clients. Servlets are served by the Apache Tomcat application server. Running servlets are the main telemedical servlet, certificate authority servlet and SMS notification servlet.
The main telemedical servlet is responsible for the user authentication, receiving and storing of the telemedical data from client telemedical applications and serving the telemedical data to the telemedical applications. All communication in the system is initiated by the telemedical applications through sending specially formed messages to the telemedical system servlets. Messages contain data containers with action commands. Main servlet is functioning according to the user rights matrix which contains definition of rights for each user of the system.
Certificate authority servlet is responsible for storing and serving public keys of user certificates along with user details and certificate details such as validity and revocation status.
SMS notification servlet is responsible for relaying messages to user's mobile telephones via to the server attached GSM module.
All actions of the system are logged in log files, to provide complete system usage traceability.
On the server several support processes also run. These are telemedical system maintenance program responsible for the maintenance of user statuses (if user has not properly logged off from the system this process cleans after unclean user logoff. Unclean user logoff occurs in cases of shutting down the telemedical terminal without logging off). Another support process is a process for regular backup of the data to the external data storage. It periodically performs a complete system backup to the external data storage media. For

implementation of backup AMANDA package is used. Further support process running on the server is server status and load monitoring process MUNIN which is used to supervise server's operational parameters.

Another part of the server setup is a VPN server – router. It is responsible for handling all incoming VPN connections and routing of the traffic within the telemedical network.

8.7 SMS notification

Short text messages (SMS messages) are used to notify users about system events through their mobile phones. Our SMS notification system comprises of a GSM module connected to the server via the serial cable and a SMS notification servlet. When a need for sending an SMS occurs in the system, a SMS send request message is sent to the SMS notification servlet. These messages are sent by telemedical applications, when it is necessary to notify the users about telemedical system events requiring their attention. Notified events are "question received" and "answer received" respectively. The message sent from the telemedical application to the SMS notification servlet contains authentication data, recipient mobile's number and actual message. The servlet interprets the message and via AT command set communicates the attached GSM module to send the message. Alternative to this approach would be a direct link to the mobile telephony operator, but this approach would need a direct connection to the internet from the telemedical system, which would be a security issue.

8.8 Database

All data of the telemedical system is stored centrally on the server data storage. Data storage consists of two modules. The first one is the relational database and the second one is the file system. The relational database is used to store all telemedical system data except images of gel-cards. Images of gel-cards are stored on the server's file system and references to these image files are recorded in the database.

The database engine used in the current version of the telemedical system is MySQL database, version 4.1.11. It contains various tables for different data objects such as gel-card image meta-data, question data, answer data, user details along with their rights, patient data and public keys of user certificates along with their details.

Files of gel-card images are stored on the file system under unique names, which are determined centrally to avoid file name collisions from sessions originating from different clients.

All data is daily backed up. Since system is online constantly it would be impossible to make system backup by just copying database files. To make a successful backup of the database a database dump operation is performed. Database dump creates a single file containing all database data at the moment of the dump. Dump file is than be backed up along with the gel-card image files. Several versions of system backups are stored enabling system rollback.

8.9 Communication

Telemedical network was established to provide data transfer between system nodes. It consists of a public packet switched data network Internet as a baseline communication network, routers with VPN gateways and a VPN server.

Internet was chosen mainly for economical reasons. Since public network Internet does not provide any level of security, VPN technology was used to create encrypted tunnels through the public network. All nodes of the system are equipped with routers with VPN gateways. Routers are configured to automatically establish a tunnel, connecting to the VPN server. Therefore connectivity is assured even if the Internet connection of certain node has been drooped and re-established. The VPN server serves as a hub for all traffic between system nodes. All traffic generated in the system passes through it. Because of the client-server architecture of the system the majority of data transfer is accomplished in direction from client to server and vice-versa. A teleconsulting system server is collocated with the VPN server. They are connected by a fast local network connection. Therefore this, on top of the Internet imposed star topology setup, does not introduce data transfer bottlenecks.

Usage of the VPN technology ensures encrypted data transfer, hiding all data from unauthorized parties. It also assures terminal and server authentication, eliminating the man-in-the-middle attack possibility. All terminals are connected to the VPN ports of the routers to which only VPN traffic is routed. Therefore the terminals are invisible from the public network thus eliminating the security threats in form of worms which lurks in the public Internet.

The majority of data between system nodes is transmitted through HTTP protocol's POST messages. Exchanged POST messages contain serialized data containers and are used to transmit data between terminals and server. Data containers contain proprietary data fields for data such as patient name and surname, birth date, gel-card images, question data, answer data, etc.

Videoconference data is transmitted through RTP protocol via UDP connections, established through the telemedical network.

Communication between existing hospital information system and telemedical applications is established through combination of the telnet and FTP protocol.

Communication between the server and the MySQL database is established using the standard SQL language queries. SQL queries are relayed to the database through Java language specific API library JDBC.

Communication between teleconsulting applications and SMS notification server is accomplished using HTTP protocol's GET messages.

Network operation is constantly monitored by a special monitoring application, residing on server side of the system, which constantly checks if all nodes of the teleconsulting system are reachable through the telemedical network. If any of the nodes cannot be reached, the monitoring application notifies the maintenance personnel about the communication failure. Notification messages are sent via SMS and via e-mail messages.

9. System usage analysis

Since all data of the telemedical system is stored in the central server's database, the system usage analysis was relatively simple. Used database MySQL can be queried using SQL queries through on the server installed database management system phpMyAdmin. Since the telemedical system must be online constantly it was not acceptable to perform system usage analysis on the live database due to possibility to make an error, which could corrupt the data. Therefore the data was extracted from the live database by executing a database dump. Resulting dump file was then used to create an offline database clone on which the analysis was then performed. Analysis was performed using for this purpose formulated SQL queries. A of number of telemedical sessions, number of signed telemedical sessions and number of transmitted images of gel-cards was analysed through time.

10. Results

The pilot version of the telemedical system was first developed and installed into the National reference immunohaematology laboratory within the Blood Transfusion Centre of Slovenia and into the transfusion laboratories of two hospitals (60 and 80 km distance, respectively). This pilot setup was intended to test and validate the telemedical system before the production version is installed into every transfusion laboratory.

Validation was performed using a series of 99 cases taken from the everyday routine. During the validation procedure immunohaematology experts first performed the read-out of the pre-transfusion tests on gel-cards by using the telemedical system. These read-outs were then repeated by independent experts using the standard visual method. There were no statistically significant differences between the proportions of correct read-outs and final result interpretations using the telemedical system and using the standard visual method (Meza et al., 2007).

After a successful pilot installation and validation all transfusion laboratories in Slovenia were equipped and connected into the telemedical system. A new organisation structure was introduced. Figure Fig. 11 illustrates the organisation of the telemedicine in transfusion of Slovenia. Two expert centres are offering 24/7 immunohaematology expertise to the hospital transfusion laboratories. In some of the shown hospital transfusion laboratories the afternoon and night shifts does not have immunohaematology expert present. These hospitals rely solely on the expert from one of the expert centres (Bricl et al., 2010).

Currently the system is in operation for 4 years and was used for 6300 consultations. During these consultations 17200 images of gel-cards were transmitted and analyzed. Of 6300 consultations, 4900 were digitally signed and can therefore be considered as valid diagnoses. Using the system, the time required for the pre-transfusion test interpretation of ambiguous cases was significantly decreased. In majority of cases, the time was decreased from several hours (required for the courier delivery of the samples to the reference laboratory) to only a few minutes.

Fig. 11. Organisation of the telemedicine in the blood transfusion service of Slovenia. Two expert centres are providing blood transfusion expertise through telemedical system to the hospital transfusion laboratories.

Smaller transfusion laboratories were also relieved of the requirement for 24/7 on duty transfusion specialists, since the expertise needed is provided through the telemedical system. Their operation can now be sustained even if transfusion specialist is not present only by the laboratory technician. Therefore, the system has introduced substantial savings to the national blood supply. Exact data about savings is matter of other study, which results will be published shortly.

11. Discussion

Telemedical system was introduced into the transfusion practice of Slovenia. Slovenian transfusion practice follows EU transfusion directives (Rozman & Domanovic, 2006). Therefore solutions, working in Slovenia are likely to work in other countries, following same directives. Since Slovenia is relatively small country, compared to other European countries, it is ideal test field for new approaches.

Our telemedical system supports remote interpretation of the pre-transfusion tests which is, as far we are aware, a new approach in the field of transfusion medicine. The system is based on the detection of the red cell antibody reactions resulting in direct red cell agglutination. Currently, the system supports agglutination detection, performed using the most widely used Diamed® micro tube gel-cards. The system can easily be modified to support other micro tube gel-cards. With further modifications, the system can also support other red blood cells agglutination detection methods. Using the system, the most important phase of the test – visual readout is performed remotely by immunohaemathology expert.

The system enables detailed and integrated patient transfusion treatment by providing the patient's previous anamnesis and transfusion history, obtained from the existing hospital information system. To provide the integration, the current information system, supporting transfusion service of Slovenia was studied and integration module was implemented. Since this information system was custom built, it would be necessary to repeat this process in case the system would be installed into other transfusion service.

The language of the system's user interface is Slovenian; therefore the system should be translated into other language if required.

Since EPR (electronic patient record) standards and widespread systems did not exist during the time of system development in future it will be necessary to develop data interchange module between our system and EPR systems.

Overall, the telemedical system was relatively well accepted among its users, regardless of quite a few problems during its initial pilot phase. We believe this is due to the involvement of its users into early stages of the system development. By including users into the development process, they have adopted the system as their own project and have tolerated higher number of errors, which would otherwise deter them from using the system. Another factor affecting the acceptation level is well organized education of the users and quick resolution of the problems they encounter.

At first the system was intended to serve as a consultation tool in ambiguous cases, but it evolved into a system enabling operation of the transfusion laboratory without immunohaematology expert present. This sprouted the need to provide legally sound electronic documents, which was satisfied by the digital signature infrastructure.

The system is relatively new with many modules, which were not jet long term stress tested. Since some laboratories sometimes depend solely on the remote immunohaematology expert available through the telemedical system, flawless system operation has become critically important. To provide flawless system operation a process of identification and duplication of system critical components was started in order to provide redundancy and increase overall system's reliability. On the top of everything a procedure protocol prescribing manual work without the functional system was also established.

Another interesting fact observed, was usage of the system as the digital magnification glass. Since the system enables up to 20 times magnification of gel-card images without any visible distortions, users use the system just to capture images of gel-cards to magnify them and observe and interpret them magnified.

12. Future work

Sometimes the interpretation of pre-transfusion tests is mundane and tiring. After whole day shifts mistakes can easily slip in. A welcoming upgrade of the telemedical system would be a system that automatically interprets the pre transfusion tests in parallel to human. If human determined results differ from the automatically generated ones, the system would warn the user. Through the use of the telemedical system a significant dataset of diagnostic data and corresponding interpretations was accumulated. Acquired data was used to build the model of the human interpretation process using the machine learning methods. A set of suitable methods was chosen through evaluation of the accuracy of the model built by those methods. Future research will be focused on the model improvements and introduction of the model into the production version of the telemedical system. The model will be used for error control of human actions.

Another future research focus is planned on identification of other types of diagnostic medicine, where the developed approach could be used. Prospective are diagnostic methods, based on visual interpretation of diagnostic data, where creation of diagnostic data is straight forward and does not require examiners interaction like in the process of ultrasound examination. Prospective candidates are x-ray imaging, CT imaging, etc...

Another focus of the future work will be support of one of the standards for medical record exchange. Currently prospective standard is open specification for interoperable, electronic health record, specified by the non-profit Foundation openEHR.

The system functionality will also be extended to serve as an archiving tool for all pre-transfusion tests, not only for those which required remote interpretation.

13. Acknowledgements

The system was financed and developed within cooperation of the Faculty of Electrical Engineering, University of Ljubljana, KROG-mit d.o.o. company and the Blood Transfusion Centre of Slovenia. Special thanks go to mag. Marko Breskvar, prim. Irena Bricelj, prof. dr. Jurij F. Tasič and prof. dr. Primož Rožman. This work is supported in part within the research group "Algorithms and optimization methods in telecommunications".

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10

Telemedicine as an Aid to Clinical Practice, Research and Education in Plastic Surgery

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1. Introduction

Telemedicine has the potential to expedite and improve the delivery of high-quality, cost-effective care by extending the reach of health care practitioners (or patients themselves) beyond their local setting, using advanced information technologies. Plastic Surgery relies to a significant degree on visual modes of telemedicine to transfer medical information for diagnostic, physical examination, and outcome measure purposes; therefore, this specialty in particular, derives major benefits from telemedicine. At the same time, telemedicine benefits from Plastic Surgery by providing an opportune model for research and for testing new developments in this technology. The two basic modes of telemedicine applications: store and forward (asynchronous transfer) and real time transmission (synchronous transfer, e.g., videoconference) are both utilized in the plastic surgery setting. Intense reliance on both static and dynamic images distinguishes this specialty to an even greater degree than dermatology as a model for telemedicine research and development as well as for an educational tool (Meyer & Friedman, 2010). Both physicians and patients have been surveyed for their perspectives on the introduction of telemedicine in plastic surgery, and their acceptance for the technology is high. Both parties assign telemedicine positive ratings in satisfaction surveys, although some potential problems with practical solutions have been noted and will be presented below.

Objectives of early studies included assessing the accuracy and usefulness of telemedicine consults in aesthetic surgery, reconstructive surgery, and problem wound care. Comparisons were made between consultations provided via telemedicine to those provided by a direct or face-to-face consultation. The specificity, sensitivity, and positive predictive values of equivalent (or different) diagnosis and potential treatment plan were calculated. We made the assumption that a correct diagnosis and indication (or lack thereof) for surgical intervention was established during direct consultation. Agreement levels between the two assessments (telemedicine and face-to-face) were judged by an independent surgeon. Typically, agreement rates were categorized as follows: total agreement, trivial disagreement (error not changing the overall management plan), and clinically important disagreement (error requiring change of approach after face-to-face consultation). Many studies show evidence of adequate overall accuracy of telemedicine as a tool in research, education and clinical practice in plastic surgery (Dobke MK et al., 2006; Dobke MK et al., 2007; Dobke MK et al., 2008; Dobke MK & Gosman A, 2009; Gosman A et al, 2009).

2. Positive impact of telemedicine on triage and management of problem wounds and other conditions by plastic surgeons, and as an example of practice pathway improvement

Telemedicine offers efficient access to specialists for patients with chronic problem wounds, eliminating the emotional and physical stress related to transporting patients to hospital/clinic settings. It allows for an immediate, relatively accurate, preliminary management step for patients prior to direct evaluation in the hospital, wound care clinic, etc. Dobke MK et al., 2006, studied the impact of telemedicine for triaging and developing management plans for patients with chronic, problematic wounds in long-term care, skilled nursing, and home care settings. Telemedicine was also assessed for its usefulness in enhancing communication with the surgical wound care specialist.

From: xxxxx@email.com
Sent: May 13, 2008 9:24 AM
To: xxxxx@email.com
Subject: Emailing: 050808 001.jpg

This patient is 96 years old, Wound measures 3.2 x 2.5 x 0.6 red with thin scattered fibrin, with slightly bloody drainage. At present the treatment is Silvasorb. This patient is new to this homehealth, so no one knows much history on the wound. They say that this was something that happened many years ago and it heals then she scratches it and it reopens. I think maybe a biopsy should be done, What do you think?

The message is ready to be sent with the following file or link attachments:
050808 001.jpg
Note: To protect against computer viruses, e-mail programs may prevent sending or receiving certain types of file attachments. Check your e-mail security settings to determine how attachments are handled.

Fig. 1. Telemedicine for the Outreach Wound Program: A “field” nurse from a home health care facility sent this email to a surgical specialist detailing a summarized patient history with the corresponding photograph (right image) from a patient being originally referred to a Wound Care Clinic. Based on the patient history (17 year history of a non-healing apparently post-traumatic left malar area wound) through a telemedicine assessment, the patient – with the approval her primary care physician – was redirected to a Plastic Surgery Consultant since surgical intervention was likely. Patient management was streamlined based on telemedicine consultation: the problem wound was identified as a squamous cell carcinoma and she underwent appropriate ablative and reconstructive treatment. Experience of others confirms that referral by digital image for skin malignancy and other cutaneous lesions is a safe, accurate and cost effective referral pathway. This significantly reduces the time interval between referral diagnosis and onset of treatment for the malignant condition (Tadros A et al., 2009).

In this study a trained “field” nurse (RN and LVN) assessed 120 problem wound patients in an ambulatory care setting between January 2003 and December 2005. The nurse relayed a summarized history, laboratory results (if any), and photographs via email to the surgical specialist establishing an asynchronous transfer mode of telemedicine. Following an initial assessment and management plan, including diagnosis via telemedicine consult, the patient was also evaluated in person by a board certified plastic surgeon within two weeks of the initial consult request. The diagnosis and indication (or lack thereof) for surgical intervention was compared between telemedicine consult and face-to-face consult with the assumption that direct consult provided the correct treatment plan.

Telemedicine consults provided accurate assessment with only 1.67% (2/120 cases) change in diagnosis during the direct consultation (Dobke MK et al., 2006). The overall sensitivity of telemedicine-based problem wound assessments (as measured by correctness of establishing an indication for surgical intervention validated by the direct consult) was 94 %, specificity was 99%, and the positive predictive value was 94%. Overall, a telemedicine consult used as a decision aid is effective, relatively accurate, and streamlines the management process (Fig. 1).

The Association for the Advancement of Wound Care (AAWC) guidelines, advise treating chronic wounds with multidisciplinary teams (MDTs) of specialists due to the frequent complexity of pathology leading the wound and high incidence of co-morbidities (AAWC online, 2007). Additionally, problem wounds require prompt treatment so management systems should reduce or eliminate redundant time spent by MDTs developing treatment plans. However, in a retrospective study (Dobke MK et al., 2007), a database of 120 patients was analyzed to determine whether every patient management plan had to be formulated by the multidisciplinary team. Agreement levels between the initial management plan established by the surgeon after the telemedicine consult and the final management plan by the MDT based on direct, comprehensive consultation were judged by an independent investigator. There was a 93.6% concordance with the management plan established by the surgeon based on the telemedicine consult alone in comparison to the plan established by the MDT with direct patient contact. This study showed that telemedicine technology in the hands of an experienced physician could streamline management of a problem wound.

Regarding patient follow-up and measuring treatment outcomes, specialty facilities or home care wound management programs using telemedicine found that telemedicine facilitated communication between health caregivers from outside to inside the facilities. This improved outcomes and provided a new benefit for home care by eliminating the barrier to accessing distant plastic surgeons involved in wound care programs (or other specialists). This study established that the low availability of specialists in wound care programs and the corresponding hindrance for rapid treatment can be ameliorated by telemedicine. (Dobke MK et al, 2006; Terry M et al., 2009).

Similar to the application of telemedicine to the wound care population, the overall accuracy of telemedicine consults as applied to facial and breast aesthetic assessment demonstrated high sensitivity, specificity, and positive predictive value and greater than 95% confidence interval. This is close to "gold standard" care in terms of the accuracy of diagnostic tests comparing telemedicine to direct consultation. Furthermore, management proposals established on the basis of telemedicine consults were rarely changed after direct face-to-face consultation. When changes were implemented they were typically dictated by patient preference (Dobke MK et al., 2009).

Limitations of telemedicine in plastic surgery are related to the quality of images and to the absence of data one would obtain by a direct face-to-face physical examination such as information obtained by the "tactile" part of physical examination (e.g., flap or replant tissue turgor). Optical problems may impact both static and dynamic visual observation

(Fig. 2). Poor quality of images (300 dpi or less), "pixelization" of the image, and/or perspective distortion may lead to clinically important differences between an electronically transmitted photo and direct examination. This may result in an erroneous proposed diagnosis and management plan (Dobke MK et al, 2006).


Fig. 2. Clinically important disagreement between the "telemedicine" and the "face-to-face" assessments. The image on the left shows a patient who transmitted her image from her cell phone and stated that she was kicked by a horse into the right side of her face and nose. With this history and the phone image strongly suggestive of the deviation of the nasal pyramid (left image) the tentative diagnosis of nasal fracture was established. On the following day the patient was seen in the clinic and her nose appeared to be only mildly swollen (right image). There were no signs of the nasal fracture or deformity. It appears that the cell phone photo held by the patient's right hand, diagonally, 45 degrees to the right in relation to the patient face, created a non-polarized image with perspective distortion leading to the clinical misjudgment.

3. Technical considerations relevant to plastic surgery

Selecting a camera for use in plastic surgery telemedicine requires consideration of various capabilities and features. Consideration of key optical parameters such as color bit-depth, white balance, focus, and macro is important. As mentioned above, image quality cannot be low, however it cannot also be impractically high, requiring lengthy downloading time and lengthy transfer time. This can be especially problematic when transferring multiple high-pixel files from "the field" to the specialist. Therefore, excellent compression to reduce image file size and retain relevant details is a valuable and desirable feature (Patricoski C et al., 2010).
There are two general types of image compression: "lossy" and "lossless." Lossless compression guarantees that the process of compressing and decompressing an image will

not alter the image in any way. However, the rate of image compression is relatively low, typically 2:1. Much better rates of compression can be achieved by using Lossy compression. Lossy compression systems discard some information from the image, usually by removing small differences in pixel color that, ideally, are inconsequential (e.g., plastic surgery documentation frequently uses Joint Photographic Expert Group, JPEG)(Jones SM et al, 2004). In plastic surgery applications it is important to test the image compressing ratios and determine the maximum compression of the image for speedy transfer that will retain the minimum image quality for accurate clinical decision-making from the recipient (Patricoski C et al, 2009).

Fig. 3. Telemedicine in action: quick communication between the primary care physician office and surgical specialist streamlines decisions regarding how quickly the patient should be seen. In this case simple transmission of patient's x-ray facilitated his care: the patient who fell on outstretched hand the evening before was asked to come see a surgeon for reduction of his radial fracture on the same day he saw his primary care physician, and actually was scheduled for surgery prior to his arriving to the Plastic Surgery Clinic.

In the case of videoconferencing, with dynamic image transfer there can be network bandwidth limitations from "the field" or at the specialist's location. Frequently, teleconferencing with clinics in remote or international locations which only have access to basic network systems necessitates a bandwidth quality that may be a communication obstacle. In this case, the teleconference becomes limited to the slowest bandwidth in the conversation.

Overall, however, cutting-edge technologies supporting telemedicine are used in wound care and plastic surgery. For example, a camera coupled to a hand held computer for data registration and encrypting that meets regulatory medical records requirements. Additionally, there are systems which interface with existing health care systems that facilitate care delivery (Fig. 3).

It is imperative that the access to and transfer of medical information by telemedicine modalities meet regulatory requirements regarding patient privacy (e.g., HIPAA in the United States or ISDN security in the United Kingdom). By equipping healthcare workers with mobile handheld computers which offer the security required for sensitive healthcare data transmission (e.g., ES400, Enterprise Digital Assistant (EDA) by Motorola, US), physicians and others healthcare professionals will be able to exchange data, communicate, and collaborate rapidly. The Silhouette Mobile by Aranz Medical in New Zealand is a portable, hand-held computer device with an integrated high-resolution camera designed specifically for the wound care and plastic surgery professional. This camera has embedded laser lighting for automated image calibration. Silhouette exports data in standard formats (running Windows Mobile 5 operating system) and is designed to support HIPAA compliance. These mobile devices will ultimately increase access and quality of care.

4. Patients' perceptions

The literature and our own observations indicate that telemedicine is well received by patients. Fears that patients will reject "anonymous" electronic communication between the patient and physician, or physician and specialist, appear unsubstantiated.

During our studies of implementing telemedicine as a decision aid for patients with chronic wounds we also evaluated the impact of telemedicine on the patient. This was measured by assessing the duration of the face-to-face consultation after or without intermediate telemedicine consult, the patient's satisfaction with care decisions, and a decisional conflict scale. The average face-to-face consultation was decreased from 50 ± 12 minutes to 35 ± 6 ($p < 0.01$) minutes for patients who had received a telemedicine consult prior to the direct consultation. Moreover, patient satisfaction with care decisions was dramatically increased (93% vs. 47%) when patients were involved in a preliminary telemedicine consult. Patients experiencing the added initial telemedicine consult reported improvement in both the understanding of their care and in their perceived involvement in shared decision making regarding their care. Finally, the decision conflict scale, which measures uncertainty over wound care management plans, was reduced from 35 ± 4.26 to 14 ± 1.73 ($p < 0.001$) in patients subjected to telemedicine decision aid. This shows that there is added confidence in the wound care management plan when a telemedicine consult is included in the treatment plan (Dobke MK et al., 2008).

Telemedicine consultations provide accurate assessment for the treatment of problem wounds. They are well received by patients and have the potential to expedite and streamline care for patients with chronic wounds. The addition of telemedicine as an initial, intermediate communication step with a patient seems to educate the patient and ultimately enhances a bond with a specialist-consultant.

The following two examples illustrate positive outcomes for patients who experienced telemedicine in a long-term and interactive manner. Fourteen patients with traumatic brain injury underwent a series of 60 Internet-based cognition rehabilitation sessions to foster their acquisition of compensatory strategies to diminish memory loss and other cognitive impairments as well as to help increase quality of life (Berguist TF et al, 2010). Traditionally this rehabilitation is long, face to face, intensive, and patients are frequently confronted with the usual barriers to access rehab/medical centers (transportation, cost, etc.) The teleconferencing patient participants were subsequently surveyed regarding their satisfaction and comfort with the experience as well as their willingness to receive this mode of care again. The study showed that the patients were not only willing to participate in cognitive rehabilitation treatment over the internet, but that they were satisfied with the treatment and would be willing to receive care the same way again. Such positive outcomes for long-term rehabilitation lends support for new endeavors in plastic surgery to provide long-term rehabilitation to wound-care and reconstructive surgery patients, such as speech therapy for repaired cleft palate patients.

Telepractice is another application of telecommunications technology to deliver professional services at a distance by linking a clinician to client (American Speech-Language Hearing Association, 2005). In an analysis of telepractice as a tool for training parents as agents of intervention for children with early autism, satisfaction was surveyed (Baharav, E & Reiser C, 2010). Parents were found to be comfortable with the telemedicine technology, and stated that it was essential in the treatment of their child. They stated a preference for continuing with the use of telepractice to deliver therapy to their child and that they would recommend it to others. This is an example of how, in the future, physicians or health care providers would be able to provide support, education and fast answers to questions of family members who are caring for loved ones with a disease or condition that requires intensive health care education.

Finally, in separate studies within transcultural and translingusitical environments (e.g., a Cleft Lip and Palate Program in Mexico coordinated from the U.S.), indicate very good reception of telemedicine as a modality of contact between a consultant and childrens' parents regardless of linguistical, cultural or economic differences (Brigden M et al, 2008; Kipps K. et al, 2010).

5. Physicians perceptions

A survey of physicians who are clients of telemedicine services indicates overall good satisfaction rates and revealed that telemedicine could result in an earlier initiation of treatment than conventional delivery of care (Bridgen M et al, 2008). Additional studies indicate that experience with telemedicine results in more positive attitudes towards this technology and more opportunities for use in their practice. Concerns that a telemedicine consultant may take over patient management and negatively impact the primary care health care practitioner practice, as espoused, by those questioning the suitability of the tele-consultations, are unfounded. Potential problems with continuity of care and uncertainty about the follow up process were not experienced. (Brigden et al, 2008; Dobke et al, 2006; Dobke et al, 2008; Hanson D et al, 2009). Observations of members of a university center and "field" plastic surgery team did not reveal concerns that there might be generational differences in acceptance of telemedicine technology, particularly in the case of plastic surgery health care providers (Loera JA, 2008). Members of plastic surgery teams indicated that the actual primary benefit of telemedicine availability is an improvement in the ability to consult others. This benefit ranges from immediate intra-operative consultations, to supporting isolated clinicians, enhancing education, and providing peer review.

There are some potential problems that have been raised by physicians when surveyed. Some general issues, not necessarily pertaining to plastic surgery, that have been raised include: problems with continuity of care, a need for improving patient comfort level with the telemedicine technologies, and absence of a complete physical examination (Bridgen M et al, 2008). Potential solutions for improving continuity of care would be avoiding referral for services that could be delivered locally, communicating a clear follow-up plan and having the specialist follow-up directly with the local family physician. To improve patient comfort with the technology a pre-orientation for new patients was suggested as well as the provision, for language difficulties, of an available and reliable translation service and technical coordinator during the consultation. As for improving the unavoidable lack of a complete physical exam, it was suggested that the local referring physician, just as is frequently practiced by community or rural emergency departments, be present to the consultation so they could provide an extra pair of hands for an exam directed by the specialist during the teleconference.

Ultimately, the success of telemedicine for patient diagnosis and treatment depends on the support and willingness of physicians and other healthcare providers (Hanson D et al., 2009). This motivation often depends on physicians experience and attitudes with prior telemedicine experiences even it is just a single prior exposure. As described above, experience with telemedicine increases a physician's predisposition to use telemedicine in their practice and even augments the breadth of implementation in different facets of his or her practice. Other ways to enhance physician acceptance is to have support from a sponsoring organization, provide structural legitimacy and a cohesive network (May et al, 2003).

6. Video conferencing as an operational, research and educational tool

The effectiveness of two way video conferencing for transmitting live video and audio of craniofacial consultations and reconstructive operations was evaluated for its potential to facilitate intra-operative consultations and enhance quality of instruction for students (with live surgery in a remote location). Prior research demonstrated that students who participated via videoconferencing remotely asked four times as many questions of the faculty, and vice versa faculty to students, than occurred when students were physically present in the operating room. Feedback from the study showed that students gained more from the telemedicine experience than from being physically in the operating room as measured by several objective and subjective criteria (McIntyre T et al., 2008).

A craniofacial operation was specifically selected for use as a telemedicine case report due its complexity, frequent need for intraoperative discussion, reliance on the input from multi-disciplinary consultants, and, in the studied case, the international approach. Unlike telementoring projects which are hierarchical in nature, where one party is the teacher and the other party is the student, this project was more of a collaboration. There is a telemedicine unit in the children's hospital operating room at the Hospital Infantil de las Californias in Tijuana, Mexico that authors and their associates currently use to record and watch operations while they occur in real time. This is a specifically ordered unit for telemedicine purposes from Lifesize Communications, a division of Logitech. The computer is connected to a high definition camera and microphone on top of a videocamera crane. This allows for visualization of operations while they are occurring, both in high definition and with a bird's eye view.

The operating room teleconference unit has been a popular education tool for University of California San Diego, School of Medicine students. Students are able to watch operations in optimal video and sound quality from a classroom in La Jolla, California. Frequently a non-operating member of the team may speak to students focusing on educational aspects of the surgery without taking time and focus away from the operating surgeon. Students are able to talk and ask questions of the surgeons directly, albeit briefly, while they operate. This has been a convenient and uniquely accessible venue for exposing students to pediatric plastic surgery, international health and volunteer work for underserved populations.

Telementoring may also serve as a sustainable way to bring mentors and trainees together in regions of the world with a shortage of certain specialists, educators, mentors, public facilitators and organizers of care (Fig. 4).

Fig. 4. Teleconferencing with the Peten (Guatemala) jungle "Plastic Surgery Clinic". This is a patient (9 year old boy) after surgical release of severe postburn axillary and antecubital fossa contractures. The patient is being guided by non-medical staff to demonstrate the range of motion of his upper extremities. A new physical therapy regime for self-implementation is being discussed. The cameraman in the background is from Guatemalan TV making a film about telemedicine for public education.

In one case study, a 7-year-old male patient in Tijuana, Mexico received microvascular reconstructive surgery to treat hemifacial microsomia (Gosman AA, 2009). The standard of care for hemifacial microsomia, a complex congenital problem, is a multi-disciplinary team. A team of volunteer specialists from Mexico and the United States participated in this rare and technical operation. Additionally, during part of the procedure, a teleconference set up between the operating room at the Hospital Angeles in Tijuana, Mexico and a group of medical students, residents and plastic surgery specialists at the University of California, San Diego. In fact, teleconferencing was evaluated, for its ability to extend the multi-disciplinary team beyond the walls of the operating room.

A low-tech videoconference system was set up using the free and universally available Skype software, which is both encrypted and compliant with Health Insurance Portability and Accountability Act regulations. The study evaluated the effectiveness of the two-way tele-communication for potential ad hoc consultations during the operation on an as needed basis. It was found that telemedicine would contribute to a multidisciplinary approach, and that it would in fact facilitate an improvement to follow-up with postsurgical patients from a distant location. After volunteer surgeons return to their respective hometowns, they along with other members of the multi-disciplinary team would be able to track the recovery of their patients remotely.

7. Assessing outcomes and providing long-term care in plastic surgery

Another area of ongoing research in telemedicine is to evaluate its use as a tool to assess outcomes in plastic surgery, such as in cleft and palate surgery (Fig. 5). In particular, we are studying it as a means of providing effective speech therapy for cleft palate patients. This exemplifies the potential and rapidly growing application of telemedicine in reconstructive surgery as well as its increasing role as a clinical practice, research and plastic surgery education enhancing tool.

Our current, across-the-border telemedicine projects, in transcultural environments, (San Diego to Tijuana, Mexico and San Diego to a medically unsupervised location in the jungle of Peten, Guatemala), include a collaboration with the Cleft lip and Palate Clinic in Tijuana, Mexico based at the Hospital Infantil de las Californias (to which a reference was already made above). Here we are performing an evaluation of whether speech therapy can be provided over a teleconference unit. Bilingual speech pathologists evaluate patient speech in real-time from San Diego, California. The child sits in front of a camera and video screen and follows the directions of the speech pathologist. Frequently, the child's parent or guardian will have to help manage the encounter and provide support to certain speech exercises such as assisting in holding closed the child's nose to prevent nasal emission. The equipment used for this collaboration includes two teleconference systems, one located in a physician's office in San Diego, California and the other is in the patient exam room of the Hospital Infantil in Tijuana, Mexico. The San Diego office utilizes a Polycom Viewstation teleconference system with a variable zoom (5.4-64.8mm) camera and the exam room in Tijuana is visualized using a TV screen. The exam room in Tijuana uses a desktop computer with videocamera and monitor for its teleconference, using a program called Viewpoint HD. Preliminary experience demonstrates that transmission of acoustic data may be equally challenging as the transmission of visual images.

This study is valuable because it may provide experience in telemedicine coupling vision and voice data. It may show that it is not only possible to provide speech therapy but also assess outcomes without being face-to-face, which could increase access to many patients in

Mexico who are in great need for speech therapy. This would conceivably alleviate a large unmet medical need to an underserved population that does not currently have access to speech therapy. In fact, there does not even exist a speech therapy profession in Mexico. Additionally, this could potentially be a model system for other international telemedicine therapy programs that would be able to provide continuous care treatment beyond the more typical use of telemedicine which has a focus on individual one-time case based interactions. As described earlier, local studies in telepractice have proven positive results integrating long-term treatment plans to parents of children with autism and to brain injury patients undergoing cognitive rehabilitation.

It appears that the delivery of healthcare through telemedicine in the field of plastic surgery to medically underserved patient populations, or even unsupervised settings is safe and meets demands of rural or wilderness settings. Plastic surgery surgical intervention outcomes did not seem to be impacted negatively by the telemedicine and remote management of certain components of the overall care. Patient participation in our telemedicine programs was completely voluntary, and yielded a high satisfaction rate reaffirming experience of other investigators (Nesbitt TS et al., 2000). Also, experience with

Fig. 5. Video-conferencing with a medically unsupervised remote Plastic Surgery Clinic in the jungle of Peten (Guatemala). The patient demonstrates to the nurse located in the Clinic in the US how well her repaired cleft palate healed. It is possible to provide basic speech assessment during video conferences as depicted in the photograph. Noteworthy is this patient's (and other children) eagerness to pose to the camera. This "Hollywood-Effect" observed when patient poses to the camera vanishes frequently, during a face-to-face encounter with a health care provider armored with a tongue blade: children frequently do not cooperate.

telemedicine consults indicate that the transcultural delivery and the presence of interpreters does not reduce the patient and or families satisfaction rates (Kipps K. et al, 2010)

Many telemedicine projects were implemented in remote areas where, by necessity, technical arrangements were limited by availability of Internet and technical equipment. However, wherever possible, the video teleconsultation should consist of a secured Internet Web-based application, a personal or even hand-held computer, a broadband Internet connection and a digital camera. There is an increasing body of evidence that video consultation has added value to the quality of care in plastic surgery and other specialties (Visser et al, 2010).

8. Future of telemedicine in plastic surgery

As technologies supporting telemedicine are developed and perfected they will help to advance plastic surgery into the digital era. Telemedicine will certainly help in globalization of plastic surgery delivery. This technology will be instrumental in addressing basic needs in medically underserved areas and the most complex surgical needs by enabling sophisticated expert consultations. With both technological advancements and growing physician exposure, telemedicine will continue to thrive in increasing applications.

Ultimately, telemedicine will be essential for the development of remotely steered or assisted procedures, both robotic and traditional, performed by a human health care professional. This too will be utilized to improve access to specialists in plastic surgery in remote national and possibly international locations.

Finally, the development of home telemedicine programs for direct communication between a plastic surgeon and a patient at home may facilitate an improved quality of care. This could occur, for example, by means of as little as a cellular phone with a camera. This will hopefully enhance postoperative follow-up by improving time spent between specialist and patient.

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11

Telemedicine in Dentistry (Teledentistry)

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1. Introduction

As expected, technologic innovations in the field of dentistry have been extensive in recent years. Most important advances have been made in the use of computers, telecommunication technology, digital diagnostic imaging services, devices and software for analysis and follow-up. Nowadays, it is hard to imagine a dentistry clinic without computerized patient registry, electronic invoicing, digital radiography, intraoral cameras, digital cameras, and better equipped centres have 3D computerized systems for prosthetic dental reconstruction, and 3D cone beam computerized tomography systems for precise intratissue imaging, measurements, and navigation in operative oral and maxillofacial surgery. There are also lots of other high-quality computer systems used.

What was considered relatively distant future some twenty years ago, today is the reality in dental clinics. Using most advanced information technology, the science of dentistry crosses much longer distances than it was ever able in the preceding twenty centuries. i.e. the beginning of the new era. New information technology not only improve the quality of management of dental patients, but also makes possible their partial or complete management at distances of thousands of kilometres away from health care centres or qualified dentists (Kopycka-Kedzierawski & Billings, 2006). However, the primary purpose of these intelligent systems is adequate diagnosis, since the natural disease course has changed (Jevtović, 2008).

These systems would not mean a lot without telecommunication assisting the process and sending information almost instantly to interested parties within an institution and all over the world. Networking, sharing digital dentistry information, distant consultations, workup and analysis is dealt with by a segment of the science of telemedicine concerned with dentistry: **teledentistry**.

The beginnings of teledentistry can be roughly traced back to the beginnings of telemedicine, but more specific the birth of teledentistry as a subspecialist field of telemedicine could be linked to 1994 and a military project of the United States Army (U.S. Army's Total Dental Access Project), aiming to improve patient care, dental education, and effectuation of the communication between dentists and dental laboratories. Teledentistry demonstrated that dental professionals can consult each other even at large distances. This military project demonstrated that teledentistry was able to reduce total patient care costs, extending dental care to distant and rural areas and offering complete information required for deeper analyses (Rocca et al., 2004; Duka et al., 2009).

A system of teledentistry further enables dentists to share patient information, radiographs, graphical representations of periodontal and hard tissues, therapies applied, lab results, tests, remarks, photographs, and other information transportable through multiple providers. This data sharing can be of an extreme importance for patients, especially those in need of specialist consultation, and co-operation of dentists facilitates and improves clinical decision-making (Sanhez et al., 2004).

Though the research in telemedicine systems in medicine has advanced a lot, being always emphasized and widely present, research in teledentistry, a science dealing with use of telemedicine in dentistry, has been markedly neglected. The search of MEDLINE, the largest base of medical information, produces only 42 publications if the searched word is „teledentistry“, out of which approximately half are descriptive, review papers (PubMed, 2010). With the availability of high quality education, appropriate telecommunication technologies, and computerized systems, we have been increasingly able to scientificaly examine and prove the results of diagnosis and treatment done at large distances, as well as to observe possible faults and areas in which they tend to occur.

2. Internet as the basis of teledentistry

Internet is the basis of modern systems of teledentistry, being up-to-date and fast, and able to transport large amounts of data. Almost all new systems of teledentistry are Internet-based (*fixed* and *mobile*), as well as all kinds of distant consultation (*Real Time*, *Store and Forward*, but *Late* as well). As the result of all the qualitative and quantitative characteristics of Internet, all other Internet-independent forms of telecommunication are thought to be of secondary importance.

There are numerous reasons why Internet-based teledentistry has taken precedence over other ways of communication:

- speed,
- low cost,
- efficacy,
- documented consultation,
- minimized occupancy,
- simultaneous communication of multiple participants,
- asynchronism,

while potential shortcomings are:

- necessity of appropriate training,
- pressure for an instant response,
- impression,
- message misunderstanding,
- privacy concerns,
- possibility to overlook/neglect the message.

It is clear that Internet offers the highest speeds in sending documents or accessing desired information. If international teledentistry is concerned, Internet is the oasis of speed with minimal associated costs, being indispensible in peer-to-peer and dentist-patient communication. Cheap and rapid transfer of digital documents, images, radiographs, laboratory assays is unrivalled both nationally and locally. Using on-line communication, dental patients can be instantly advised or referred to other available Internet resources,

with additional information about the necessary procedures in their further management (Jadad et al., 2000).
Asynchronous communication and web pages are often an ideal choice both for patients and their dentists. For instance, an oral surgeon postoperatively advises his patients about the procedures and actions necessary for a successful postoperative course. The instruction can take a printed A4 page form, containing the information such as „do not wash out the mouth and wound during the first day“, „on the second day use a specific solution to wash out the mouth“, „do not take hot food“, „do not use pain killers with anticoagulant properties“, etc. These instructions may be written, but it is often the case that patients forget orally given advice or lose their writter instructions. In such cases, 24 hours teledentistry access of www pages with detailed relevant instructions can be of huge practical importance, especially because of the fact that their scope does not need to be limited.
More and more used every day, the forms of teledentistry consultations popular with students and young dentists, are „e-learning“, Internet-based instructions, on-line libraries, search tools, computer-based student-professor interactions, with students in fact subjecting themselves a large portion of their academic life to living on-line. In that regard, information and communication technologies used in conjunction with Internet have become a central part of academic life in colleges and campuses in many developed countries (Jones et al., 2008). Internet-based teledentistry education enables students to choose themselves the place, time, and mode of learning. It is invaluable especially for students outside university centres. There are numerous message boards where students can post their questions. The availability of free-of-charge and necessary on-line journals adjusted for undergraduates should be mentioned too. In postgraduate and continued professional education, modern telecommunication systems offer on-line video-conferencing, broadcasting operations and treatments, and on-line training courses (Reynolds & Mason, 2002).

3. Computerized dentistry

Massive use of computers and informatics in dentistry practice has produced the requirement of processing and understanding of huge amounts of digital data. Since these processes cannot always be performed at the place of data entry, computerized dentistry requires the methods of telemedical data transport and expert consideration of obtained data. Digital data, relying on telemedical methods, are convenient for both interhuman and intermachine data exchange and processing, leading to improved patient care in dentistry, better research, education, and management.
Computerization in dentistry begins with use of software to manage the clinic, electronic patient histories, appointment scheduling, through non-invasive and invasive diagnostic systems, problem-solving softwares, computerized prediction of complex color patterns, consideration of esthetic requirements, planning of osteotomy routes and use in other radical maxillofacial and oral surgery interventions and other applications, all the way to support in the processes of intelligent decision-making and research.
If we imagine these applied elements of computerized dentistry as cars, the methods of telemedicine would be the roads to drive on.
The main classification of computerized systems in dentistry (Schleyer & Spallek, 2001), relying on telemedical methods, would be as follows.

COMPUTERIZED METHOD	DESCRIPTION	TELEMEDICAL METHOD
OralCDx	System for imaging oral lesions, brush biopsies, and computerized analysis of histologic slides.	Telemedical consultation with pathologists to confirm the diagnosis. Distant access to slides by clinicians and therapists.
Digital radiology	Equivalent to traditional x-ray, but with lower level of radiation of both patients and staff. Exceptional image quality, 2D and 3D computerized reconstruction and immediate measurements of anatomic structures.	Telemedical transfer of files from x-ray centre to dentistry clinic, distant consultations of doctors and specialists, and distant planning of dentistry interventions and reconstructions.
Decision support systems	Support to dental clinicians in making proper decisions and choice of adequate therapy. Especially important for complex or rare cases, and in differential diagnosis.	Case reporting through Internet to the provider of support system for decision-making, and downloading of received file with suggestions for diagnosis and treatment of the case.
CAD/CAM systems	Computer-guided machines for the production of prosthetic restorations (crowns, bridges, onlays and inlays).	Distant support in designing the shape of dental prosthetic restoration and in determining interjaw relationships. Sending of digital models in the lab for the production of restoration.
Dental practice management	Automation of many routine activities in dentistry clinics, running of electronic patient histories and support in general management of the clinic.	Distant appointments, provisional review of the situation to be resolved, exchange of information with health insurance companies.
Educational resources	Educational interactive softwares, mechanical media or on-line resources in learning the manifestations of dental pathology, therapy, and practical use of critical knowledge and thinking.	On-line accessible integrated educational courses, certificateas, and titles for students and post-graduates, or acquirement of new and updated knowledge by present professionals and specialists.
Computerized research	Analysis of large amounts of data to generate new knowledge, complex analysis of data obtained with research.	Telemedical infrastructure facilitates the work of research teams in different geographic locations.

Table 1. Foundation of computerized dentistry systems on telemedical technology.

3. Telemedicine in oral and maxillofacial surgery

Use of new technologies in dental surgery provided better diagnosis, situational analysis, and planning of appropriate treatment solutions. Technologic development has been at its highest level in computerized support in dental implants placement, where it is possible to observe the patient in one part of the world, and in the other part make a digital project of complete implant and prosthetic construction and route the direction for navigational technique of dental implantation. One of the first cases was scientifically presented by the Karl Landsteiner Institute for Biotelematics, Vienna (Schicho & Ewers, 2008), consisting of a specially devised telenavigation server and telenavigation clients.

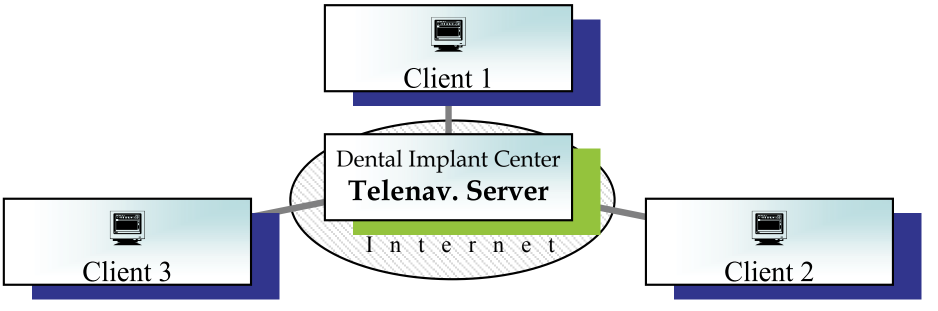

Fig. 1. Scheme of teleimplant distribution of information via Internet

Generally, the procedure of teleimplantologic consultation is as follows: at the site of surgical dental implantation, it is first necessary to obtain CBCT image and 3D computerized jaw reconstruction. DICOM files are then transferred to the main server for storage, enabling multiple downloading of the files for review or intervention planning. Dentists, distant teleconsultants, then download the files, perform the requested actions such as software planning of the position, size, and shape of dental implants. If necessary, based on the digital placement scheme, a template for the implantation process is made, leading surgical drill in the jaw area, and navigation markers are positioned, enabling intraoperative navigation of surgical instruments during surgery itself. At the end, teleconsultants post the amended files to the server, and operators are then ready to begin the process of dental implantation (Mihailovic, 2009).

During the intervention, telenavigation server is able to send information to a large number of telenavigation clients, with live data on the surgical process of dental implantation. Teleconsultants are able to watch the intervention, giving advice to operators if necessary, or present the procedure further to other distant colleagues. During the operation, each computer client functions as an independent navigation system, and each user is therefore able to choose 2D or 3D view or section plane. In essence, users actively participate in the operation, without any negative impact on computer performance or navigation system in the surgical room (Schicho & Ewers, 2008).

Some very good telemedical results have been achieved in one of the principal areas of oral surgery, impacted wisdom teeth. Impacted third molars take up a high percentage of oral surgery pathology, both in incidence and the consequences they produce. Clinical picture of impacted third molars may markedly vary, from scarce and asymptomatic, to very difficult, associated with dramatic, life-threatening complications (Mihailovic, 2006).

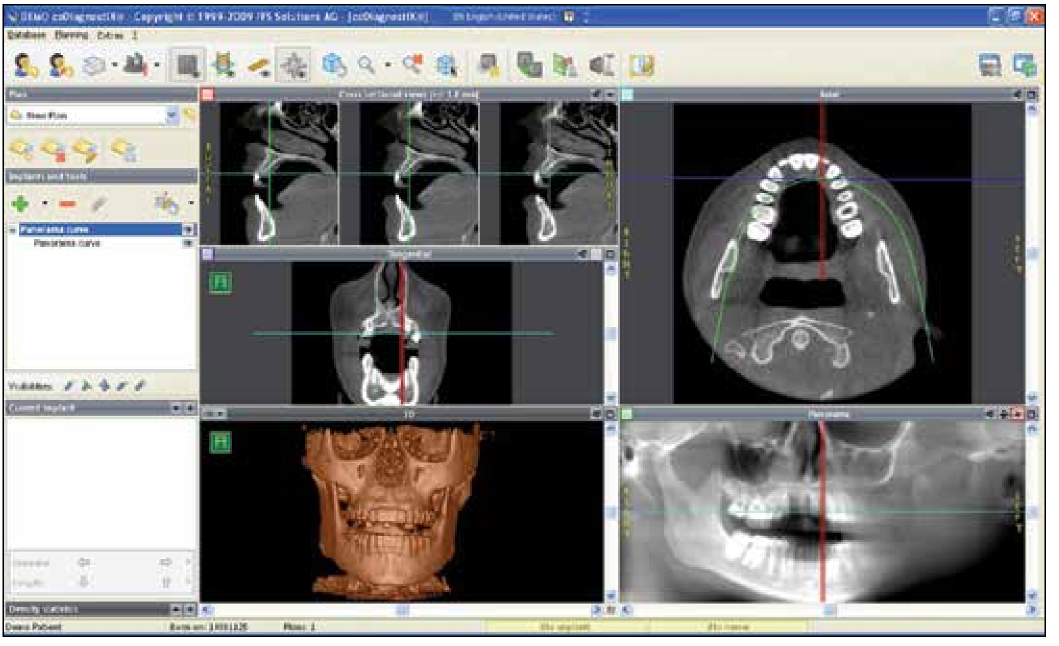

Fig. 2. Distant computer analysis and design of the whole project of surgical-prosthetic reconstruction with dental implants. The screen of software for dental implant planning and other oral surgery interventions is shown in the figure: coDiagnostiX, IVS Solutions AG, Germany.

A very common practical problem is differential diagnosis by dentists or doctors who are not specialists of oral surgery that the cause of patient's complaints is an impacted or half impacted third molar. Then, an appropriate treatment should be established in the form of extraction, some minor surgery or conservative treatment. As the presence of oral surgeons outside large centres is very limited, the availability of high quality telemedical consultation is essential. It has been documented by a study that telemedical examination does not differ from clinical examination of the dentists of this specialty (Duka et al., 2009).

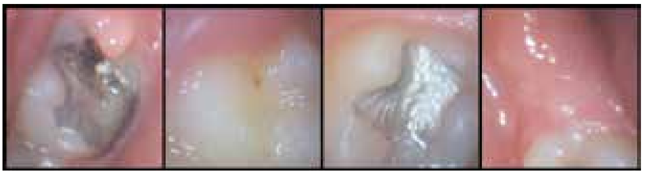

Fig. 3. Photographs of the region of all four third molars with intraoral camera, as the key element of telemedical oral surgery consultations

A proven procedure should be described. In regular orthopantomographic jaw imaging or after the suspicion of a dentist of possible consequences of some other form of impaction or retention of the third molar, 2D digital orthopan image is translated into a binary record on HDD as a JPEG file of minimal size, 998 x 494 pixels, and 83 pixels per inch with 24-bit RGB color palette. Facial and bilateral en face photographs of the patient are taken with digital camera, as well as photographs of intraoral structures and teeth of both jaws, using the technique of dental photographing.

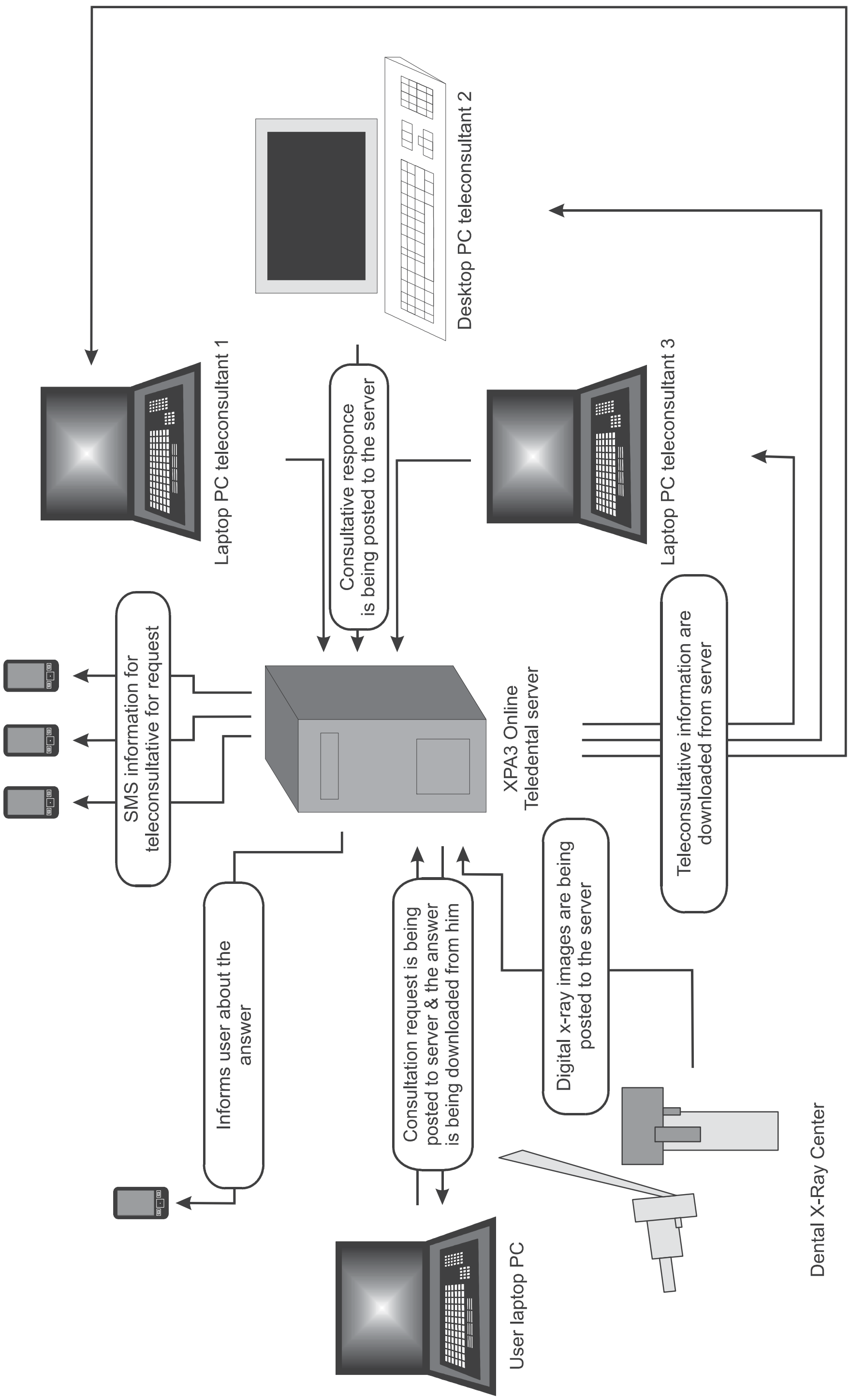

Fig. 4. Scheme of telemedical transfer of information in oral surgery – *Store-and-Forward* technology.

Digital photographs are stored in JPEG format of minimally 2592 x 1944 pixels and 300 pixels per inch resolution, with 24 bit RGB color palette. Then, using intraoral camera, photographs of all four third molar areas are taken, with images having the following minimal characteristics: 640 x 480 dimensions, 72 pixels per inch resolution, and 24-bit RGB color palette. Each patient therefore has one digital orthopan radiogram, frontal facial image, intraoral photograph of both upper and lower jaws, as well as four images of third molar areas obtained with intraoral camera. All these date are uploaded on the Internet server, with specially developed application with user interface for direct uploading of personal patient information, uploading of accompanying images, patient history and questions related to the areas of possible impacted molars. Authorization and used authenticity check are done before being allowed to access the application, and server access is secured using minimally the SSL (Secure Sockets Layer) cryptography protocol. With the SMS sending system oral surgeons are informed about the received requests for distant consultation. Teleconsultants access the server via computers or smartphones, and based on the available information give their opinion, including diagnosis and treatment recommendation. In some cases, there are requests for additional information. In this way, using teledentistry methods, the problems related to the growth, position, and status of the third molars can be assessed equally well as in real time. Based on the obtained information, a plan of oral surgical management can be devised in the sense of treatment or extraction (Duka et al., 2009).

The advances and availability of smartphone technology have contributed to the feasibility and availability of telemedicine in oral and maxillofacial surgery. Smartphones are able to read and display 3D computer reconstructions of head skeleton, giving instantly the necessary information to distant teleconsultants in oral and maxillofacial surgery. Even on the move, they are able to record the consultation and send an answer. It is very useful in emergency conditions requiring immediate interdisciplinary consultation. Maxillofacial surgeons are thus able to monitor the condition of their patients even after very complex interventions, such as osteotomies, removal of ameloblastic fibromas, and so on (Aziz & Ziccardi, 2009).

4. Telemedicine in orthodontics

Clinical orthodontics advanced the most in routine use of computerized technology, and the presence of distant assistance in everyday work cannot be compared to any other area of dentistry. The matter is, above all, about the fact that instead of traditionally used study casts present orthodontics makes use of digital 2D and 3D models and all specialist analyses, measurements, and assessment of relationships are done using software to process the images (Mladenović et al., 2009). Orthodontic specialists, after taking dental impressions of the jaws, instead of casting jaw models in plaster, send the impressions by special postal service to specialized companies for 3D digitization of working models; then they create digital 3D models using patent-protected systems for 3D scanning and digitization, form a computer file, and return it via Internet to the therapist. The therapist share this digital model of the jaws with others via network, effectuating necessary consultations with his colleagues. Peer teleconsultants, if required, may also participate from a distance in the creation of a plan and program of orthodontic management, using digital patient model (Mihailovic et al., 2009). The two most renown computerized digitization systems are OrthoCad i eModels.

We should describe the functioning of this method of telemedicine. An orthodontic specialist takes impressions in hydrocolloid alginate and bite impression using polyvinyl siloxane, wax, or compatible materials. The impressions and bite are then sent to the OrthoCAD™ company by post. There, casts are made from the impressions, being after that scanned with special methods of 3D digitization. Upper and lower jaw models are articulated using the bite impression. Few days after being contacted, OrthoCAD™ uploads on its Internet servers the electronic file containing digital study model. The orthodontist is informed, and he downloads the file from the Internet and analyzes it with special 2D and 3D orthodontic softwares. Such a teleorthodontic system offers numerous benefits in the practice and markedly reduces processing and model storage costs (Okunami et al., 2007; Peluso et al., 2004).

In the age of intense development of mobile communications, telemedicine in orthodontics has one more simple and, above all, practical use. Patients get distant consultations and help in everyday problem with orthodontic devices. A specialist in orthodontics is able to offer appropriate expert support if rubber bands fall off the braces, in cases of discomfort wearing braces, and in assessment of the solution if irritations occur, without the need for patient visits to the clinic (Favero et al., 2009). Patients are able to take photos of the areas of their mouth and the devices producing complaints with high resolution digital cameras, and to send the photographs to their orthodontist in order to get proper advice. Such a solution is especially attractive to younger patients (most common orthodontic patients).

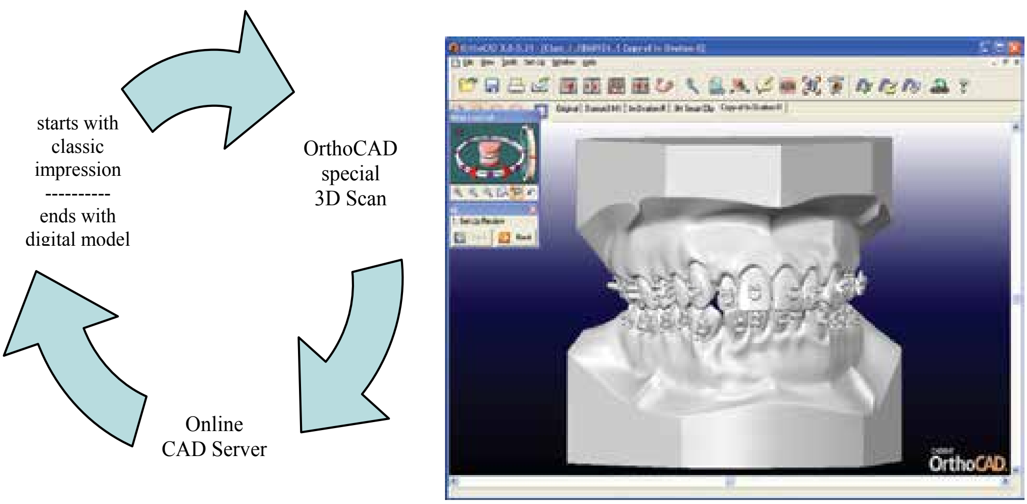

Fig. 5. OrthoCAD system for distant 3D digitization and easy analysis of digital models

Orthodontics is able to successfully help in the management of children with special needs. Travelling-associated problems constitute an aggravating factor in such cases, and distant management is the approach of choice whenever possible. In spite of the presence of some insuperable limitations, orthodontic treatment monitored from a distance via teledentistry systems (intraoral cameras, digital cameras, transfer of digital radiographs, video-conferencing approach) has still been very promising in the management of occlusions in these children (Berndt et al., 2008).

5. Telemedicine in endodontics

Any faults in differential diagnosis and prognosis of treatment of periapical lesions can be the source of subsequent complications, problems, additional waste of time and money, sometimes being the cause of complete revisions of prosthetic restorations based on poorly treated teeth. Periapical lesions constitute a large portion of dental pathology and their treatment is commonly performed by dentists who are not specialists in endodontics. Modern telemedical systems are an ideal solution for seeking and obtaining timely expert help in that regard. Zivkovic et al. have practically demonstrated that with the use of teledentistry methods based on Internet, diagnosis of periapical lesions can be adequately assessed; based on that, a necessary plan can be devised for a proper endodontic or oral surgical management of these lesions. Teledentistry based on Internet as a medium for distant communication enables its use worldwide, wherever the world wide web is present as a wire or wireless connection, reducing the costs of management and increasing the availability of urgent help to all patients (Zivkovic et al., 2010).

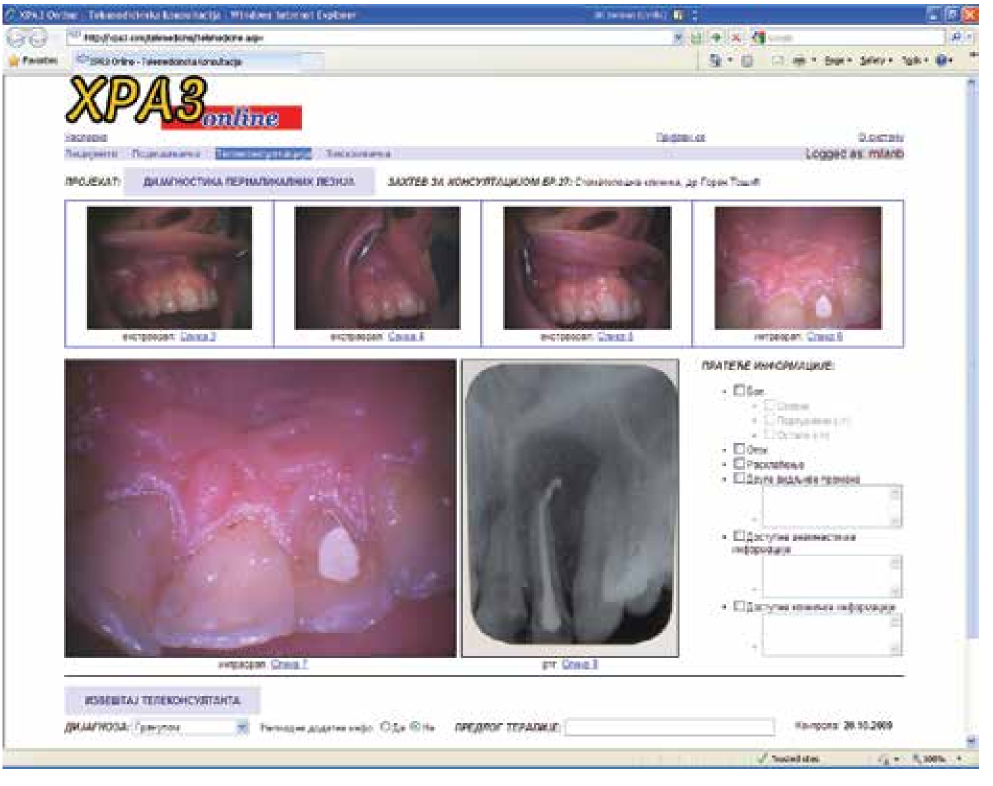

Fig. 6. Telemedical online server XPA3 Online, Serbia, distant help in cases of periapical lesions

The method is based on the creation of digital information for each of the teeth of interest:

- sequence of digital extraoral photographs (frontal and bilateral),
- sequence of digital intraoral photographs (vestibular portion of the alveolar ridge in the area at the level of tooth root, palatal/lingual portion of the alveolar ridge of the target tooth, and dental crown),

- retroalveolar dental digital x-ray,
- anamnestic information in the format of text.

Using mobile Internet connection, photographs and text are uploaded to an on-line server. Distant consultants, specialist in endodontics, are informed via their mobile phones about the received request, after which they download the digital images and accompanying anamnestic data. They establish the diagnosis and suggest a treatment, then post these information on an on-line server, which informs the consultation-requester dentist about the received response.

Baker et al. have also demonstrated that there is no statistically significant difference in the interpretation of periapical lesions between the images viewed locally (using a viewbox) and images transmitted via a video-conferencing system and viewed on monitor screen (Baker et al., 2000).

6. Telemedicine in pediatric and preventive dentistry

Prevention and early detection of caries are the key factors in the suppression of this mass disease of etiologically insufficiently known nature. In that sense, in children and young people regular dental systematic check-ups are performed, and in adults regular control examinations. Telemedicine is here too a method of choice in many situations where direct clinical inspections are not possible. Amável et al. have demonstrated in real conditions that distant diagnosis of pediatric dental problems, based on non-invasive imaging, is a valid grounding for an appropriate insight into dental problems and dental treatment preparation (Amável et al., 2009). Kopycka-Kedzierawski et al. have successfully performed the study of prevalence of dental caries in children using the telemedicine method and dental photographs taken with intraoral cameras and web-based storage of images (Kopycka-Kedzierawski et al., 2008). These authors, in their study evaluating a telemedical system of distant systematic dental check-up in children, using again the transmission of digital images taken with intraoral cameras in the children mouths, have been able to get a complete insight into the status of teeth of these children, with speciall emphasis on early dental caries (Kopycka-Kedzierawski et al., 2007). The success with these teledentistry systems largely depends on the quality of intraoral cameras. An intraoral camera should be adequately shaped to be easily placed in any place of interest and take dental photographs from any available angle; in addition, sufficiently strong and focused illumination from the camera itself is required, as well as optical or software reduction of light reflected from the smooth surface of the teeth. Together with high resolution, the obtained digital image is able to demonstrate initial caries stages or enamel and dentine pigmentations. In addition to its basic role in providing dental screening in distant, rural, and other inaccessible areas, the method of teledentistry has been demonstrated as a high quality alternative in children afraid of dentists, reducing their fear and anxiety compared to clinical examination in real time.

7. Telemedicine in oral medicine

Even beyond general indications for telemedical approach in clinical setting and with the presence of specialists, the significant need for adequate consultation with a colleague of the same or different specialty may exist. Practical examples can always be found in oral medicine and dermatology (as its closest medical specialty). When histopathologic sampling is not possible or when it can result in impaired esthetics and function, one of the principal steps is intercollegial (peer) consultation. Telemedicine, based on high resolution images and a broad spectrum of colors (32-bit or more), is able to provide high quality consultation even with the colleagues at a distance of several hundreds of kilometers (between two or several experts at a time) (Janković, 2007).

Torres-Pereira et al. have shown an effective distant access to oral lesions and benefits of use of e-mail services and a Store-And-Forward image system. Oral lesions are electronically photographed using a 50 mm macro lens and circular illumination system, and clinical and anamnestic data are stored in a textual file with minimal resolution of 600 dpi. The files are appropriately renamed according to the patients' identification numbers in order to avoid confounding and indentity errors. Specialist of oral medicine then analyze independently the obtained images and clinical information. They make the diagnosis (usually one or two) and electronically return the results (Torres-Pereira et al., 2008). The approach such as this is able to produce good results, which could be further improved with the use of a comprehensive electronic patient history, containing the complete history of all current and past diseases, medications taken, diagnostic and therapeutic procedures, and recorded all other factors of influence on the status of currently assessed lesion.

Fig. 7. Achieved teleconsultant diagnostic agreement for the Dg. Giant cell epulis (K06.8) and treatment agreement: surgical removal.

8. Telemedicine in dental prosthetics

CAD/CAM (computer-aided design and computer-aided manufacturing) systems are gaining precedence in the manifacturing of individual dental crowns, dental inlays and onlays, over traditional hand modelling and casting of prosthetic reconstructions. Modern computerized systems are capable of manufacturing even the bridges of up to three units, with satisfactory medical characteristics. The process of manufacture of these dental structures is based on 3D imaging of the status after tooth-carrier preparation with intraoral camera using the active triangular principle. Then, CAD projection of tooth restoration is then performed, and if inlay or onlay is to be done, the software is capable of automation of a large part of the job; however, if crowns are to be done, greater participation of the user (computer operator) is required. Since there are dentists and dental technicians who are not very skillful doing this somewhat complicated process of designing shapes and interjaw relationships using CAD softwares, the usual practice is to request teledentistry help of computerized dentistry specialists. The resulting project file is encrypted and sent by e-mail to a teleconsultant for model analysis, projection of the shape of restoration, of its height and interjaw relationships using a virtual articulator; the completed project is then encrypted and returned to the clinic, usually by e-mail (Späth & Kordass, 2006; Hartung & Kordass, 2006). The clinic put the CAM system into motion, which in a short time produces dental restoration using the project file, and submit it to the patient.

Some dental companies offer the service of 3D scanning of already cast and posted model obtained from the impression of the teeth prepared by the dentist. These are large, specific, and patented systems for 3D digitization, in which the errors with approximate imaging (as with 3D intraoral cameras) are excluded, but require destruction of the plaster model in the process. On the obtained 3D digital model the company produces the restoration design, tests for digital interjaw and interdental relationships, and the completed project is made accessible to the requesting dentist or technician on the company web server. After distant receipt of the project, the dentist is able to precisely cut out the restoration using his CAM system (Mihailovic et al., 2009).

In addition to its vital role in the CAD/CAM systems, telemedicine in ofter used in the practice of dental prosthetics in the examination of patients in order to obtain general information about the choice of prosthetic solution and gross costs of the job. Patient in search for high quality and/or cheaper dentists often use google.com and after finding the clinics send to them their requiest for additional information and digital photographs of the mouth and/or 2D orthopantomograms of the jaws. In practice, dentists usually state that assessments that could be made based on such information are satisfactory and usable. Though this type of communication is fairly common, we have not been able to find the studies to confirm the quality of such consultations.

9. Systems for the storage of dental data, their analysis, and *Evidence Based Dentistry*

Dental institutions are nowadays extensively using computer systems to register their patients, diagnoses, and treatments. These systems are divided into two basic groups related to the type of data storage and sharing:

- Central
- Local

Central systems are still scarcely present, although they represent the choice for the future. Being continually Internet-based and serving a large number of dentists and dental hygienists, they are able to offer the best performance in the collection, triage, analysis, and timely information of distant users in almost every aspect of dental disease and treatment, using the potentials of modern telemedicine.

Local systems are represented by smaller computer networks or individual computers present in dental clinics and institutions, without planned data sharing with other users. These systems are abundantly present. There are potentials for scientific research of information from electronic patient histories within Evidence Based Dentistry, then for statistical analysis of large datasets and possible discovery of interesting patterns from them. The new challenge appeared of distant access for research purposes to the data stored locally, but there is also the challenge of automated data collection from a number of local systems and their merging into a large dataset for the purpose of more reliable queries over large amounts of data.

In such situations, telemedicine in the service of scientific research becomes an indispensable tool in confirming or rejecting of scientific hypotheses, improving the ability of researchers to undertake case-control studies using dental information collected at distances of thousands of kilometers (Miladinovic et al., 2010; Ballini et al., 2007).
Finally, effectuating distant access to dental data, the systems of teledentistry enable high speed and effective forensic identification of victims based on their dental status recorded in electronic histories of dental patients (Hanaoka et al., 2007).

10. Future research

The research of telemedicine in dentistry has been neglected for no reason compared to other disciplines of medicine (Kopycka-Kedzierawski & Billings, 2006). The results achieved so far are very encouraging, setting the roadsigns for future investigations. The issues to be addressed are the use of telemedicine in emergency dental conditions, not covered by the present adequate distant support, posttraumatic and postoperative controls, postprosthetic patient surveillance and so on.
If we consider the situations with long-term inavailability of dental care, e.g. during space flights, on transoceanic ships, in various rural areas, distant telemedical control of robotized instruments could be an appropriate solution.
Telemedicine can also be of help in the application of dental nanotechnologies, stem cell research, research and control of bioinductive and bioregenerative materials, and so on.
Probably the most important area of use of these valuable methods is to support the processes of collection, triage, sorting, counting, and analysis of raw electronic data for the purpose of induction in the systems of artificial intelligence.

11. Acknowledgement

This chapter is created and published in the name of God and our Savior Jesus Christ.

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12

Advances in Teleophthalmology: Summarising Published Papers on Teleophthalmology Projects

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1. Introduction

Teleophthalmology is a branch of telemedicine that delivers eye care through digital medical equipment and telecommunications technology.[1] It does this through either a store and forward method or real-time communication, and so enables doctors to attend to patients in remote areas.[2]1 It has been of increasing interest to researchers in the field of telemedicine over the last decade. This may have been due to the significance and prevalence of eye diseases, as well as a lack of specialists interested in working in remote areas.

A simple search for teleophthalmological research via the Medline database yielded hundreds of results with varying aims and objectives. There had been a significant increase in the research over the past decade, and this made summarising the papers challenging.

Although the studies possessed diverse aims and objectives, most focused on a particular eye problem, such as DR, glaucoma, adnexal disease etc. For instance, some of the projects questioned the feasibility of a particular type of teleophthalmological system for the screening of DR. Others concentrated on issues of cost and patient satisfaction. Whatever their main aims, each article took one or more eye diseases as its central theme.

The question of what eye problems had been of interest to date is important. Regardless of design or conclusions, each paper was proof of the field's increasing relevance. But what were the strengths and weaknesses of the teleophthalmological publications in terms of focusing on different type of eye problems? In other words, having considered the wide variety of eye disease which can be consulted through a telemedicine system, which area have been more of interest for researchers?

There were also other important questions. For example, the type of telemedicine used in teleophthalmological projects (pre-recorded or real-time) would have been of interest to eye care specialists.

Finally, the general conclusions made by the studies were also very significant. Were they positive, thus encouraging others to pursue the study, research and development of teleophthalmology?

This short report discusses the findings of a systematic literature review of published papers that have documented teleophthalmological projects and been indexed by major bibliographic databases. It will also attempt to classify them in order to answer the following questions:

1. What types of eye problems have been focused on?

2. Which type of telemedicine has been used, store and forward or real-time?
3. What proportion of papers has been conducted using a control group?
4. Are the papers' conclusions positive or negative?

2. Method

A comprehensive literature review was conducted.

2.1 Databases

Three bibliographic databases were searched: Medline, EMBASE and CINAHL.
Medline was searched via Pubmed, while CINAHL (Ebsco) and EMBASE (Ovid) were searched through the library of University of Western Australia.

2.2 Dates

All published papers through the end of 2009.

2.3 Keywords

The databases were searched for the following keywords: telemedicine, e-health, telehealth, telemetry, tele ophthalmology, teleophthalmology, teleretinology, telediagnosis, teleconsultation, telemonitoring, tele screening, web-based, internet, remote or virtual. These keywords had to occur in conjunction with one of the following: ophthalmology, teleophthalmology, tele ophthalmology, eye, eye care, retina, retinal or tele ophthalmology.
All three databases were asked to show only papers that had abstracts and were in English. A very broad range of keywords was chosen in order to ensure all relevant papers would be included.

2.4 Criteria for inclusion

Papers had to be about remote eye care delivered via digital devices or telecommunication technology, and had to be published in peer-reviewed journals. They also had to be in English and contain an abstract.

2.5 Criteria for exclusion

The first criterion for exclusion was that the material was presented in the format of a letter, editorial or review. The second criterion was that the paper was not about an actual teleophthalmological project. For example, articles that evaluated the potential of digital photo diagnosis for use in future teleophthalmological services were left out. Studies about research conducted on computerised models or on non-human models such as animal eyes (criterion three), were also eliminated from the review. Finally, double publications, i.e. a single project reported in two different formats (criterion four), were disqualified from this review.

2.6 Selection of papers

Papers retrieved from all three databases were entered in Endnote Reference Manager XI, and duplicates were removed. In total, 2,095 titles were retrieved. All papers were then reviewed and assessed for relevance to the topic at hand. In the second phase of the research, the abstracts of all shortlisted papers were analysed, with the full texts being evaluated when necessary. Paper selection steps are summarised in Table 1 below.

There were significant disparities between the selected papers in terms of their methodology and aims. They assessed the economy, feasibility, reliability and patient satisfaction of teleophthalmological projects on the screening or diagnosis of eye problems. Since the paper's main aim was to discover what types of eye problems had been explored thus far, this heterogeneity was ignored.

All shortlisted papers were read, and for each paper, a simple questionnaire was filled out. The options for each question were based on the abstracts of the papers.

Question 1: Type of Eye Problem	Diabetic Retinopathy (DR)	☐
	Premature Retinopathy (ROP)	☐
	Glaucoma	☐
	Strabismus	☐
	General	☐
	Other	☐
Question 2: Type of Telemedicine	Store and Forward	☐
	Real-Time	☐
	Both	☐
Question 3: Study Design	With Control Group	☐
	Without Control Group	☐
Question 4: Paper's Final Conclusion	Positive	☐
	Negative	☐
	Unclear	☐

Table 1. Questionnaire for the Classification of Papers

Number of papers retrieved from Medline	1573
Number of papers retrieved from CINAHL	169
Number of papers retrieved from EMBASE	1133
Final number of original papers	2095
Number of abstracts selected for further exploration after reading	351
Number of papers selected for in-depth reading	168
Number of papers excluded due to Criterion 1 (The paper was presented in the format of a letter, editorial or review)	183
Number of papers excluded due to Criterion 2a (The paper did not conduct an actual teleophthalmological project)	59
Number of papers excluded due to Criterion 2b (The paper conducted a teleophthalmological project using a computerised model)	11
Number of papers excluded due to Criterion 3 (The paper conducted a teleophthalmological project using a non-human model)	1
Number of papers excluded due to Criterion 4 (The teleophthalmological project was covered in more than one publication)	4
Final number of papers selected for the study	107

Table 2. Paper Selection Process

3. Results

3.1 Subspecialty

As Table 3 shows, 37 per cent of the research focused solely on DR and one or two other diseases. Twenty-three per cent concentrated on general ophthalmology (without a focus on a particular eye problem), fifteen per cent on ROP and ten per cent on glaucoma. In addition, two per cent focused on Strabismus.

Disease focused on in each paper	Number of papers(reference number)	Percentage
Diabetic Retinopathy	37(3-39)	34.58
General ophthalmology*	25(40-64)	23.36
(Retinopathy of Prematurity)ROP	16(65-80)	14.95
Glaucoma	11(81-91)	10.28
Strabismus	4(92-95)	3.74
Adnexal and Orbital disease	4(96-99)	3.74
DR and DME	2(100-101)	1.87
DR and AMD	1(102)	0.93
(Acute Macular Degenration) AMD	1(103)	0.93
DME	1(104)	0.93
SDME	1(105)	0.93
HTN (Hypertensive Retinopathy)	1(106)	0.93
Post-operative care	1(107)	0.93
Suspicion of abusive head trauma	1(108)	0.93
Retinoblastoma	1(109)	0.93
TOTAL	107	100

Table 3. Particular disease which each paper had focused on.

More than 37 per cent of all published projects on teleopthalmology studied only DR, while an additional three per cent also targeted macular degeneration.[100, 101, 102] These studies evaluated either the feasibility of DR screening or diagnosis.

Twenty-five per cent of all papers were on general eye problems. This category covered projects that had been conducted in general practice clinics or that had not addressed any specific eye problem. These projects were merely targeted at confirming whether teleopthalmology had the potential to assist general practitioners in the treatment of patients with eye problems. Some of these projects focused on cost, patient satisfaction and other issues, rather than discussing a particular disease.

At sixteen per cent, ROP was the third main reason for the execution of teleophthalmological projects. The majority of papers on this eye disease aimed to evaluate the utility of teleopthalmology in its screening and diagnosis.

3.2 Type of telemedicine

Eighty-eight papers (83.02 per cent) focused on store and forward projects, eight (7.55 per cent) on real-time projects, and ten (9.43 per cent) used a mixed system.

3.3 Study design

Only two papers possessed a Randomised Controlled Trial (RCT) design,61, 98 and only four had used a control group.

3.4 Final conclusions of papers

Ninety-eight papers had a positive view of teleopthalmology. However, five papers did not arrive at a clear conclusion and four expressed a negative view towards teleophthalmology.[5, 91, 98, 104]

4. Discussion

This chapter has attempted to locate all the teleophthalmological projects that have been published in peer-reviewed journals and indexed by the three popular bibliographic databases for biomedical research, Medline, EMBASE and CINAHL. It demonstrates that:
There is strong evidence that teleophthalmology is suitable for the treatment of retinal diseases, particularly DR and ROP;
Teleophthalmology has been successful when provided via the store and forward method;
Although the majority of studies to date have concluded on a positive note, only a few of these conclusions were based on high quality study designs involving controlled or randomised controlled trials.
The results show that most teleophthalmology projects to date have been focused on the treatment of DR. The health complications caused by diabetes and the importance of DR screening are likely major factors in the evaluation of teleophthalmology.[110]
However, other eye problems also require more attention. These include strabismus, cataracts and infectious diseases. Trachoma, for example, is a highly prevalent condition in developing countries.
Although the papers in the 'general eye problems' category were very diverse, it appears that the use of teleopthalmology to deliver eye care service to general practice clinics and optometrists has also been reasonably successful.
Teleopthalmology is still largely considered a store and forward application; this can be seen from the fact than less than seven per cent of the papers examined a real-time project. This might be explained by the requirement for high bandwidth. A considerable number of publications indicate that while store and forward teleophthalmology is both feasible and reliable, further evidence of the feasibility and reliability of real-time teleophthalmology is needed.
Approximately 90 per cent of the papers held positive views on teleophthalmology. However, ten per cent took a sceptical or negative view. This favourable statistic shows that teleopthalmology is a reliable method of eye care delivery. It was not possible to compare the feasibility and reliability of teleophthalmology across different subspecialties. Nevertheless, it is important to take into account the significant lack of papers using RCTs or comparable groups. This fact reveals that our evidence is undeniably inadequate and that we are not yet able to draw an informed conclusion.

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Part 4

Regional Applications

13

The Use of Telemedicine for the Management of Hepatitis C & the California Telehealth Network

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1. Introduction

Despite a plateau in the incidence of acute hepatitis C infection since 2003 (Daniels, 2009), chronic hepatitis C virus (HCV) infection continues to pose a significant public health problem with a large cost burden to society. HCV is the most common blood-borne infection in the US with an estimated 3.2 million chronically infected people nationwide (Daniels, 2009). HCV is the leading cause of chronic liver disease and a major cause of hepatocellular carcinoma in the US with an estimated 8,000 to 13,000 deaths annually (Daniels, 2009; Wise et al., 2008; Armstrong et al., 2006).

Injection drug use continues to be the main risk factor leading to HCV infection. The peak prevalence occurs among adults aged 40 to 49 years with individuals of lower socio-economic status bearing a disproportionate burden compared with other groups (Daniels, 2009; Armstrong et al., 2006). The majority of liver transplants in this country occur in patients with cirrhosis due to HCV (Verna & Brown, 2006; Freeman et al., 2008). It is estimated that the associated total direct and indirect cost of HCV associated cirrhosis and hepatocellular carcinoma is greater than $5 billion each year (Leigh et al., 2001).

In California alone, an estimated 600,000 persons have been exposed to HCV and about 450,000 Californians are living with chronic HCV. Racial disparities in infection rates exist with African Americans having the highest observed rate of HCV infection among all racial and ethnic groups. The prevalence of HCV infection among African Americans living in California is estimated at 3.2%, among Latinos, 2.1% and among Caucasians, 1.5% (CDC, 1998).

2. Closing the gap of access to specialty care

Prior studies have shown that HCV patients without access to a specialist are less likely to be treated (Rocca et al., 2004). This is significant from a clinical and public health standpoint because almost half of patients treated with the current standard of care (6-18 months of therapy with pegylated interferons and ribavirin) achieve long term cure with a resultant improvement of liver-related mortality rate that approximates the one experienced in the general population (Simin et al., 2007; Veldt et al., 2007; Kasahara et al., 2004).

Rural communities are particularly affected by the lack of access to specialty care (Yawn et al., 2002; Rossaro et al., 2008). Telemedicine consultation offers the potential to increase access to specialists in remote and underserved areas. Increasingly, primary care providers (PCPs) in remote areas are being called upon to diagnose and treat patients with HCV. Unfortunately, many PCPs are unprepared to evaluate and manage the complexity of patients with chronic HCV and practice patterns are highly variable. Few rural practitioners have experience with the complex mental health and substance abuse issues that are common among patients with hepatitis C infection (Arora et al., 2010). In addition, they may perceive greater challenges when managing treatment side effects of pegylated interferons and ribavirin (depression, thrombocytopenia, neutropenia, anemia, GI side effects and skin rash). Optimal management of HCV infection requires consultation with highly trained specialists or academic institutions with dedicated hepatologists.

Furthermore, it can be difficult for patients with HCV infection living in remote or underserved areas to access specialists. Often patients are required to travel long distances to academic centers that offer specialty care, experience long wait times to see specialists at these centers, and may not be able to schedule follow up visits in a timely manner due to the high volume of patient care at these centers. While undergoing treatment for HCV infection, close monitoring and follow up with a specialist and/or close communication between a PCP and specialist is essential due to the potentially life threatening side effects of interferon and ribavirin. These factors may impede patients in remote areas from initiating treatment for HCV. Table 1 lists the different barriers to care of HCV in rural areas.

Barriers to the Management of HCV in Rural Areas

- Access to specialists
- Lack of transportation
- Distance to clinic
- Limited education of providers
- Low socioeconomic status

Table 1. A list of barriers to HCV management that patients in rural areas experience

Telemedicine can close the gap of access to specialty care and provide clinical decision making support to PCPs with regard to best practice treatment strategies for managing HCV patients. In the last ten years, we have provided consultations to patients with HCV via telemedicine at about 50 different locations throughout California. Our telemedicine sites have included primary clinics in rural areas with a high prevalence of HCV and low socioeconomic status as well as correctional facilities.

3. Use of telemedicine consultation for the management of HCV patients

Telemedicine is the use of high speed, wide band width transmission of digitized signals in conjunction with computers to provide an audio-visual interaction in real time between a patient and physician who are physically separated. Telemedicine is an effective tool to improve access for patients with HCV in underserved areas. In addition, the presence of the PCP in the room with the patient provides educational opportunities for the provider and the patient and improves the overall quality of patient care.

Telemedicine offers a unique opportunity for real time interactions among a triad of individuals (Figure 1): the patient, in need of specialty care, the PCP who actively participates during the consultation, and the specialist, who provides consultation services and education in management to both patient and PCP simultaneously.

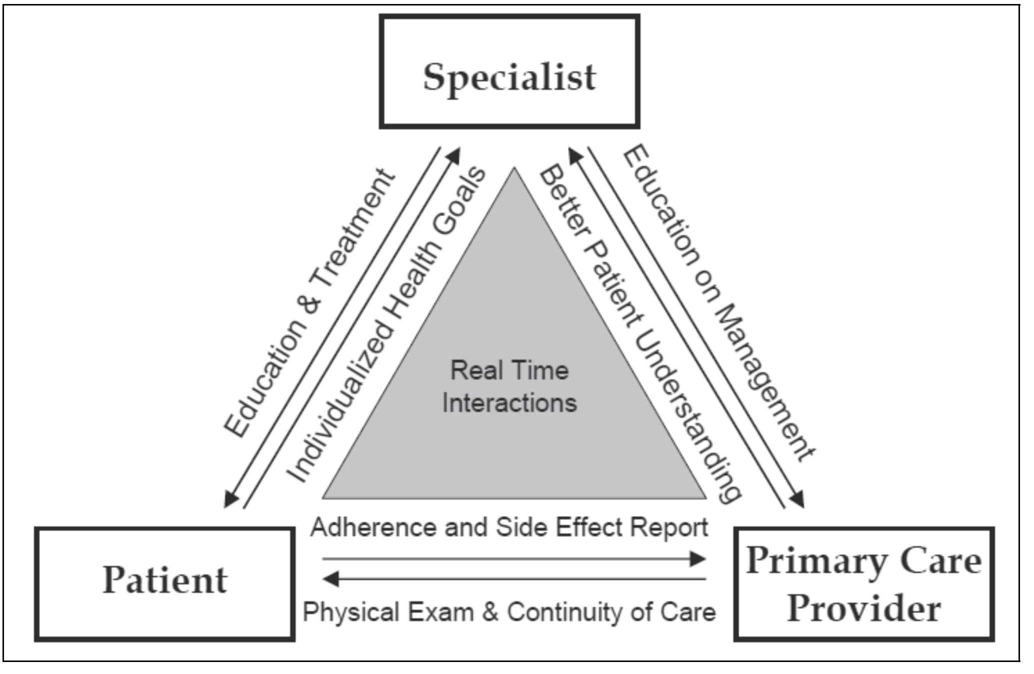

Fig. 1. Telemedicine Triad: patient, PCP, and specialist with multidirectional interactions in real time, providing care and education.

In a recent retrospective review of our data (Rossaro et al., 2008), we found a surprisingly high severity of disease in a difficult to treat population in a rural area in California (Figure 2 and Table 2). From 2000-2007, we provided consultations for 103 patients with hepatitis C living in small California rural communities with high rates of poverty and a high incidence of HCV. Of these patients, approximately half (37% Stage 4 + 12% Stage 3 = 49%) had advanced fibrosis, and 64% had never undergone therapy with interferon and ribavirin. Twenty-three percent of the patients were candidates for therapy. The most common contraindication to therapy was the severity of their disease and the risk of decompensation

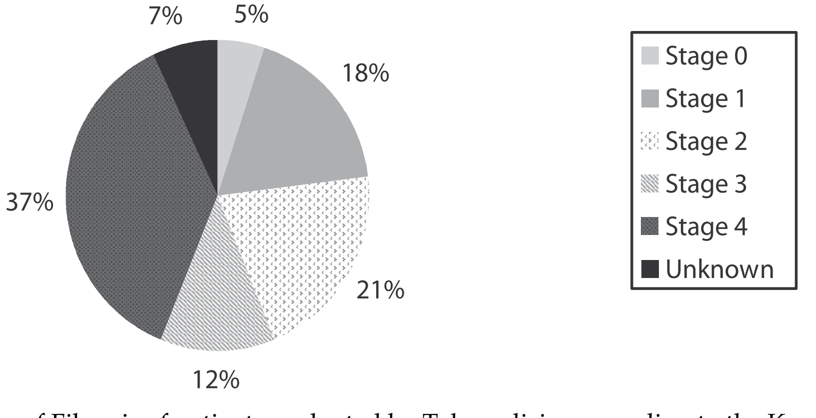

Fig. 2. Stage of Fibrosis of patients evaluated by Telemedicine according to the Knodell score (Rossaro et al., 2008)

Male	47%
Female	53%
Weight (mean)	88.46 kg
Age (mean)	49 yrs
Patient Insurance	
No insurance	6%
County	25%
Medi-Cal	61%
Medicare	6%
Private	2%
Viral genotype	
1	71%
2	11%
3	15%
4	2%
6	1%
HCV Viral load > 450,000 IU	37%
Advanced liver fibrosis	49%
Model for End Stage Liver Disease (MELD) > 12	19%
Treatment naïve	64%
Treatment recommended	23%

Table 2. Characteristics of Patients evaluated by Telemedicine (Rossaro et al., 2008)

during treatment due to advanced cirrhosis. Fifteen patients were evaluated for liver transplant. Two patients were listed for transplantation but neither survived long enough to receive a liver.

Our data suggest that a large number of patients with hepatitis C and advanced liver disease are living in rural communities, some of whom may need treatment or liver transplant. Telemedicine is an effective tool for identifying and treating patients with hepatitis C who live in rural communities who may otherwise go untreated or not listed for liver transplantation.

4. Improving practitioner hepatitis C knowledge by video conferencing

Telemedicine can also be utilized to provide education to practitioners regarding HCV. In a recent study, we compared the impact of multipoint videoconferencing versus standard lecturing on level of knowledge attainment in different groups of PCPs including physicians, nurse practitioners, physician assistants, and registered nurses (Rossaro et al., 2007).

The hypothesis was that the educational impact of teaching through telemedicine is comparable to the traditional didactic method. The aim was to provide participants with clinically relevant information and knowledge about the natural history, diagnosis, and management of HCV. Improved knowledge was scored from a 10-item questionnaire administered before and after the educational intervention. For all practitioners combined, the videoconferencing group scored significantly lower on the pretest than the standard lecturing group (Table 3).

All three types of learners improved their knowledge scores following intervention in both methods. However the videoconferencing group scored significantly higher on the posttest

	All Providers (MDs, NPs/PAs, RNs)		
	Videoconferencing n = 62	Standard Lecture n = 113	p value **
Pretest Score *	4.3	4.9	<0.05
Posttest Score *	8.7	7.9	<0.001
Score Improvement	4.4	3.0	<0.001

Legend: MDs, Medical Doctors; NPs, Nurse Practitioners; PAs, Physician Assistants; RNs, Registered Nurses. * Pre and Post-test scores range from 0-10 items correct. ** T-test analysis

Table 3. Knowledge Scores: Videoconferencing Method vs. Standard Lecture

and had a significantly greater score improvement. Nurses showed the greatest improvements, correctly answering an average of four to five more questions following the video conferencing educational intervention. The results of this study indicate that video conferencing is equivalent, if not better, than standard continuing medical education. Video conferencing can potentially improve clinician education regarding the history, diagnosis, and management of HCV, thereby making a substantial impact on the clinical course of patients with this condition. In addition, video conferencing has the potential to eliminate the financial and geographic barriers to professional education for rural practitioners.

5. Hepatitis C in the correctional system

HCV infection is rampant within the correctional system. A study of about 4500 inmates entering the Californian correctional system found that 39% of males and 53% of females were chronically infected. This is becoming a serious concern to public health officials, health care providers and policy makers. Infected inmates may continue to engage in high risk behaviors and infect others while in custody, they may transmit the disease to people in the community to which they are released and the cost of providing care to HCV infected inmates with chronic liver disease or hepatocellular carcinoma is rising (Ruiz et al., 1999). Subsequent studies have reported the prevalence of HCV to be 34% and independently correlated with age, history of intravenous drug use, cumulative time of incarceration, male biological sex > female, and history of sex with a male intravenous drug user. (Fox et al., 2005)

HCV has also been implicated in the high prevalence of end stage liver disease in state prisons. A study from Texas with more than 370,000 prisoners during a period of 3.5 years found the prevalence of end stage liver disease to be as high as 131 per 100,000 prisoners with 57 per 100,000 dying during the study period due to complications of end stage liver disease. The estimate of mortality for end stage liver disease in the Texas prison population was approximately 3 times higher than that of the general population. Risk of high mortality were found in the following groups: Hispanics, greater than 50 yrs of age, HIV monoinfected, HCV monoinfected, HCV-HIV coinfected (Baillargeon et al., 2007).

It has been advocated that inmate education and counseling are important in preventing HCV infection as well as HIV and hepatitis B infection. Counseling should be culturally appropriate and consistent with the learning skill of the inmate. Prevention strategies should be designed to encourage voluntary behavior change and effective risk reduction.

Finally it has been advocated that an assessment of the risk factor profile of all inmates entering the correctional system should be conducted (Ruiz et al. 1999)

The enormous cost of organ transplantation and management of end stage liver disease are serious challenges to the health care budgets of most prison systems. Consequently, it is crucial that correctional health care programs expand HCV treatment and infection prevention strategies. (Baillargeon et al., 2007) It is well known that treatment of HCV early enough, before end stage liver disease and liver cancer occur, is highly cost effective. While HCV therapy appears expensive, many cost effectiveness analysis suggest that treatment with Pegylated interferon and ribavirin provides value comparable to many well accepted medical interventions (Bhavesh & Wong, 2006).

A study from the Medical College of Virginia, utilizing telemedicine consultation services, showed that HCV therapy can be effectively managed in correctional facilities with response rates similar to, if not better than, the non-inmate population (Sterling et al. 2004). This study included a retrospective analysis of 59 consecutive inmates who received HCV therapy under direct observation with standard interferon (non pegylated, 3 MIU TIW and ribavirin 1000-1200 mg per day). As expected, sustained virological response (cure) was higher in Caucasians (41%) compared with African Americans (28%), although the differences were not statistically significant. Even more so, when the analysis was concentrated on HCV genotype 1 alone, Caucasians and African Americans performed similarly (33% vs. 29%). The above results are remarkable given the fact that non-pegylated based therapy was utilized and partly related to the high adherence allowed by direct observation of therapy.

Since year 2000, at the UC Davis Center for Health Technology, we have provided hundreds of telemedicine consultations and videoconferencing educational events with several correctional facilities throughout California. We found inmates to be highly motivated to initiate treatment and their compliance while on treatment has been excellent. The drop out rate while on treatment appears to be similar to that of the non-inmate population (about 10%) (Unpublished observations). One key factor for successful therapy is continuity of care once therapy is initiated. It is desirable that the inmate not be transferred to another facility during treatment (6-18months).

6. Next steps: The California telehealth network

The California Telehealth Network (CTN) (California Telehealth Network Website, 2010) was established in 2007 with a $22.1 million grant from the Federal Communications Commission's Rural Health Care Pilot Program (RHCPP) and matching funds of $3.6 million from the California Emerging Technology Fund. CTN is a statewide dedicated health care broadband network, developed to ensure that California communities, especially rural communities, have access to a wide range of telemedicine and eHealth activities. CTN will provide the connectivity necessary to access high quality, collaborative health services, continuing education, research and peer networking activities. The connectivity provided by the CTN will create new telecommunications infrastructure, eventually allowing California's rural communities to access a broad range of technology-enhanced services to improve the quality of health care services in California.

Collectively, the Federal Communications Commission award and other new resources will help California develop an effective, sustainable and forward-looking telehealth network, focusing first on rural communities and subsequently expanding to serve increasing numbers of California health providers in both rural and urban areas. Over the course of the project, the new network will connect more than 860 rural sites with each other, and with a network of specialty providers at academic medical centers and other nonprofit and for-profit health providers statewide. Strong emphasis will be placed on infrastructure development, telecommunications quality and technical support. The University of California (UC), with the UC Davis Health System serves as the lead technical and operational entity for the CTN.

The California Telehealth Network is intended to improve access within rural and underserved areas to high quality, collaborative health services and to make new networking capability available for more California health providers. The CTN will link California providers to a nationwide broadband network dedicated to health care.

7. Current research

New models for delivery of telemedicine delivery have been developed and offer promising delivery of specialist services to remote and underserved areas. One model, The Extension for Community Healthcare Outcomes (ECHO) Model was developed by the University of New Mexico Health Sciences Center to deliver complex specialty medical care to underserved populations (Arora et al., 2007; Arora et al., 2010). The ECHO model was first developed for the management of HCV. ECHO provides health care delivery and clinical education to rural primary care practitioners via video conferencing (Arora et al. 2007). The ECHO model uses "telehealth technology, best practice protocols, and case-based learning" to train and support primary care providers in the development of their knowledge and self-efficacy for managing chronic diseases (Arora et al., 2010). Initial survey data of the project have demonstrated a significant improvement in provider knowledge, self-efficacy, and professional satisfaction through participation in ECHO HCV clinics (Arora et al., 2010). However, no patient outcome data are yet available for this project.

In 2007, we completed a retrospective chart review of 103 telemedicine patients with HCV from Peach Tree Clinic in Marysville, California to characterize the patient population seen in rural clinics. The study found that there is a need for more consultation and education of primary care providers for patients living with HCV in rural communities, and telemedicine appears to be an effective modality for increasing access to liver specialists and education (Rossaro et al., 2008).

Telemedicine consultation offers the potential to increase access to specialists in remote and underserved areas and has been successfully utilized in the field of trauma with non-inferior outcomes for injured patients treated at rural centers (Duchesne et al., 2008). To our knowledge, however, no studies have examined the utility, safety or efficacy of telemedicine for the management of chronic diseases in terms of patient outcomes.

8. Future research

8.1 Next steps

Our next research study will attempt to fill this telemedicine HCV patient outcomes research gap. We will expand our previous observational study and compare actual patient outcomes with HCV patients treated via telemedicine consultation at Peach Tree Clinic and other telemedicine sites as compared to standard hepatology office practice.

8.2 Study methods

We will perform a retrospective analysis, in two phases, using standard chart review of HCV patients seen at all available telemedicine sites and the UC Davis Gastroenterology (UCD GI) Clinic between the years 2008 and 2010. Our initial retrospective cohort study will be a descriptive comparison of telemedicine patients vs. traditional visit patients without matching to characterize group differences in these patient populations. We will attempt to identify general group differences by comparing the following variables between groups: mean age at initiation of therapy, gender distribution, ethnicity distribution, hepatitis C genotype, stage of fibrosis, viral load at baseline, 4, and 12 weeks after the start of therapy to assess for rapid and early virological response, rates of therapy completion and rates/types of side effects experienced by patients. Our goal number of cases for each comparison group is approximately 50, for a total of 100 patients for this pilot study.

As a second phase of investigation, we will conduct a case-control study matching telemedicine cases with traditional visit controls by age, gender, ethnicity, Hepatitis C genotype and stage of fibrosis in order to compare outcomes of early virological response at 12 weeks and side effect profiles of patients treated with interferon and ribavirin. Our final study will include an anticipated total of 100 controls and 100 telemedicine cases in order to achieve a power analysis of 80%.

Inclusion criteria for study subjects will include: a) age 18-75 years; b) hepatitis C positive by PCR; c) treatment naïve; and d) referred for HCV treatment by primary care provider. Exclusion criteria will include a) patients active substance use; b) psychiatric diagnosis of uncontrolled clinical depression; c) co-infection with HBV or d) co-infection with HIV.

Once all cases are identified and inclusion criteria are met, we will match each case with at least one control patient from the UCDMC based on the following variables: a) age, <50 years or >=50 years; b) gender; c) ethnicity/race ; d) hepatitis C genotype, type 1 vs. non-1; and e) stage of fibrosis (0-2 vs. 3-4).

Once all cases and controls are matched on the above variables, we will collect outcome data on the following variables: a) rapid virologic response at 4 weeks (yes or no); b) viral load at 4 weeks; c) early virologic response at 12 weeks (yes or no); d) viral load at 12 weeks; e) completion of therapy (yes, no or in progress); f) termination of treatment due to side effects (yes or no); and g) side effects experienced.

We will collect data on each patient at 4 and 12 weeks that will allow us to determine treatment response and track side effects which include anemia, thrombocytopenia, neutropenia, weight loss, rash, fatigue, GI upset and depression. This data will be collected, coded using a standard coding system and entered into a standard database system. This patient database will be encrypted with a password as it is developed and accessible only to approved research project members for data entry. Once all data has been collected, this data set will be converted into a non-identifiable database and the original encrypted database will be kept on a CD ROM in a locked file cabinet inside a locked office.

8.3 Statistical considerations

We will consider whether a patient has an early virological response (70% predictive of sustained virological response 24 weeks after completion of a 48 week course of treatment) after completing therapy for 12 weeks, measured via PCR as the primary endpoint (outcome), which is a binary outcome (response) variable. Let π_1 and π_2 be the early virological response rates in the traditional office visit group and the telemedicine group, respectively. We want to test the null hypothesis of no difference in the early virological response rate between the two groups (cases and controls), i.e., $\pi_1 = \pi_2$ (OR = 1), versus the alternative hypothesis that there is a difference in the early virological response rate between the two groups, i.e., $\pi_1 \neq \pi_2$ (OR$\neq$ 1). Then, a total of 100 patients (50 patients in each group) can provide the power of 12.3% to detect the difference of 10% (π_1 = 60%, π_2 = 50%) (0.5 in terms of OR) in the early virological response rate between the two groups by using two-sided Fisher's exact test at significance level of 5%. However, a total of 200 patients (100 patients in each group) can provide the power of 80% to detect the difference of 11.6% (π_1 = 60%, π_2 = 48.4%) (0.568 in terms of OR)] in the early virological response rate between the two groups by using two-sided Fisher's exact test at significance level of 5%.

8.4 Statistical analysis plan

Cohort comparison group demographics and clinical features will be analyzed qualitatively and quantitatively. A Fisher's exact test will be used to compare each of the dichotomous (or polytomous) outcome variables of interest between the two groups. As secondary analyses, logistic regression will be used to control for possible confounding factors while comparing a category variable between the two groups in which the group variable will be treated as a predictor.

8.5 Anticipated results

We anticipate that our study will demonstrate non-inferiority in terms of early virological response, treatment failures and side effect profile in patients seen through telemedicine consultations compared to regular office visits.

9. Conclusion

Telemedicine consultation offers the potential to increase access to specialists in remote and underserved areas and may be an effective tool for identifying and treating patients with HCV who live in rural communities who may otherwise go untreated and progress to serious liver diseases, such as cirrhosis and cancer. It offers a unique opportunity of real time interactions among the patient, the PCP, and the specialist. Telemedicine can also be utilized to provide education to practitioners regarding HCV and provide clinical support to primary care providers in the complex management of HCV patients. Future outcomes research is needed to examine the safety and efficacy of telemedicine for the management of chronic diseases such as HCV.

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14

Avera eCARE®, a Comprehensive Telemedicine Program for the Rural North Central Region of the United States

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1. Introduction

1.1 Early history of telemedicine in the North Central United States

South Dakota is the 17th largest state in America with an area of 77,000 square miles. It has a total population of 812,000 which ranks 46th of the 50 states. The population density of the state is also 46th of 50 states. The state can only be represented by one member in the House of Representatives, while it has two senators. Sioux Falls is the largest city with a population of 160,000 and is located near the southeast corner which borders Iowa, Nebraska, and Minnesota in a tri-state strategic location, often described as providing services to an estimated 1 million people. North Dakota and Wyoming form the north and west borders nearly 200 miles and 400 miles away respectively.

The Avera Health system is a Catholic non-profit system of hospitals, clinics, and long term care facilities which supports the population not only in South Dakota but to the surrounding states of this North Central region of the Midwest. It began with two separate religious groups. The Benedictine sisters in 1897 began to provide health care in the original capital of the Dakota Territories, Yankton, South Dakota. The Presentation sisters began their health ministry far to the north and west during diphtheria and typhoid epidemics in Aberdeen South Dakota in 1901. Nearly 100 years later in 1999 the two ministries joined their numerous sites of service to become Avera Health. This system now supports integrated facilities and non-integrated independent partners. Included in the growing Avera network are one tertiary care, university affiliated, health center in Sioux Falls, a series of smaller community hospitals, critical access hospitals (rural hospitals smaller than 25 beds and more than 35 miles from another hospital), many isolated clinics, several nursing facilities, and many free standing clinics. Figure 1 shows a 4-state area in the upper Midwest consisting of Minnesota to the East, North Dakota to the North, and Iowa to the Southeast. Shown are many of the approximately 228 sites in the system or in partnership. These entities are usually separated from each other by 50-100 miles. Many do not have a physician residing in those towns but are supplied by outreach from the next largest location of health professionals. Known challenges to rural care in this region include workforce shortages due to difficulty in recruiting all types of caregivers to an area with geographic isolation and substantial inclement wintry weather. Many communities are experiencing diminishing economic growth. The facilities are experiencing lower healthcare margins, but also an increased attention to sustain high quality of services.

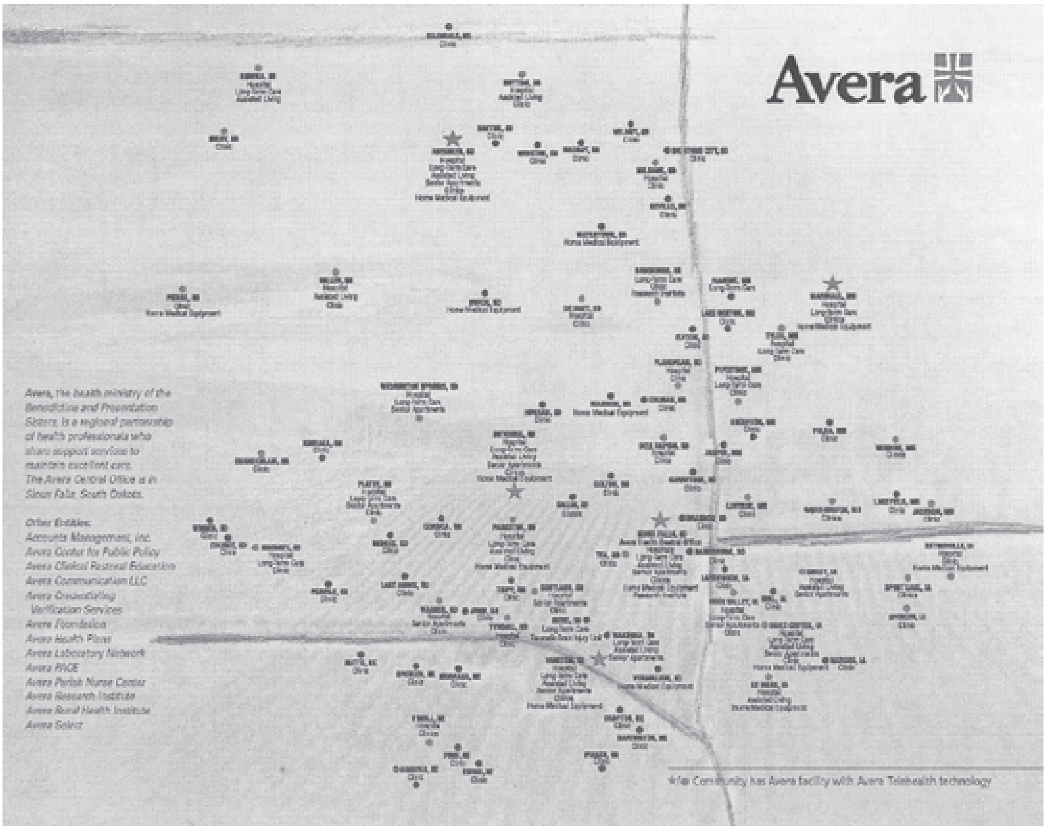


Fig. 1.

In 1993 the Avera Health System realized the importance of using telemedicine to add more services to this wide geography and launched its first telehealth services. Isolated projects continued to be developed, and now a comprehensive telemedicine program called eCare Services is provided to the region. The financing of the program has also grown in part by the willingness of the multiple isolated locations to bear the costs, but later due to the acquisition of grant support.

1.2 Telemedicine provision specialty and subspecialty consultations

Telemedicine consultation to the region was the earliest project. It began by installing televideo connectivity from a location usually in the main hospital to a clinic room at the distant site. The model now has the video equipment in the specialist's office suite. At the distant site a nurse attends the patient and can use a variety of electronic tools to transmit video and audio information back to the specialist. The audio and video is two-way, providing an interactive consultation aided by exam cameras, electronic stethoscopes, and video otoscopes. Figure 2 gives a brief example of this program called eConsult.

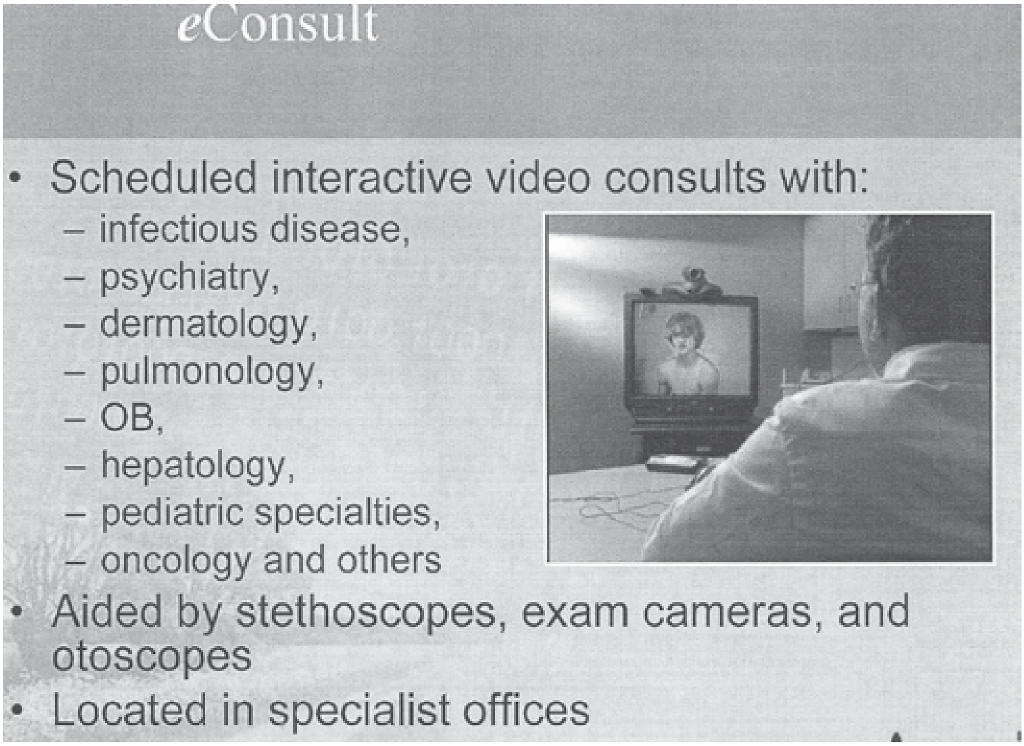


Fig. 2.

At first specialists in short supply were requested, such as psychiatrists and obstetricians as the region primarily delivered care by Family Medicine Physicians. Later, demand for subspecialties increased, including pediatric subspecialties and internal medicine subspecialties such as pulmonology and infectious disease. The visual nature of dermatology has made it easy for family physicians or mid-level providers to seek clarification of several possible diagnoses by ease of close-up video augmentation. The demand for eConsult services has continued to grow. As new subspecialties arrive at the tertiary care facility, their services are in great demand since the outreach areas have always had to send their patients long-distances out of the region. Figure 3 gives an idea of the growth of eConsult services since inception.

1.3 A tele-intensivist program, eICU®

The tele-intensivist program was the next large project to be launched. It now has expanded the quickest into the most number of sites connected to the tertiary care health center. In 2004 the medical leadership of Avera was impressed by a vendor (VISICU^{T,} now Phillips) offering a product called e-Care Manager^{T} which could provide 24-hour tele-video supervision of seriously ill patients. The product included a high quality camera with zoom characteristics and a two-way microphone. Computer software was installed at the hub or Core site, located at the tertiary facility, that screened physiologic and laboratory data and medication lists streaming from each patient's database for abnormal trends. Once an abnormal trend was identified as outside pre-set limits based on admitting diagnoses, an alert was sounded at the Core for possible intervention. A steering committee was

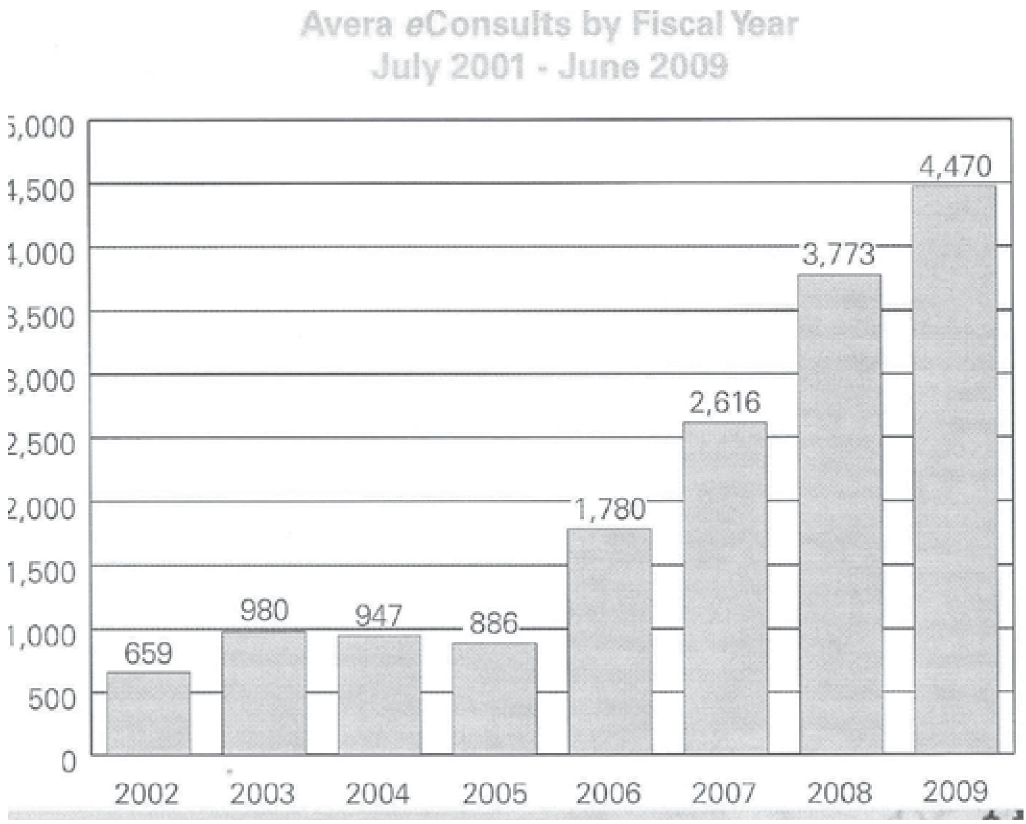


Fig. 3.

developed to implement what was called Avera eICU® CARE[T]. This committee spent approximately 9 months recruiting physicians and nurses to staff the control center which became identified as the "eICU®," arrange hospital privileges for the staff to practice in each participating hospital, obtain approval at each site for protocols for intervention, and supervise the schedule of the electronic set-up process in each institution. On September 21, 2004 the first site connected to the eICU® was launched. Over the next few weeks a total of four regional hospitals were having 24-hour supervision of their seriously ill patients. As of October 1, 2010 our eICU® is now responsible for the oversight of 25 sites and 102 patients. Figure 4 illustrates our core-station now simply called Avera eICU®.

In the control center, there are critical care nurses able to respond to bedside nurses at the remote sites to assist with more advanced monitoring than might ordinarily be provided routinely at such rural sites. Assistance is often provided for titration of medication drip infusions, preparations for special tests, and advice as to when a physician's input is needed concerning a particular patient problem. The core nurse also compiles a task list for the core physician that includes assuring for each patient that best practice strategies such as deep vein thrombosis prevention and gastrointestinal ulcer prophylaxis are in place. Nursing services are provided by two 12-hour shifts: 7 a.m. to 7 p.m. and 7 p.m. to 7 a.m. The eICU® nurses have assumed the greatest role in compiling and managing data, including attending physician and consulting team notes in order to create the initial admission note and daily

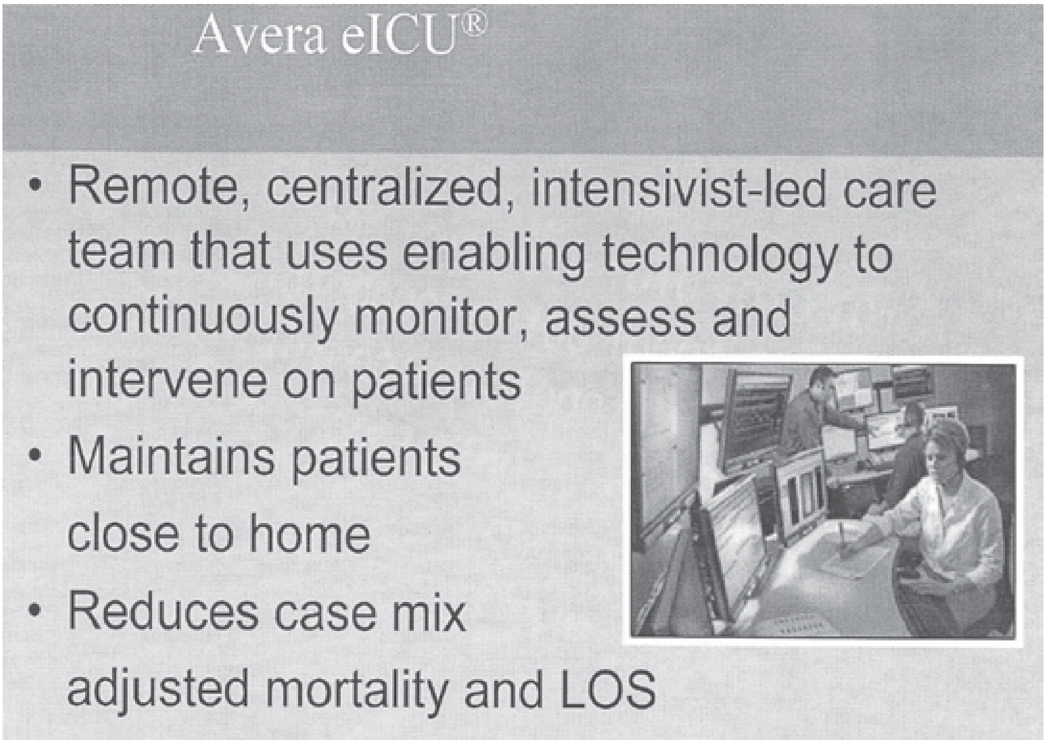


Fig. 4.

comprehensive progress notes. Accurate data is also necessary to obtain risk adjusted mortality and length of stay predictions. The eICU® nurses also assist in transfer of patients from remote sites to the tertiary care facility when it is requested by the local attending physician or determined by collaboration between the eICU® physician and the primary local attending team.

Figure 5 is a close up view of the five screens monitored by staff. At the top left is a screen on which are displayed the alerts detected by the software monitoring the bedside vital signs. The lower left screen is the audio-visual interaction with each patient room. The lower center screen contains the composite electronic database of all patients monitored at a given time. It includes admission and follow-up e-notes; up-to-date medication lists electronically linked from the patient's medication record at the bedside; electronic order writing capability; and laboratory flow sheets. The top right screen reproduces in real time any of the specific patient bedside monitors to create telemetry for that patient. In other words instead of only delegating the telemetry to the computer software, the clinician can also note changing vital signs, worsening ventricular rates in patients with arrhythmias, and deteriorating oxygen saturations in recently extubated patients to give a few examples. Finally, the lower right screen allows entry into each hospital's electronic medical record to be able to display additional data kept separately in those databases including imaging data.

A critical care physician is available for all but the usual morning rounding time for most physicians. This allows the critical care physician to be a resource when the primary physician is not directly available to the bedside. The primary bedside attending physician chooses in advance from several categories of requested communication frequencies from

Fig. 5.

the eICU® physician. Category I means that the bedside physician requests emergency interventions only and best practice initiation before being contacted. Category II physicians want the eICU® to adjust the care plan but to call them or their local covering partner regarding the need to initiate any new therapies. Those who request Category III status give full authority to the eICU® staff to manage their patients in their absence. They ideally check out their patient at the end of the day and check in for an update of patient status before their morning rounds. They will be notified of major or significant changes in their patient's conditions by the tele-intensivist.

The eICU® physician performs electronic rounds upon arrival for their shift. They use the software to stratify the patients in three categories of severity with a color-coded icon attached to the electronic database. Red patients are new admissions or unstable patients and generally require some evaluation by the physician hourly. Yellow coding suggests that the patient has reached a point of stability to where evaluation by the e-Care physician is suggested approximately every two-hours. Finally, a green icon suggests that the patient has reached a phase in which the care plan is being completed and only minor adjustments in care are expected for the day. However, ongoing monitoring does occasionally find a crisis in these patients which requires new major diagnostic or therapeutic interventions. Such activity is likely to result in change back to a "yellow" or "red" status.

The eICU® team is constantly monitoring all the remote patients and is assisted by the software which generates abnormal trending alerts. These are often not apparent to the bedside team because they are only seeing real-time vital signs, laboratory tests, and pharmacy lists. The alerts compare current vital signs with previous values and identify the abnormal trends. The software also alerts when pharmaceutical interactions are possible when a new drug is ordered. The alerts suggest change in dosing for changing renal and hepatic status as the software monitors renal function by estimated glomerular filtration and monitors hepatic function by liver function test results. The eICU® staff is notified immediately when laboratory results are reported as they interface to the core computer. The laboratory tests are also color-coded: green if normal, yellow if slightly out of range, and red if markedly out of range.

Finally, the bedside team can request immediate televideo connection by the eICU® into a given patient room by pressing a red "e-Alert" button located near the "code" button. This can summon the eICU® team to assist with initial management of a code blue, to assist with urgent hemodynamic or oxygenation issues, or also for updates on status. Such updates might include reporting when patients are transferring out of the room or returning from tests, have recently been intubated or extubated, or even when family is requesting additional input such as an update from the eICU® physician.

Each day there is a to and fro set of interactions between the bedside team and the eICU® team. For example, requests are made by the bedside nurses to the eICU® nurses for assistance with unexplainable monitoring data that appears to be artifactual. They may request the eICU® nurse assistance to confirm nursing diagnoses. There are requests by the bedside nurses to the eICU® physicians for routine orders such as pain or sedation needs. The bedside nurses may request the eICU® physician to review x-rays for evidence of proper position of endotracheal tubes, central lines, and oro- or nasogastric tubes before their use. The eICU® nurses and physicians may call the bedside team to clarify whether an abnormal change in a vital sign has come to their attention, whether there is a bedside activity such as a bath or suctioning which might explain the abnormal trend, and to jointly determine a solution to the alerted problem. The eICU® physician writes orders electronically in the software database which is printed in the given ICU and then is included on the patient chart. The eICU® physician will give a detailed explanation of the rationale behind orders in a printed note that is placed on the patient chart. These notes serve as a reference for the bedside physician for events than occurred in their absence.

1.4 ePharmacy

Once the Avera eICU® CARE was up and running, it was noted that frequent requests would be made by the local attending physician or the local hospital pharmacist for information on dose adjustments or drug formulations. The eICU® team had easy access to critical care pharmacy interns, fellows and staff for detailed explanations and the rationale behind their suggestions. As a consequence of these frequent requests, the Avera Health System eventually launched a tele-pharmacy program in 2009 which is located in the eICU® core facility as well. This allows for independent contracts by local hospitals for remote medication order review and order entry. Location inside the eICU® also allows for interactions between the eICU® core nurse and physician with the pharmacists for clinical adjustments in doses based on ideal weight, concomitant medications, and reduced hepatic and renal function. Smaller rural hospitals may not even have pharmacists on site for much time each day. The ePharmacist can meet the needs of the nurses and physicians at those sites. ePharmacy services are available 24 hrs a day. They are physically located in the eICU® from 7 a.m. until 9 p.m. and work out of the main hospital Pharmacy the remainder of the time. The goal is to become a 24/7 service in the eICU® CARE as soon as staffing allows. The ePharmacist uses the eICU® software to write consulting notes to explain the formulations of adjustments and to offer suggested times for drug levels to be sent to the laboratory. Such pharmacokinetic advice is well-received. Figure 6 illustrates the ePharmacy program.

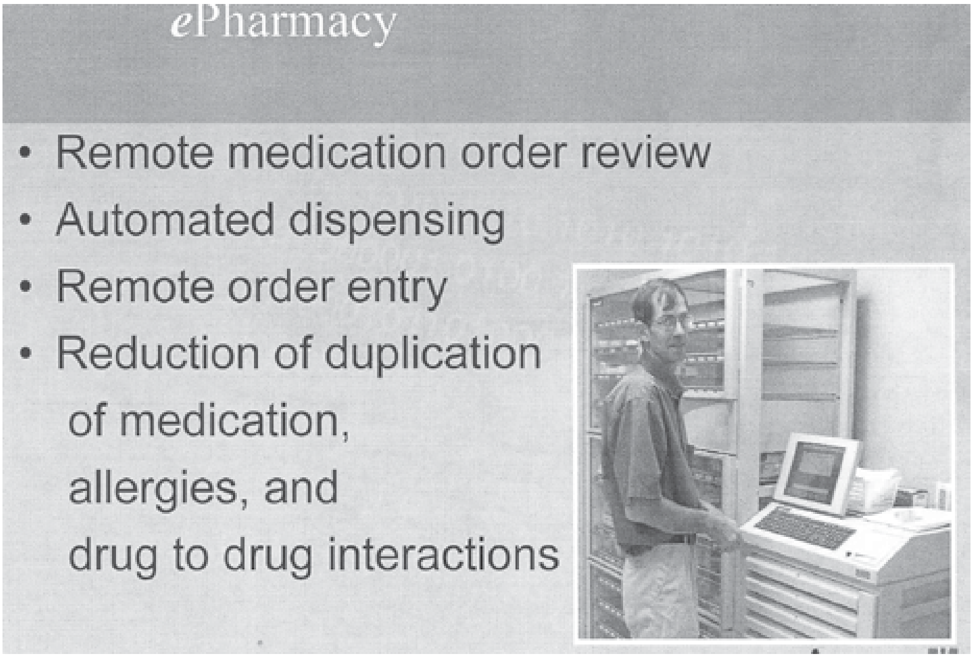


Fig. 6.

Figure 7 illustrates the growth (success) in utilization of this program over time. Numbers reflect interventions, not reviews of orders.

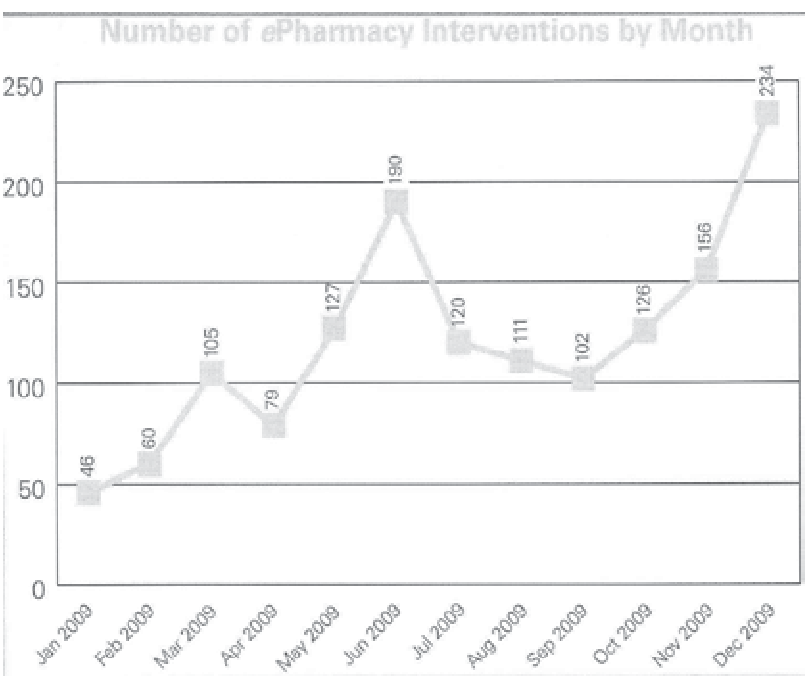


Fig. 7.

1.5 Electronic Emergency Services (eED)

The eED, also launched in 2009, has exploded in popularity with rural physicians. Figure 8 illustrates this program. The ability of the rural physician to have a resource to assist with immediate stabilization and triage decisions has been considered of utmost value in meeting an urgent need for problems which they have little time to prepare. Triage decisions are made in a timely manner, protocol initiation for such issues as goal-directed therapy as part of the Surviving Sepsis Campaign, thrombolysis for acute myocardial infarction patients with elevated ST-T electrocardiogram segments (STEMI patients), and therapeutic hypothermia preparation are examples.

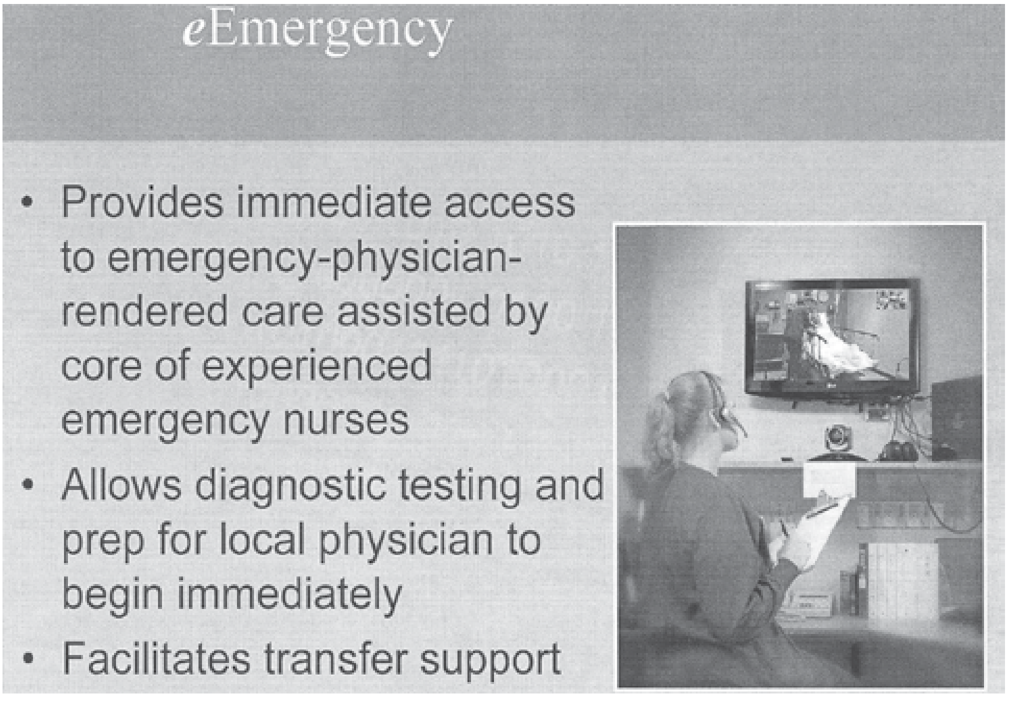


Fig. 8.

Figure 9, the circle graph the diagnostic diversity of the patients in whom eED has assisted.

1.6 Mobile Units

The eICU® vendor made available a mobile unit in 2007. As it was demonstrated to our rural sites, it quickly became a way to create flexibility for use in their hospitals. By wiring rooms in several locations, they could have patients monitored in their “emergency room,” during a “rapid response,” or on different floors of their hospitals. Even at our tertiary care hospital the mobile units have been used in a similar way. They are available for “rapid response” and to create “step-down” type of supervision for patients such as trauma or general surgery patients who have been transferred out of the ICU. In this way the mobile units can help with throughput of critically ill patients to avoid situations where no beds are available for new admissions or bounce back patients to the ICU. Figures 10 and 11 illustrate a mobile tele-intensivist unit.

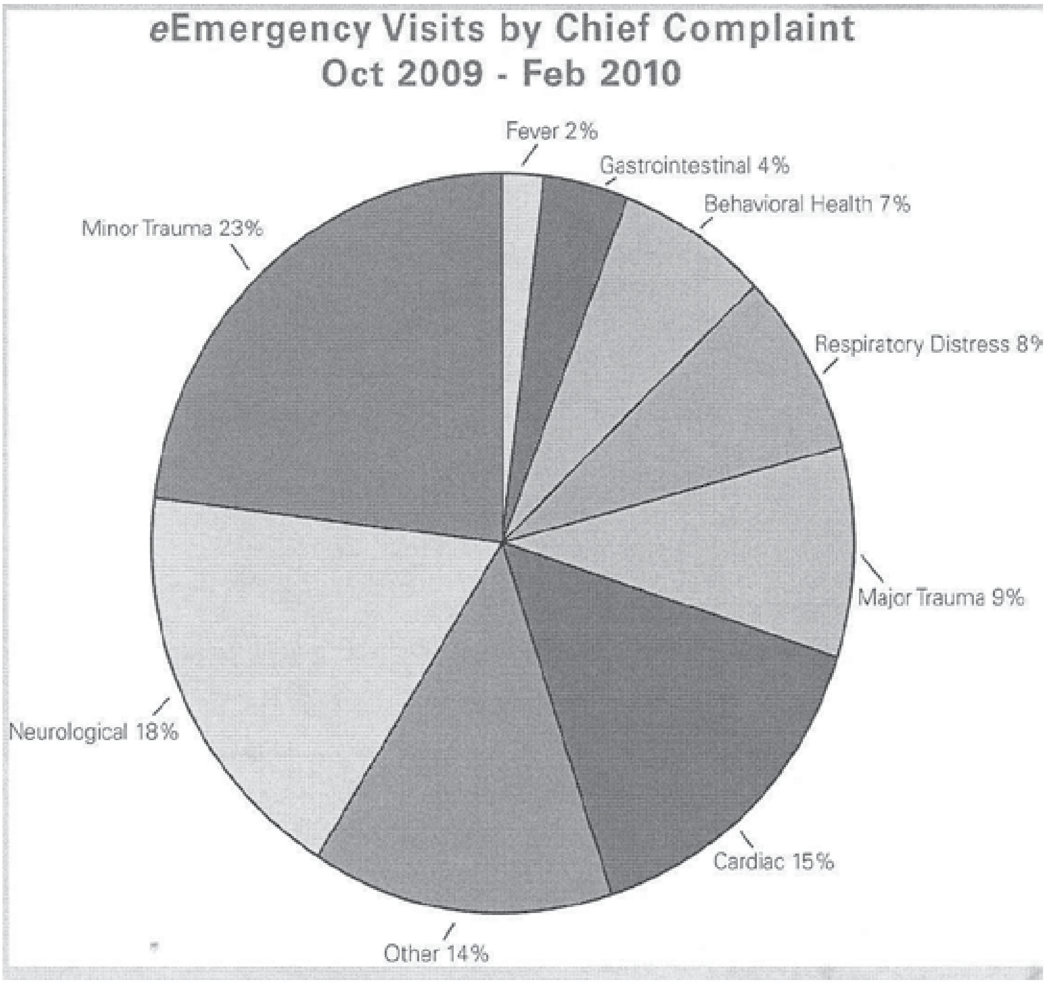

eEmergency Visits by Chief Complaint
Oct 2009 - Feb 2010
Fever 2%
Gastrointestinal 4%
Behavioral Health 7%
Respiratory Distress 8%
Major Trauma 9%
Cardiac 15%
Other 14%
Neurological 18%
Minor Trauma 23%

Fig. 9.

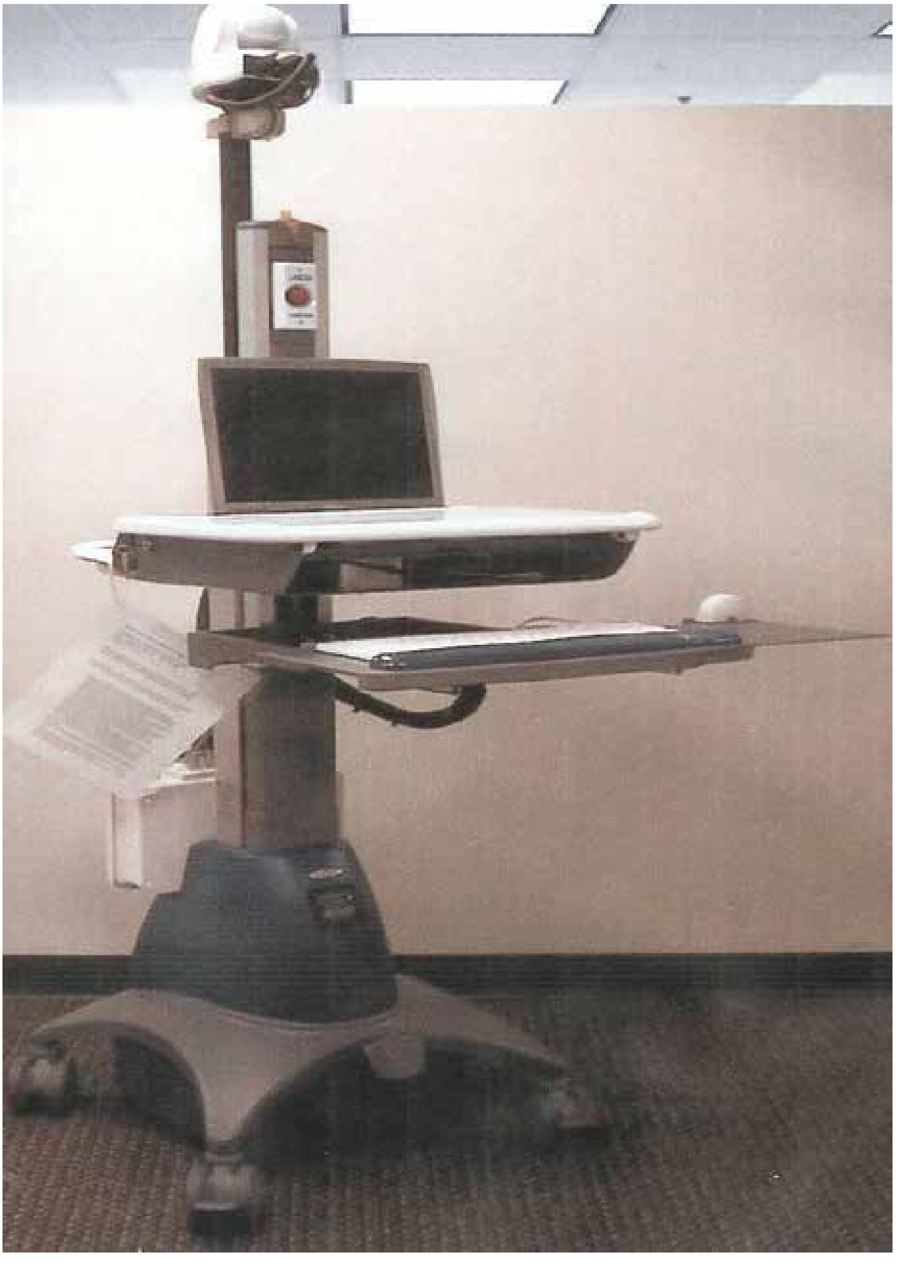


Fig. 10.

Fig. 11.

1.7 Two-way video

Two-way video was implemented in our newer tele-intensivist sites as of 2007 since it was a later upgrade by the vendor to their product. Figure 12 illustrates the two-way video screen which appears in the core control center when activated in a given patient room. Feedback from our patients and staff as well as that from other eICU®'s around the country confirms that patients and staff feel more reassured and supported by being able to view the remote staff who are assisting with surveillance and the execution of their care plan and most especially when responding to critical changes in clinical course.

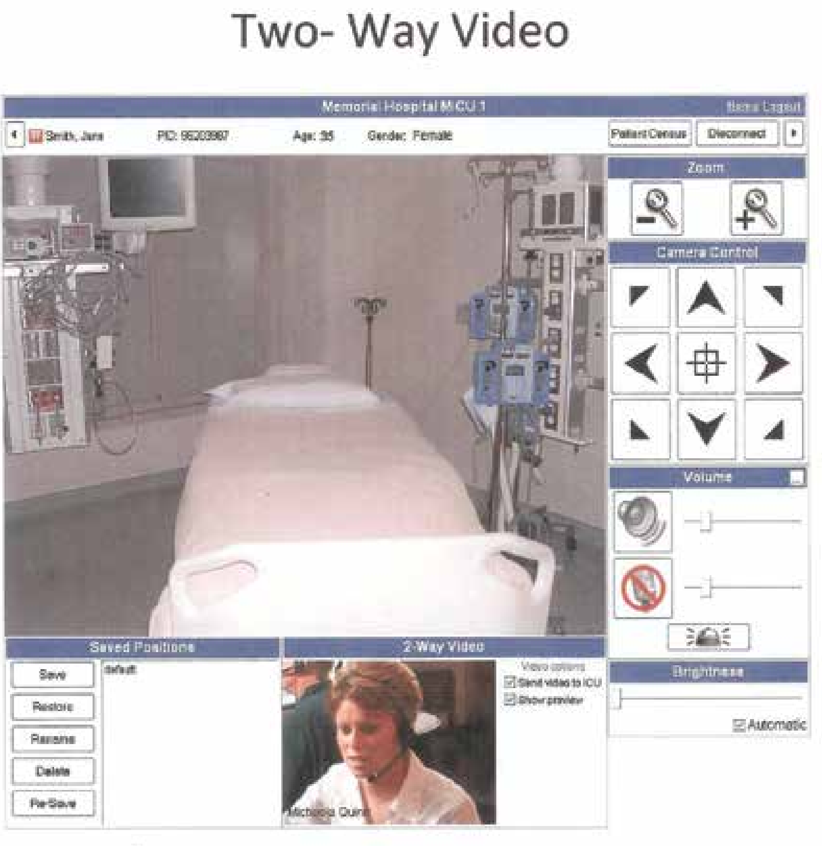


Fig. 12.

1.8 Partners from other health systems

We expanded from our initial regional hospitals all in one state to multiple smaller hospitals including critical access hospitals. This growth was extremely successful but also created new challenges. One problem was the need to have physician and nursing licensing for multiple states and credentialing of each eICU® physician at each institution. In our case that means a staff of 8-12 intensivist physicians (some are part-time) need credentials in soon to be 27 hospitals. Also, to access patient databases at each hospital, multiple passwords and sign-on directions are required. This was especially true when we contracted for services to hospitals in other Health Systems. In those cases there might even be different servers for the patient databases which required different navigation training. When monitoring patients from different health systems, there was often a greater need to build relationships from the eICU® team to local caregivers. Because of a lack of prior interactions, there was no basis for trusting the care provided by the tele-intensivist nursing and physician staff. As a result there were episodes of local provider resistance to the telemedicine supervision of their patients until trust grew from excellent outcomes as a result of co-management of dangerously ill patients.

1.9 Operating in multiple states

The biggest issue in operating in multiple states is nuances with licensure. Different states have different requirements for background checks, fingerprinting, and depth of education certificates that must be forwarded. Some states require on-site visits to their licensing offices. There can also be legal restrictions to scope of practice which impair the full utilization of telemedicine capabilities in that state compared to others.

2. Outcomes

2.1 Severity scoring

One of the first benefits we experienced after launching our tele-intensivist program was the ability to track data now captured by the vendor's software which was previously not available to us. The eCare Manager[T] began feeding back data after the first quarter of operation. For example, we began to compare severity scores of our patients not only in our tertiary care facility but also in each participating hospital. The severity scores from our patients were also compared to other sites in the country which were utilizing this product. At present there are more than 45 sites in the United States and approximately 10% of all critically ill patients are monitored at any one time by the same technology. APACHE ® III (Acute Physiology, Age, Chronic Health Evaluation) algorithms were used to define the predicted mortality risk for these ICU patients. The APACHE III database is used to estimate the mortality risk for individual ICU patients using chronic health status information, severity of illness on ICU admission, age, prior length of stay and ICU admission diagnosis. (APACHE is a registered trademark of Cerner Corporation). This tool calculates a severity score based on acute physiology that includes 18 measurements of vital signs and laboratory tests, age of the patient, Glascow neurologic score, and chronic comorbidities. In our first analysis of our patients with APACHE III software, we noted that our severity is comparable to any other site in this large database of patients and published our initial data reports (Figure 13).[1]

The vendor's software has now changed its severity scoring system to APACHE IV. Ongoing analysis of our markedly expanded population of patients reveal that the severity of all the patients in our monitored beds remained greater than a majority of the other sites to whom we compare ourselves.

2.2 Mortality

The APACHE scoring system has continuously been validated on a rotating database of over one million patients to be highly predictive of mortality and length of stay outcomes. Over the first few years we were able to determine that our actual ICU mortality was considerably less than predicted by the APACHE score.[1] In quarterly reports we consistently ranked the best among all of the eICU® groups across the country in actual to predicted ICU mortality, actual to predicted ICU length of stay, actual to predicted hospital mortality (for the group of patients who spent part of their hospitalization in the ICU), and

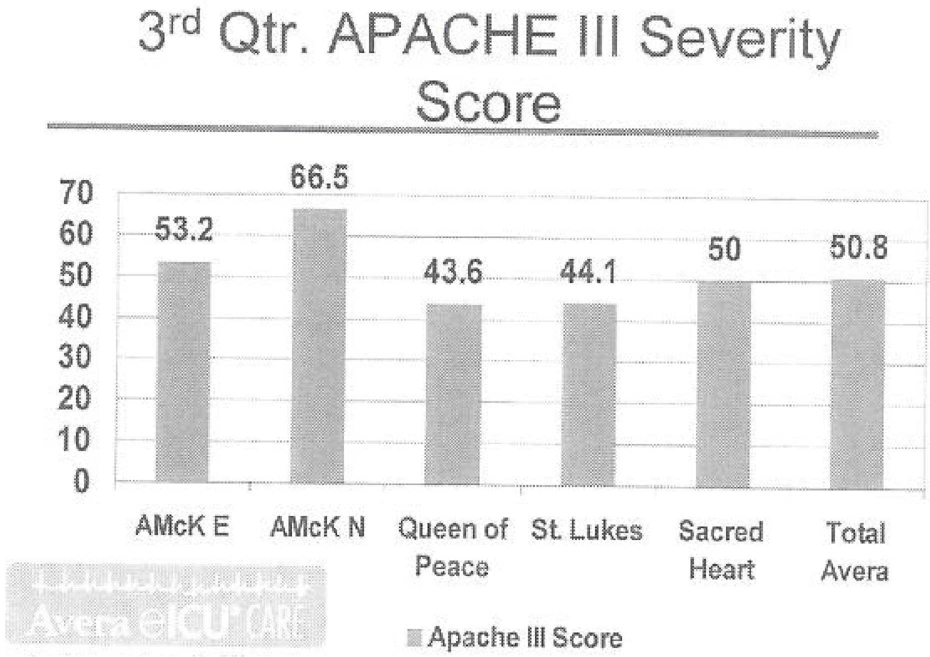


Fig. 13.

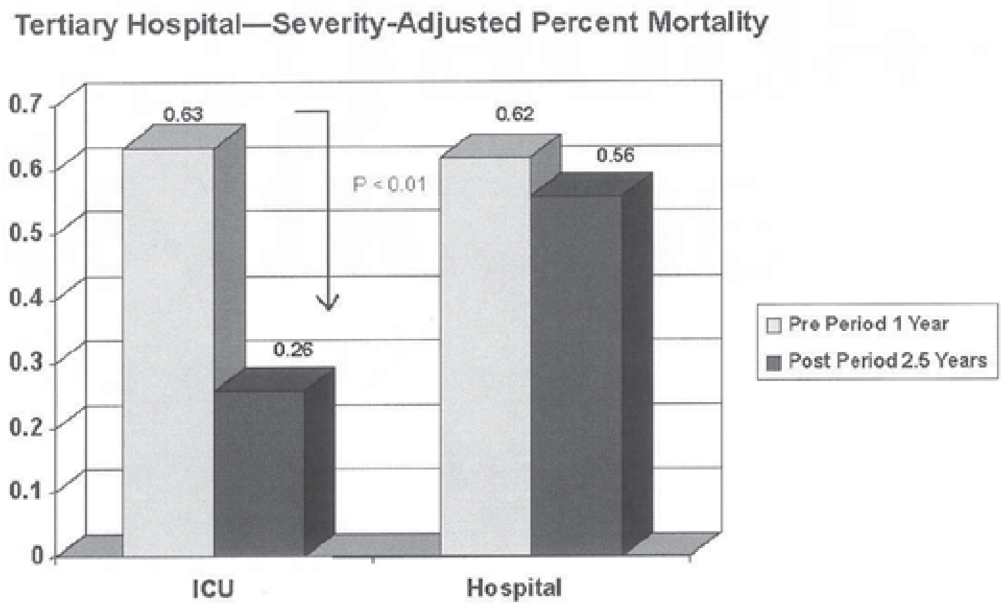
actual to predicted hospital length of stay (for the same group of patients). It was not clear whether these outstanding outcomes were due to the implementation of the tele-intensivist program. We therefore conducted a study in which we compared these measurements over the 2.5 year period after implementation of the eICU® to two year's worth of randomly sampled charts before the implementation.[2] Figure 14 demonstrates that there was a statistically significant improvement in these outcomes with the initiation of this telemedicine clinical program.

2.3 Lengths of stay

Since we were able to monitor our severity-adjusted actual to predicted ICU lengths of stay, we began to calculate the ICU days saved.[2] We continue to record this in our quarterly quality reports. Figure 15 illustrates this calculation before vs. after the project was begun.
Since ICU length of stay has continued to be less than predicted we have also been able to calculate cost savings in the care of our seriously ill patients.

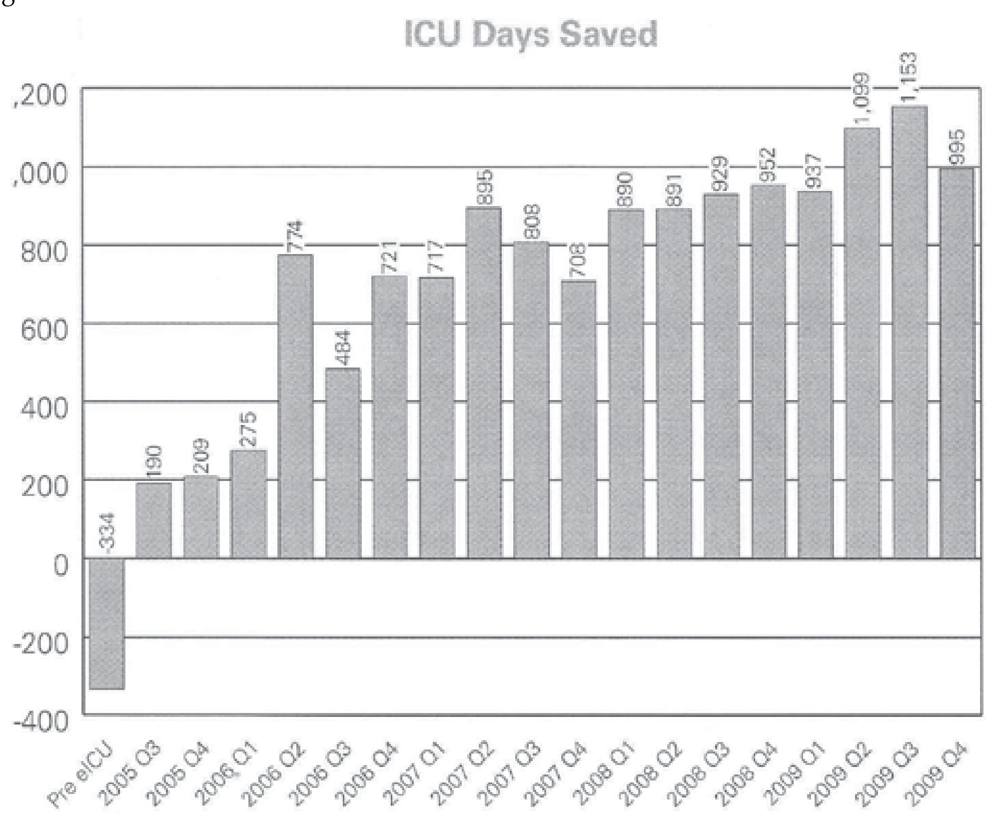
2.4 Ventilator days

Another important outcome we realized soon after the initiation of the tele-intensivist program was the improvement (decrease) in ventilator days. The 24-hour close supervision of patients allowed the weaning protocol to be facilitated by reassurance from the eICU® physician at all hours of the day or night. Figure 16 illustrates the reduction in ventilator days on average by 2 days. Even into our 6th year now, our average ventilator days still hover around 3.0 days.
We created a special program called eICU® ventilator rounds each afternoon to be described below which formally focused attention on weaning even before we had a bedside intensivist program.



Tertiary Hospital—Severity-Adjusted Percent Mortality
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.63
0.26
P < 0.01
0.62
0.56
ICU
Hospital
Pre Period 1 Year
Post Period 2.5 Years

Fig. 14.



ICU Days Saved
,200
,000
800
600
400
200
0
-200
-400
-334
190
209
275
774
484
721
717
895
808
708
890
891
929
952
937
1,099
1,153
995
Pre eICU
2005 Q3
2005 Q4
2006 Q1
2006 Q2
2006 Q3
2006 Q4
2007 Q1
2007 Q2
2007 Q3
2007 Q4
2008 Q1
2008 Q2
2008 Q3
2008 Q4
2009 Q1
2009 Q2
2009 Q3
2009 Q4

Fig. 15.

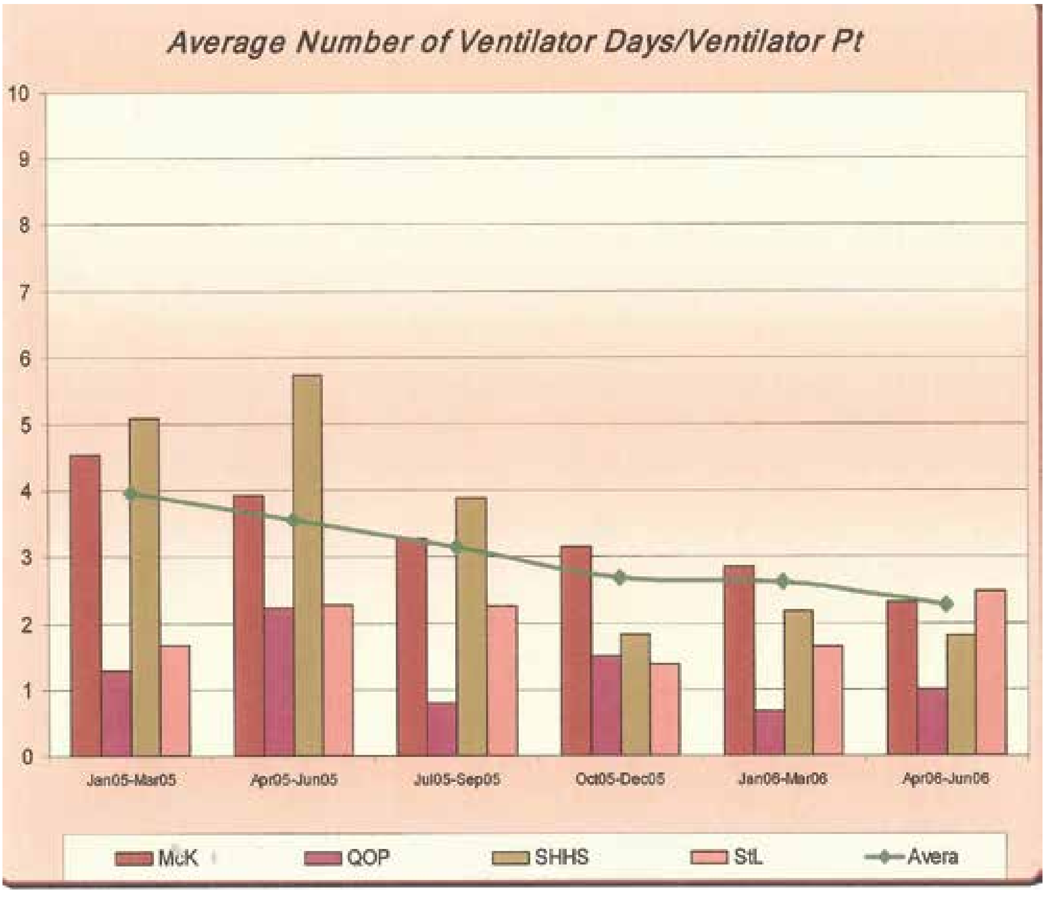


Fig. 16.

2.5 Transport savings

As a result of growing trust and comfort in having the assistance of the eICU® team, excellent satisfaction was voiced by remote providers and patients and families because many of them were able to remain in their local community. This satisfaction was documented by us in surveys and published in our second major publication of our experience.[2] As we investigated this benefit further we found that we could prove an enormous savings to the patients in our area through avoided transfer costs. Transfers would usually require helicopters or fixed wing transfers because of the geographic separation and severity of cases. Figure 17 estimated over a million dollars in such savings after implementation of the tele-intensivist program.

2.6 ePharmacy quality programs

Figure 18 demonstrates the influence of the ePharmacy program on quality of care. After implementation a variety of potential adverse events were avoided.

First-Year Fiscal Impact of Avera eICU® CARE

Hospital	Go Live Date	Total # of ICU Admits Since Activation	Avoided Transfers	Avoided Cost Per Transfer	Total Saved
Estherville	02/2006	36	5	$9,296	$46,480
Flandreau	08/2006	17	14	$5,697	$79,758
Marshall	09/2005	183	46	$8,234	$378,764
O'Neill	10/2005	35	10	$10,889	$108,890
Parkston	08/2005	34	17	$7,647	$129,999
Sioux Center	07/2007	7	2	$6,228	$12,456
Spencer	03/2006	74	62	$8,588	$532,456
Tyndall	09/2006	8	4	$7,644	$30,576
TOTAL				$64,223	$1,319,379

Fig. 17.

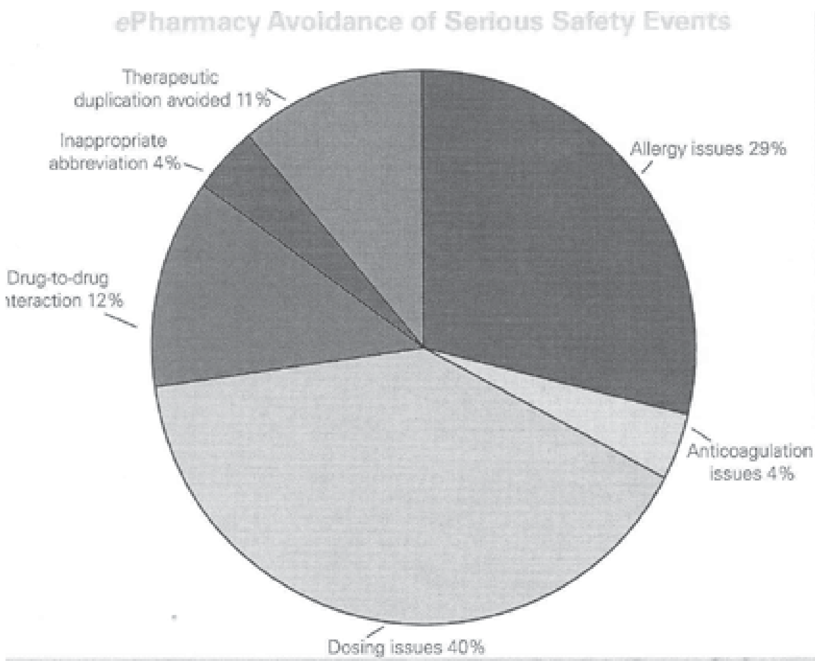


Fig. 18.

2.7 Special programs

Concomitant with launching of each component of telemedicine care, special focused projects to improve quality of care were incorporated into the daily routines. In the tele-intensivist program, the eCARE Manager^{T} prompted many best practice improvement strategies. For, example alerts appeared when deep vein thrombosis prevention and GI ulcer prophylaxis were not being addressed. In our 6 years of operation we also included 3 main internal projects: Ventilator Rounds, Glucose rounds, and Sepsis screening.

2.8 Ventilator rounds

Before our bedside intensivist program was launched, we performed daily multi-disciplinary ventilator rounds at 2:00 p.m. The eICU® physician activated the camera in each patient room sequentially where the bedside nurse and the assigned respiratory therapist reported on the progress with weaning. Families were involved as they were available. In patients who were hemodynamically stable, we ensured that sedation had been stopped for a time, that weaning parameters were measured off controlled mechanical ventilation, and also verified the ability of the patient to handle secretions and protect the airway. Any barriers to weaning were identified with a plan for solution. As mentioned above, there was quickly seen a significant reduction in ventilator days.

2.9 Glucose rounds

Each evening shift in our eICU®, the physician began Glucose Rounds which consisted of a systematic evaluation of the degree of control of glucose levels in our most seriously ill patients likely to remain in the ICU for several days. If control was not near a target for mean daily glucose less than 180 mg/dL, more aggressive therapy was prescribed. An example might be a switch from sliding scale subcutaneous insulin to a constant insulin infusion. In this way we were able to lower our mean daily glucose for the entire unit from a mid 140 mg/dL range to an upper 130 mg/dL range.

2.10 Sepsis screening

A team approach to early sepsis detection has also been included in our daily workload. To ensure compliance with the Surviving Sepsis Campaign, we decided to use both the software alerts and an initial screen by our eICU® nurse to fill out a form which documented SIRS criteria in every patient admitted for our supervision. Those patients with SIRS criteria are reviewed by the physician for evidence of infection. If found, the intensivist ensures that early goal directed therapy has been initiated and choice of antibiotics is appropriate.

2.11 eStroke

At the time the eED project was being planned, several national initiatives (even ACLS guidelines) were launched to identify candidates for thrombolysis in stroke patients. Also during that time the emergence of stroke teams occurred in many hospitals to rapidly respond with multidisciplinary care for any hospitalized patient with a possible impending cardiovascular event. It was therefore a natural development that such a team could be summoned through telemedicine activity. Figure 19 illustrates the eStroke program which has become an important part of the eED effort.

3. Financing

Initially our programs were funded solely from our participating sites by an initiation fee and then by monthly support based on the number of beds which were supervised. The initiation cost covered the hardware fees, any vendor's software and management support fees, and the time required by information technicians and nursing and physician staff to launch each new site. The subsequent monthly requirement was needed to cover salaries of health care technicians, Pharm.D.'s, critical care or emergency department nurses, and intensivist or emergency department physicians. No charges were made to any patient or

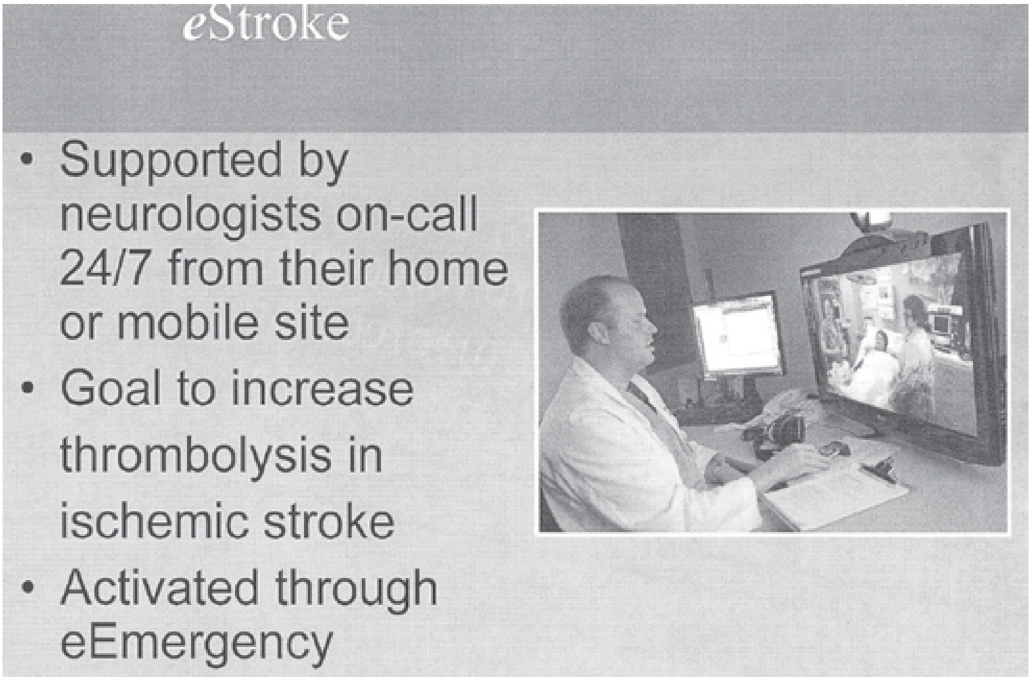

eStroke
• Supported by neurologists on-call 24/7 from their home or mobile site
• Goal to increase thrombolysis in ischemic stroke
• Activated through eEmergency

Fig. 19.


Funding
Grants awarded since 2005:
• Office for the Advancement of Telehealth, Telehealth Resource Center Grant
• 7 U.S. Department of Agriculture, Distance Learning and Telemedicine Grants
• Office of Rural Health Policy Network Planning Grant
• Office of Rural Health Policy Outreach Grant
• 3 Grants from the South Dakota Department of Health
• 2 Grants from private foundations
• Federal Communications Commission Rural Health Care Pilot Program Awardee
• Center for Medicare and Medicaid Emergency Divergence Grants
More than $21 million total grant dollars garnered

Fig. 20.

third-party payer. The programs were basically supported by the cost savings from the prevention of complications, the improved throughput of patients, and the reduction of numbers of outliers for any given diagnosis-related group (DRG).

The telemedicine effort of our institution has met the needs of our rural population separated by a vast geography whose mobility is often challenged by both distance and the threat of inclement weather. As mentioned patient and provider satisfaction has been excellent. The improved quality that has been demonstrated and the cost savings to rural medicine programs has been well received by granting agencies in the recent time of search for new health-delivery strategies. Figure 20 lists many funding sources which have enabled us to leverage expertise from the tertiary center to a great variety of hospitals and multiple different hospital departments.

4. Future considerations

4.1 Pediatric tele-intensivist care

The eICU® has received several requests for assistance with the care of pediatric patients, usually during urgent or emergent situations. These requests have resulted in a potential program aimed at this population. The pediatric tele-intensive care would consist of a dedicated e-Consult set up as described earlier but located not in the doctors' offices but at the pediatric intensivist work site adjacent to the tertiary care pediatric intensive care unit. Calls coming in are handled by the pediatric critical care nurses. They would involve the critical care pediatric nurse practitioner or intensivist physician as needed. Often arrangements for transfer to the tertiary care site will be made at that time. The pediatric intensive care team then can prepare the resources needed after the arrival of the patient and family. This program is expected to be launched within the next 12 months.

4.2 e-Labor and delivery program

Our tertiary hospital has had in-house obstetricians for a few years. These laborists are available to monitor patients in the hospital at any given time. They respond to calls from the emergency department in consultation to assist with care. Finally, they are available by telephone for calls from outlying sites. Setting up a telemedicine suite to assist with outside OB/GYN procedures is being considered.

4.3 eHospital

eHospital services, monitoring non-ICU inpatients, has also been identified as a potential future program. Many of the smaller community and critical access hospitals have a limited number of providers in their communities to care for patients. Quality of life can be impacted by frequent after hours calls to these providers. Providing inpatient monitoring for an expanded number of patients could potentially provide support to these providers.

4.4 Concierge care

It has been envisioned that seriously ill patients who can afford to pay for a telemedicine station in their homes would desire such connectivity to a tertiary care team of specialists. It is also possible that federal agencies might be interested in extending telemedicine into the home to empower more patients to perform self care of serious illnesses. One such program which has been considered is the telemedicine supervision of home hemodialysis or nocturnal dialysis programs.

4.5 Airline emergencies

Airlines have desired to be more prepared for health emergencies in recent times as evidenced by the expanded availability of automatic external defibrillators (AED's). Several airline carriers have expressed interest in contracting for telemedicine services to supervise the management of in flight emergencies.

5. Part V. Summary and conclusions

In summary, telemedicine has been a good fit to leverage health care expertise in our health system and to neighboring partners because of the geographic separation of many sparsely populated towns and cities in the upper Midwest. Although planning began as early as 1993, the major growth has occurred in the past 10 years. From one on one consultation, the newer programs have provided specialty supervision by one team to an ever-increasing number of patients and sites in multiple health systems and multiple states. The quick acceptance and great satisfaction of the tele-intensivist project with its documented cost-effective care markedly catalyzed the development of similar services in other departments of the tertiary care medical center. Figure 21 summarizes how these multiple individual projects have now come to be coordinated in a effective and innovative telemedicine system of care.

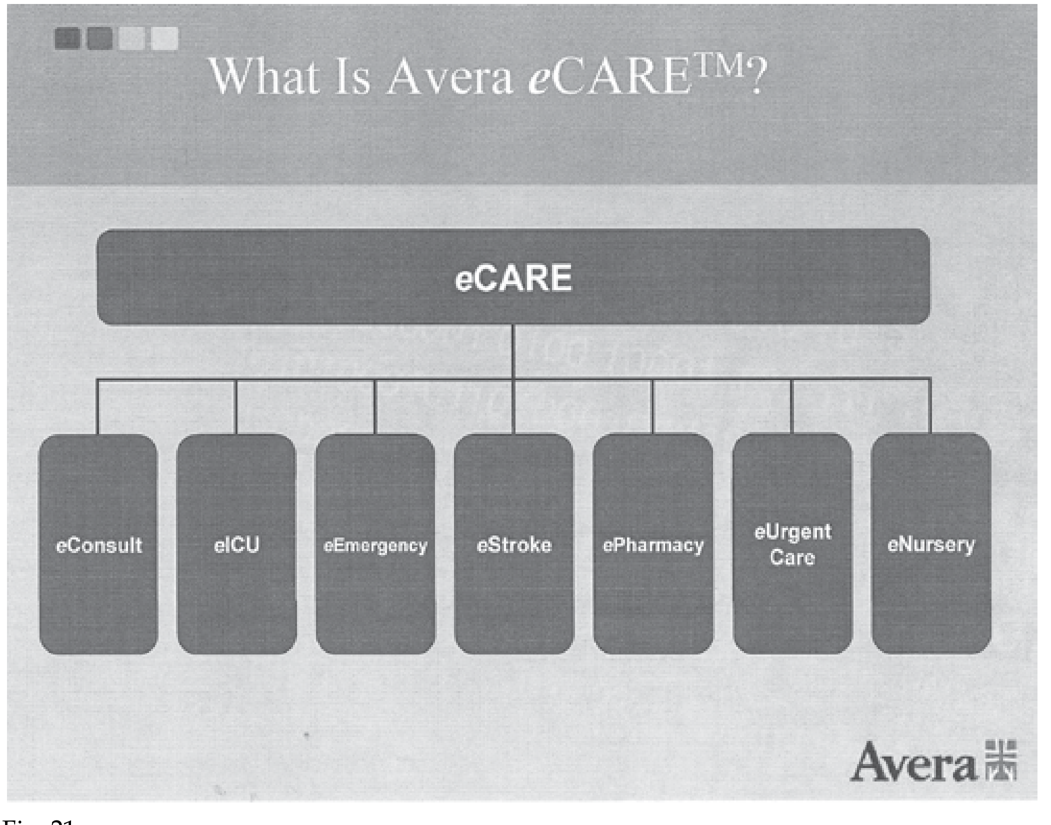


Fig. 21.

Figure 22 is a snapshot of the sites now covered by one or multiple of our telemedicine services at the present time. The eICU® alone will soon cover 28 sites with the capability of monitoring up to 117 seriously ill patients.

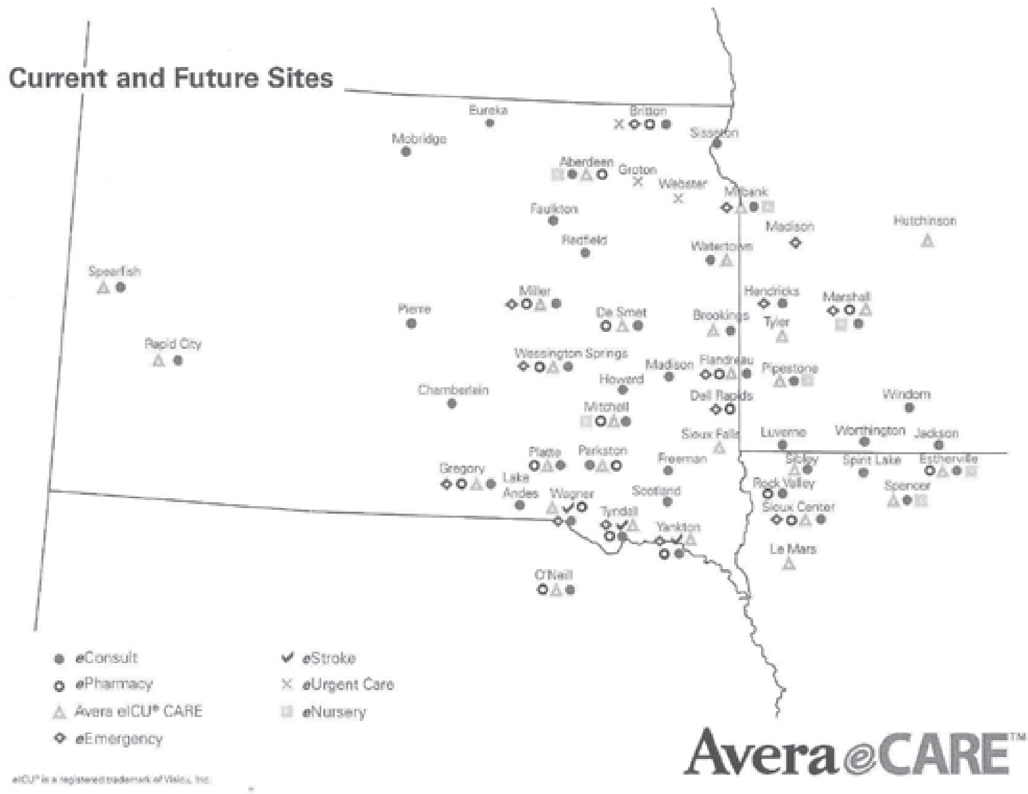


Fig. 22.

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[2] Zawada ET Jr, Herr P, Larson D, et al: Impact of an Intensive Care Unit Telemedicine on a Rural Health Care System. Postgraduate Medicine 2009;121:160-170.

[3] Lilly CM and Thomas EJ. Tele-ICU: Experience To Date. Journal of Intensive Care Medicine. Sept 2009;1-7.

15

Recent Advances in Telepathology in the Developing World

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Nigeria

1. Introduction

The main challenge in healthcare delivery for most developing countries has been how best to take medical services to the remotest locations, because the greatest population lives in rural areas, where socioeconomic conditions and the means of communication are quite rudimentary (International Network for Cancer Training and Research, 2005). Particularly, there is a general paucity of pathology services in the developing countries and so often the correct diagnosis, which is key to survival, is hard to come by. Even in those centers where pathology laboratories exist, these are often the least developed clinical specialty. Hospitals and clinics located in these regions are generally limited in the care they could provide by the lack of pathologists and many of these institutions do not have well equipped laboratories with adequate number of staffs. Additionally, in view of the considerable distances between some rural and referral centers in the developing countries, consultation with an expert pathologist is a rarity, time consuming and expensive.

A wide range of factors have influenced the deployment and growth of pathology resources throughout the developing world. In sub-Saharan Africa, the shortage of medical staff in pathology laboratories is particularly severe. Except in a few cities, majority of specimens are not even sent for pathological examination. Delays and low quality of service makes the pathology tests of limited value to clinicians. General laboratory quality standards including quality control and quality assurance are non-existent or suboptimal (Malami & Iliyasu, 2008a) and the skill of the technicians is highly variable. Other pervasive problems for pathology laboratories in sub-Saharan Africa are related to limited opportunities for basic training in pathology and the lack of books, CDs and other educational materials for continuing improvement. The result is a lack of operational competency with little back-up (Ahmad, 2005; Ahmad, et al 2009). It is therefore apparent that, perhaps more than anywhere else, it is in these resource-constrained nations of Africa that the greatest unmet need for pathological services exists. It is crucial that innovative interventions address these needs to improve the quality of laboratory services. In the context of these considerations, therefore, it is quite fortuitous that the world has witnessed phenomenal advances in technology that incorporate new methods in communications and information technology into medical practice. This has virtually revolutionized the practice of pathology and helped to facilitate professional linkages and dissemination of cutting-age knowledge. These improvements in technology have largely solved the technical requirements for telepathology (Wells & Sowter, 2000). Consequently, there is a considerable literature on the

potential use of telepathology in the developing world resulting in a new look at how secondary and tertiary healthcare can be provided in these resource-constrained settings.
In the last couple of years a number of institutions and individuals have attempted to introduce telepathology to some developing countries with varying degrees of success but these had been hardly reported or properly documented. This chapter will, therefore, dwell on the background, opportunities and barriers to telepathology in these underprivileged locations.

2. Telepathology in perspectives

Telepathology is the subspecialty of telemedicine in which pathology is practiced at a distance using imaging and telecommunications. But unlike other applications of telemedicine, characteristic of telepathology is that data are transmitted mainly in the form of images. According to Weinstein et al telepathology can be defined as the remote primary diagnosis, consensus diagnosis, case conferencing, or expert consultation of either electronically transmitted, static, digitalized images, or real-time pictures obtained using remote robotic microscopes (Weinstein et al, 1987). In other words, telepathology may involve the acquisition of histological, cytological, and macroscopic images for transmission along telecommunication pathways for diagnosis, consultation, or continuing medical education (Baruah, 2005).
It is a comparatively new technique in medical practice whose initial use arose from the need for real-time diagnosis of frozen section material at hospitals that lacked tissue pathologists (Nordrum, 1996). From these humble beginnings, telepathology has entered a digital age and a level of sophistication that permits the practitioners to currently view high quality real-time colour images and to control all aspects of a robotic microscope at a remote location in the course of consultations that often take a fraction of a second (Wells & Sowter, 2000). Routinely, telepathology systems nowadays enable remote diagnosis (intra-operative frozen section and permanent section), subspecialty consultations, and better educational feedback. Second opinions, including even remote consultation across the globe, are not only technically feasible but also reasonably user friendly (Weinstein et al, 2001). Studies have shown that its accuracy is comparable with that of conventional light microscopy for most diagnoses. These and other advantages have influenced the decision of some developed countries which have made it a priority to incorporate telepathology applications into their healthcare systems in an effort to provide better services.
Telepathology links have evolved from the era when analog telephone lines were used characterized by slow data transfer to the extremely rapid transmission of today using wireless technology. The principle feature of telepathology is that communications are bidirectional, so data can be sent to and fro. It may employ store-and-forward method (static), real-time approaches (dynamic) or a third approach which is a hybrid system that combines static and dynamic elements. Store-and-forward systems are more widely used owing to their simpler technical requirements and affordability. Commonly, images were submitted by email or presented on a web based platform. Store and forward telepathology has its own limitations due to the disjointed nature of the images, and the significant diagnostic errors incurred with this method have been attributed to inappropriate field selection by the submitting pathologist (Weinstein, et al 2001). Although the real-time approach represents a reasonable substitute for in-person consultation and has the advantage of enhancing interaction, it is more time-consuming and expensive. Nonetheless,

dynamic telepathology using fully motorized robotic systems has revolutionized the field, and a concordance rate of 99-100% has been reported between telepathology and light microscopy diagnosis (Dunn et al, 1999; Weiss-Carrington et al, 1999).

Much progress has been made in the past couple of years in the field of digital imaging and virtual microscopy making the hybrid systems a lot more convenient than ever before such that 'virtual slides' can now be made where the entire slide is scanned at a very high resolution and then viewed by multiple pathologists (Leong & McGee, 2001) and without any loss of resolution. In this non-robotic real-time telepathology, the sampling error so common in static telepathology is eliminated and there is no requirement for expensive equipment. The significant deterrent is the high capacity needed for storing images which is on the average 150 Mb (Baruah, 2001).

3. Telepathology in developing countries

Characteristic of many developing nations is that scarce but highly-skilled manpower and healthcare services are concentrated in the urban centers. With specific reference to some of these nations, the uneven distribution of pathology service had resulted in serious consequences for the patients in the past (Ahmad, 2005). A continuing challenge is how to motivate and retain workers who are cut off from specialist support and up-to date information by poor road networks, archaic communication gadgets, lack of library facilities and an absence of opportunities for professional development. Also the type and sophistication in the level of diagnostic facilities varies widely from one developing country to the other. In view of these variations, the pertinent question had been how to evolve a cost effective strategy to guarantee steady improvement in pathology diagnosis and training of local personnel.

On the authority of Ahmad, the causes of poor pathology laboratories services in the developing countries are protean and primarily revolve around the failure to follow regulations, or in some cases, even to establish the relevant regulations (Ahmad, 2005). He goes on to point out other pertinent issues that impede the growth of pathology as:

- Low budgetary provision for laboratory services as a whole; traditionally most funds are spent on high-profile capital projects.
- Scarcity of laboratory staff: The rapidly rising demand for pathology services is not matched with the availability of skilled laboratory personnel.
- Poor training: The training of pathologists and technicians is suboptimal.
- Lack of appropriate equipment and infrastructure: There is often no infrastructure for maintenance, or even an assured supply of electricity.
- Lack of regulatory mechanisms: No license is required to establish a clinical laboratory in many developing countries.
- Lack of continuing education: Only in a few developing nations does provision for continuing education for pathologists and technicians exists.

The scenario in most developing nations can thus be summarized as that of pervasive weakness of laboratories facilities. Ironically, experience has shown that these peculiar circumstances also offer a unique opportunity for interventions. Importantly, there is almost universal enthusiasm from the local pathologists and technicians in the developing nations to improve the quality of pathological diagnosis and this should be an important incentive and motivation to organizations with interest in these kind of partnerships.

Conceivably a telepathology link utilizing simple and relatively cheap technology, like some of those in use in the industrialized world, would be quite ideal in these locations. Typically, the processes of setting up telepathology tend to pass through certain stages in developing countries. Funding for telepathology, so critical in these initiatives have largely been on one-on-one bases, and derived mostly from international organizations.

Of the available methods, static telepathology appears to have been accepted across most centers in the developing world. In a sense this can be justified as it has proved itself to be the more robust, least complicated and low-cost telepathology tool. Basically what the so-called 'store and forward' technique offers is that a large data set, in this case still images, are entered into a computer ('stored') and then sent ('forwarded') slowly to an expert in form of e-mail attachments. After examining the images, the recipient responds with a diagnosis. The use of improved hardware and software has made it possible to produce higher quality images that could be easily transmitted to remote locations by this method. Special telephone lines (ISDN lines) are used in some developing countries that transmit data faster than simple phone lines and allow real-time videoconferencing. On the other hand, the main advantage of using an internet-based system is that it is becoming even more accessible and a pathologist with basic equipment can utilize it to contact a consultant when the need arises. The advantages of these methods include the increased speed of the diagnostic process and convenience of use since both users do not have to be online simultaneously when an immediate response is not necessary. However, another limitation of static as compared to dynamic telepathology is the fact that the observer cannot control viewing of the specimen. Store and forward has therefore been found to be very effective in many developing nations.

4. Case studies of selected telepathology projects in the developing world

Attempts to practice telepathology in the developing world are not new. It is reported that one of the earliest uses of telepathology in practice occurred in 1973 from a ship docked in Brazil through a satellite that transmitted bone marrow smear images to Washington (Weinstein et. al., 1987).

iPath and telepathology.org are the best known websites that have been instrumental in the increasing level of awareness and usage of telepathology in developing nations. These and other websites provide web applications for discussion forums in telepathology that create a quick and easy method for tele-consultation from a pool of expert consultants.

The iPath network is based on software which was developed by the Department of Pathology of the University Hospital Basel, Switzerland, as an open source framework for building web- and email-based tele-medicine applications. (Brauchli et al, 2005). iPath was the first web-based platform that stored and shared medical cases together with attached images (both radiologic and microscopic) as well as other patient data in closed user groups. Since its inception, members of each of the closed user groups of pathologists, in particular had been enabled to review cases, suggest diagnoses and submit comments (Brauchli, et al 2004 and Brauchli, et al 2004b). Through this particular initiative, several successful telepathology projects have been established in the developing countries. By 2005, it was reported that the iPath telepathology server at the University of Basel (http://telemed.iPath.ch) was being used by many doctors from around the world for

second opinion consultations including pathologists from Bangladesh, Cambodia, Fiji, Laos, India, Iran, South Africa, and Thailand.
Some telepathology links that are still active in developing countries are described below.

4.1 Solomon Islands
One of the most celebrated telepathology collaborations is the one between National Referral Hospital of Honiara, Solomon Islands and the University Basle in Switzerland. Prior to the commencement of this service, the State of Solomon Islands had no pathologist at all and what little pathology service that existed consisted of sending specimens to the Royal Brisbane Hospital, Australia, for processing and diagnoses (Brauchli et al, 2004a).This was very frustrating as it often took 8 weeks or more for the results to return. This unacceptable scenario compelled an emigrated Swiss surgeon who had practiced in the Solomon Islands for 8 years to request for help from Basle University Hospital. After the appropriate contacts and consultations it was decided to explore the possibility of exchanging images and diagnoses over the internet on slides prepared from specimens in a new small histology laboratory that was to be established in Honiara. Basically, pictures of slides were taken with a Nikon OptiPhot microscope and a Nikon CoolPix 990 in Honiara and then digital images were sent to the iPath-Server in Basel where they were reviewed by a number of Pathologists from Europe and USA.

4.2 Egypt
Similarly, a pilot project began in the year 2003 between an institution in Egypt (the Italian Hospital in Cairo) and the Civico Hospital in Palermo, Italy applied static and dynamic techniques for telepathology which resulted in ease of consultations on many problematic pathological cases (Ayad & Sicurello, 2008). Subsequently, this project also expanded to two other hospitals (Charing Cross Hospital in London and the University of Pittsburgh Medical Center Health System in the USA). When fully functional this network will facilitate improved diagnosis for difficult cases and make available E-learning opportunities for individuals both in Egypt and the wider Mediterranean region.

4.3 India
Aside from the above projects that are driven by organizations from outside the developing world, there are also examples of projects that exist as partnerships between South-South groups/institutions. Some good examples of these could be found in India. Illustrative of the success of telepathology between institutions located within a developing country is the experience of using static telepathology consultation between a tertiary cancer centre (Tata Memorial Hospital) and a rural cancer hospital (Nargis Dutt Memorial Cancer Hospital) in Barshi, Maharastra both located in India (Desai, et. al., 2004). In this project it was proved that using existing telecommunication facilities and a 56 k modem, it was possible to have good telepathology consultation and a concordance rate of 90.2% was observed for diagnoses (Baruah, 2005). This telepathology successfully allowed quick and timely access to expert opinions and thus effectively bridged the gap between medically underprivileged, geographically distant rural areas and advanced centres using the static store and forward methodology.

PathoIndia, is a virtual pathology community hosted on iPath that aims to bring all the pathologists in India online, on one common interactive platform, so as to share and participate in the active telepathology quiz and group discussions; receive information about conferences, CME, etc; and collaborate on projects or publish articles on the website.

4.4 Argentina

Furthermore, it was reported that a telepathology and continuous education link had been established between a Latin-American Pathologist from La Rioja, a small Province of Argentina, from 1997 to 2007 and other pathologists based in Spain linked to a server (Jará & Barcelo, 2008). This network had evolved through many stages. At the beginning the digital images obtained were scanned from paper photos. The pictures had at least 1 MB each and when sent by e-mail took as long as 20 minutes each, through an analogue telephone modem connection. Subsequently, a Cybershot Sony 1.3 Megapixel (mpx) digital camera with 3× optical zoom, was used to capture the images directly from the eyepieces of the microscope. Then Corel Photo paint program was used for editing, compression and resized to 640 × 480 pixels (VGA). Since 2007, the center has had broadband ADSL Internet connection with the process becoming easier and faster.

4.5 Cambodia

Following on the successes of earlier initiatives, the telepathology project at Sihanouk Hospital Centre of Hope in Phnom Penh, Cambodia, has been used to successfully diagnose thousands of cases related to GI tract, thyroid, serous membrane and skin diseases using the iPath server at University of Basel. Furthermore, a case report emanating from Angkor Hospital for Children in Siem Riep, Cambodia, illustrated how telepathology enabled advice from distant providers for diagnosis and treatment of a paediatric patients (Froehlich et al, 2009). This is further proof of the extent the practice of telepathology continues to be used to improve healthcare delivery in a developing country.

4.6 Iran

Some of the earliest telepathology projects in Iran, which is a country like most other developing nations where there is no special telepathology network, have been highlighted in the literature (Mireskandari et al, 2004; Abdirad et al, 2006). These links between the University of Kerman in Iran and also the Cancer Institute of Tehran Universities of Medical Sciences with the iPath telepathology server based in Basle and UICC server Berlin were used for only telepathologic consultations. Based on the success recorded in these projects other institutions in Iran have also followed on to use the iPath website generally, even though there have been peculiar challenges which significantly restrict the use of telepathology in Iran.

Pathologists in developing countries display a great deal of enthusiasm about the open access to the latest expertise provided through these platforms that are free to all users. It has emerged that in the constant struggle to keep abreast of all new developments in the rapidly expanding field of pathology, telepathology could play a significant role in bridging the so-called digital divide. For many communities, their first experience of the practice of pathology has happened only with the advent of telepathology in which histopathologic diagnoses using the electronically transmitted images instead of conventional glass slides that are transmitted electronically to a recipient. In these locations not only has it allowed for sharing of difficult cases with experts who are worlds away, but also for teaching and other applications.

In the ongoing search for cost effective interventions, an interesting scenario would be to employ Skype and MSN for remote consultation and web conferencing for telepathology in the developing countries. The capture systems in these modalities have been determined to be simple, which re-enforces the viability of the system for use in developing countries (Clóvis et al, 2008). The programmes MSN and Skype can be used for discussion of cases, second opinion, or even, in the case of Skype, for a video conference (chat) with the participation of some specialists in the most varied localization. In both systems one can even create a conference with many users.

5. Telepathology in Sub-Saharan Africa

There is paucity of data on the current status of telepathology in sub-Saharan Africa. Even within each country, it is difficult to provide current and accurate information on its numeric strength or successes with any degree of certainty. Nonetheless, a review of the literature showed that a few telepathology projects have been launched or are planned in sub-Saharan African nations though there is little or no information about progress in many of them.

5.1 Burden of disease, manpower status and healthcare funding in Sub-Saharan Africa

Africa occupies an area of approximately 30 million square kilometers with a total population of approximately 800 million people (United Nations, 2006). Sub-Saharan Africa can be defined as that part of Africa lying to the south of the Sahara desert. It is made up of 42 countries and 6 island nations, extending as far east as Mauritius in the Indian Ocean.

The continent has witnessed declining economic performances, a history of political instability, some of the lowest levels of development in the whole world and 41% of people in sub-Saharan Africa live on less than US$1 per day (United Nations, 2008).

The health sector in most of Africa presents a peculiar set of challenges and lags far behind its counterparts in the developed nations. The burden of disease is great and diseases such as tuberculosis and malaria each kill up to a million people annually. In recent years, acquired immunodeficiency syndrome (AIDS) has spread rapidly, especially south of the Sahara. Today, Africa has most of the HIV-positive people in the world according to current estimates. Maternal mortality is very high and there is a high prevalence of measles, lower respiratory tract infections and diarrhoeal diseases among children, and poliomyelitis has re-emerged as an important pubic health problem. The huge difference between Africa and the industrialized world is highlighted by the fact that the WHO African Region has 24% of the global disease burden but only 3% of the health work force; commanding less than 1% of world health expenditure. In terms of provision of doctors, most sub-Saharan African countries fail to meet the WHO recommended minimum standard of at least 20 doctors per 100 000 population. To compound this scenario, healthcare funding is grossly deficient in that the average per capita expenditure on health in sub-Saharan Africa is a dismal US$22.

5.2 Opportunities and examples of telepathology in sub-Saharan Africa nations

Since healthcare provision in sub-Saharan Africa is so precarious, many Pathologists practice alone in isolated and remote locations without adequate infrastructure. Opportunities for expert opinions or second opinions on histopathology, cytopathology or haematopathology are not readily available to the reporting pathologist in these settings. Coming from a realistic understanding of the situating on the ground, success in raising the standard of pathology services in these countries will probably take many years of careful planning and persistence. But current initiatives to transfer professional knowledge and expertise, including initiatives that employ telepathology, could improve on the available diagnostic capabilities, and do have an important place.

The advent of telepathology in sub-Saharan Africa is best viewed in the context of its growth in the rest of the developing world. Telepathology in sub-Saharan Africa stands to benefit from the previous successes and limitations experienced by telepathology networks and projects located in other developing countries which were implemented in similarly sparsely populated remote areas, where means of communication are simple and socioeconomic conditions are generally poor. It goes without saying that in view of the existing infrastructural and manpower limitations in these countries, these novel initiatives on the use of information and communication technologies (ICTs) in the health sector have been largely limited to the urban centers.

Currently, a few countries in sub-Saharan are at different levels of sophistication in their practice of telepathology. These projects have employed several technologies, ranging from simple telephony to e-mail to facilitate exchanges. Nowadays, a few initiatives have also embarked on more sophisticated practices, such as real-time image transmission and analysis over digital networks with chat and voice transmission over the Internet Protocol (IP).

In the last couple of years a number of influential publications have appeared in the literature on the limited experience with telepathology in a few African nations and some of these will be briefly highlighted here.

5.3 South Africa

South Africa has a national telemedicine system incorporating telepathology that was initiated in 1999 with 28 pilot sites established in six provinces.

5.3.1 Walter Sisulu University Medical School

In the Republic of South Africa, at the Walter Sisulu University Medical School, store-and-forward telepathology services have been used since 1995, with links to the Armed Forces Institute of Pathology in Washington and various pathology departments in Europe. In this network a digital microscope with Internet connection for 'live' telepathology now operates in the country, with full real-time remote control, and this has revolutionized small, remote histopathology departments lacking sub-specialists. The telepathology network facilitates histopathology teaching at the University, by using a library of 400 virtual (electronic format) slides that are easily shared and reproducible with an indefinite lifetime as compared with 3 or 4 years for glass-based slides (Banach, 2008).

5.3.2 Phone-based Telepathology linkup between UNITRA and MEDUNSA

The first South African phone-based linkup between Department of Pathology, UNITRA and Department of Anatomical Pathology, MEDUNSA was setup in 1995. The telepathology and teleradiology workstations (now Telemedicine Unit) were installed at the Department of Anatomical Pathology, Histopathology and Cytology, UNITRA. The system has allowed sending still images (microscopy, x-ray, CT, ultrasound) to Telepathology Services of Armed Forces Institute of Pathology in Washington, USA, via the Internet. Results were obtained within 24 hours.

As an extension of the above project, the Department of Pathology, University of Transkei, Umtata has been involved in the development of telemedicine in the Transkei. Using existing facilities (PC, microscope and camera), which was later upgraded, they have managed to also establish a good telepathology, telecytology and teleradiology connection with Armed Forces Institute of Pathology in Washington, USA. There has also been the establishment of a real time pathology/cytology/haematology remote consultation with Anatomical Pathology Department at MEDUNSA and eventually to connect smaller hospitals around and establish telecytology services.

The growth of telepathology in South Africa has continued with the introduction of digital microscopes combined with Internet technology. Through the digital microscope it is possible to view in real-time whole slides as well as different chosen fields in different magnifications. In this project, three Nikon Coolscope were installed in the NHLS laboratories in Mthatha, East London and Port Elizabeth. All these microscopes are connected to NHLS server allowing real time viewing of the full slide on any PC connected to NHLS Intranet using Internet browser at any time of the day.

5.4 Cameroun

In Cameroun there is a notable experience from the body named Pathologie, Cytologie Dévelopment (PCD) in the use of telepathology for the detection of cervical cancer in Yaoundé (Cameroun). This organization has an important experience on providing equipments (second hand material) to pathology laboratories in Africa.

5.5 Ethiopia

A project was launched in 2004 and operated under the National Telemedicine Coordinating Committee of Ethiopia (Schneider, 2005). The project, in which telepathology is an integral component, connected ten hospitals in the country with the Tikur Anbessa Hospital and the Faculty of Medicine in one internet based network. It has improved access to continuing education and training, raised the level of access to care and drastically reduced the waiting time and cost associated with long distance travel by patients for diagnosis.

5.6 Africa calls programme on cytology

The dearth of training opportunities in cytology in Africa, has stifled the growth of this subspecialty and current economic considerations make the traditional short clinical attachments in cytology abroad increasingly difficult or impossible (International Academy of Cytology, 2007). A seldom mentioned, but critical role of telepathology is in cytology consultation and education. However, there is limited expertise in all but a few Africa nations, including Nigeria, where the opportunity for local training and continuing education in cytology is lacking (Malami, Iliyasu, 2008b). The concept of cyto-teleconferencing formed the basis of an innovation designed to promote diagnostic cytopathology in evolving countries of Africa by means of audio teleconferences. The project arose in response to needs assessments from sub-Saharan African countries and was designed to facilitate the exchange of scientific information and technology from the western countries for practice improvement. The link provided participants from African Departments of Pathology with customized educational programmes in cytopathology (Annenberg, 2010). Since 1999, six sixty-minute programmes are broadcast live annually to centers in Botswana, Ghana, Namibia, Nigeria, South Africa, Sudan, Swaziland, Tanzania, Uganda and Zimbabwe. The programme was attributed to have improved the knowledge and skills of the participants in the practice of cytopathology and is thereby an effective method of telepathology achieved at a relatively low cost (Malami, 2008). In this model, the long distance phone and networking costs are assumed through a grant from the Anenberg Center for Health Sciences and Hologic Inc, and each of the participating hubsites was provided with teleconferencing equipment and downloadable PowerPoint presentation together with adjunctival educational materials.

5.7 UICC Telepathology Consultation Center (UICC-TPCC)

In 1999 the International Union Against Cancer (UICC) had established the Telepathology Consultation Center at the Institute of Pathology, Charité, Humboldt-University, Berlin, Germany. The strategy had been informed by the findings of a needs assessment of available facilities in different developing countries. This center had provided a free access to rapid second opinion and inexpensive diagnostic aid to pathologists all over the world (Dietel et al, 2000). True to the plans of its founders the UICC-programme has offered local pathologists in developing countries an easy and time-saving access to high-quality histopathological diagnoses with bias towards laboratories and institutions based particularly in Eastern Europe, Asia and Africa. The participating centers have benefitted in the form of expert advice on diagnosis which has often been of invaluable benefit to the local clinicians' decision making processes. This is an example of a telepathology link that has arisen from need for regional and international interactions for support in pathology diagnosis/education and training.

5.8 INCTR project on telepathology and teleoncology

The success of the UICC-TPCC provided the perfect setting for a new project of the International Network for Cancer Treatment and Research (INCTR) under the auspices of INCTR Pathology Education Program. The INCTR was founded by the International Union Against Cancer (UICC) and the Institut Pasteur. Its goals include assisting in controlling cancer in developing countries. INCTR with the support of the National Cancer Institute (NCI) Office of AIDS Malignancies is working to establish improved pathological diagnosis in the context of its African study of HIV+ and HIV- Burkitt lymphoma in equatorial Africa. In the initial stage efforts were made to scale-up basic and continuous education of pathologists and technicians in Kenya, Tanzania and Nigeria.

This project was the fallout of a meeting that was convened by the UICC in Paris in October 2008 specifically to explore how to support and promote diagnosis, therapy, education and research in the developing countries. It is intended that this project will offer central pathology review related to the highlighted clinical studies. As a secondary strategy, a telepathology project built on iPATH, the free web-based application developed at the University of Basel, will be introduced with the objective of using this for review, consultation and education (continuing and post-graduate).

The INCTR Telepathology Network would be an important means of combating the isolation of pathologists on the African continent and the lack of up-to-date information and education that impedes their work.

5.9 RAFT

The Réseau Afrique Francophone de Télémédecine (RAFT) project is an Internet-based tele-medicine network started in 2001 in developing countries of Western Africa. The technology used for the webcasting works with an internet connection, a Java-enabled Web browser (e.g., Internet Explorer or Mozilla) and the free RealPlayer software. The bandwidth is 30 kbits per second or the speed of a basic telephone modem, which is sufficient, and enables the participation of remote hospitals. The Geneva University Hospitals have been involved in coordinating the development of this network for eHealth in Africa, first in Mali, and now extending to 10 French-speaking African countries including Mauritania, Senegal, Morocco, Tunisia, and Madagascar. The core activity of the RAFT is the webcasting of interactive courses targeted to physicians and other care professionals, the topics being proposed by the partners of the network. These sessions put the emphasis on knowledge sharing across institutions, usually in the form of presentations and dialogs between experts in different countries (Geissbuhler et al, 2007). The results are a tele-medicine network that has been in productive use for over 5 years and has enabled various collaboration channels.

5.10 Proposed East Africa telepathology program

Another ambitious tele-education project, requiring a small bandwidth, is planned for East Africa. The development, long-term funding, legal framework, and other details and this project to be hosted at Nsambya Hospital, Kampala Uganda is still to be widely circulated.

In summary, the experience from some selected sub-Saharan African nations has shown that telepathology links have been introduced many of which rely on only a light microscope, a high resolution camera (video or digital) a workstation and internet access through a telecommunications network. This is appropriate as several nations do not have adequate national or regional capacities presently to replicate some of the highly sophisticated systems common to the developed world. International Internet bandwidth is rare and monopolistic national policies that tend to protect the inefficient national telecommunications providers are not helping the situation either (Dlamini, 2001). The motivation for new telepathology projects is provided by the glaring absence of opportunities for continuous capacity building. Therefore a critical element of most telepathology collaborative projects is that in addition to long-distance consultation, they also provide continuing medical education (CME) for physicians who submit cases. In terms of sustainability, there is a huge question mark still as most of the links or projects have developed from personal communication between local pathologists and overseas consultants rather than being corporate or government sponsored. Potentially, the mandate of these projects could be expanded or extended to establish national networks.

6. Barriers to telepathology in the developing world

Most of the existing telepathology systems were not really designed with the developing countries in mind. Demonstration projects for telepathology have been done for some years in the developing world, with a few spectacular successes. But given its potential benefits to these nations, telepathology is still a far underutilized and largely unexplored technology.

The matter is not helped by the heterogeneous nature of the countries involved and the pervasive problem of access to telecommunications services at affordable cost. Though there is scant quantitative data on the reliability and cost effectiveness of telepathology, a few isolated reports have published the assessment of the logistics, economic feasibility, and barriers to telepathology in South Africa and India and these data could be extrapolated to other developing countries.

The development of telepathology is a complex matter. This is more so in the developing world where a satisfactory ICT environment is frequently unavailable. But the impediments to the successful implementation of telepathology cannot be viewed in isolation of the larger picture that affects telemedicine and the practice of pathology itself. Weinberg argued that the same factors responsible for the inertia to the full-scale introduction of telemedicine might also explain some of the impediments to telepathology (Weinberg, 1996).

Detailed analysis of the barriers to telemedicine and telepathology appear in the works of Wootton, 2009; Mars, 2009; Desai, 2009; Weinberg, 1999; and also Sood & Bhatia, 2005. Some of these impediments are worth highlighting:

6.1 Socio-cultural barriers

Successful introduction of any new system into a community requires an indepth understanding of the social environment. Preliminary studies and demonstration projects have shown that there are could be significant socio-cultural challenges to integrating telepathology into the healthcare systems of developing countries. These factors may be political or cultural in nature or even just the natural tendency of the staff to initially resist any new technology. Ownership issues may need to be clearly settled too so that this does not threaten the sustainability of the telepathology project. Sometimes because of the limited number of doctors in developing countries, local physicians and health workers may be concerned that telepathology systems will be time-consuming and generate unnecessary extra work. It is therefore crucial that they be made aware of the potential and relative advantages of the technique from the onset. The local people, technicians and even physicians may also adopt a negative attitude to the use of telepathology. It is therefore pertinent to note that the design and development had to be such that would not dislodge existing practice of working in hospitals. Such attitude may arise from inadequate information. To establish a lasting collaboration a genuine effort should be made to familiarize with the local circumstances.

6.2 Inadequate laboratory infrastructure

Pathology, and by extension, telepathology is not the main focus of government health expenditure in the developing countries. Available resources are allocated to the control of life-threatening infectious diseases and some fanciful capital projects, while very little is directed at upgrading or maintaining the laboratories. Even the essential components of a telepathology system such as a microscope, a camera with software and a computer, may not be readily available in some developing countries. Procurement of these items may be difficult. Also, where they are available initial difficulties due to inexperience in using the equipment need to be overcome.

6.3 Archaic telecommunication facilities

Without modern telecommunication it would be difficult to introduce and sustain telepathology services in developing countries. The development and availability of telecommunication facilities may be non-uniform, may not be developed at all, or they may be so poorly developed that it would be difficult or impossible to transmit data. In many existing networks connections are sometimes unreliable. For successful implementation of telepathology there must also be a stable communications strategy that reliably connects the centers with the Internet, without huge debts to pay for the connectivity. The improvements also should extend to internal communication in hospitals and remote medical centres. Internet services need to be widely accessible, even in rural parts of the developing world. In practice, a substantial proportion of telepathology work in developing countries is done by email or by web messaging. Email has many advantages in poor countries: it is cheap, hardware and software requirements are simple, and the information does not have to be transmitted in real time.

6.4 Funding and sustainability

Financial support is an important determinant of the sustainability of telepathology projects. Except for a few countries, there is a lack of telemedicine policies at national and regional levels and, as a result, a lack of budgets. Because of the cost of Internet access, even simple store-and-forward telemedicine is not always an affordable option in Africa or the rest of the developing world. Videoconferencing via ISDN is also expensive. Economic analyses of the viability of telepathology projects in countries with low resources have been rarely done. Besides, most telepathology networks in these countries are funded by international professional organizations. This heavy reliance on foreign donors may not guarantee sustainability of these services. Obviously, for the execution of telepathology services it is necessary to obtain steady funding to cover project costs comprising the costs for equipment, maintenance, telecommunications charges and staff training, as well as the costs related to the operation and running of the project, acquiring the physical space, supplies and travel.

6.5 Shortage of personnel

Local healthcare workers should always take a lead in developing and operating the projects whereby often what the practitioner needs is a passing knowledge of communication protocols, modems, and software. But it is wrong to assume that every pathologist, technician or health worker in the developing world is computer literate or able to use the Internet. Training is also required for not only information technology but also handling of camera and computer. Additional training in ICT is therefore critical to success in the developing countries in addition to support to improve their technical and media skills, prior to their involvement in telepathology projects. Also, it is often difficult to find dedicated personnel to carry out telepathology or to staff a telemedicine department. Thus staffs are expected to perform multitasking, especially in a low-volume centre. Telepathology would benefit from initiatives to train African healthcare workers in the use of information technology, such as those set up by the Fogarty International Center of the US National Institutes of Health. The training should emphasize simple, low cost techniques, rather than expensive video conferencing approaches that struggle to achieve sustainability even in developed countries.

6.6 Poor technical quality of slides

The limiting step in telepathology is availability of a well-processed histology or cytology glass slide. This is dependent on the skill of the technician. Lack of trained manpower for histopathology processing has a very negative effect on the subsequent quality of a telepathology consultation. In the developing world, other contributory factors for poor pathology product or suboptimal technical material include the lack of infrastructure, equipment and uniform standards.

6.7 Unresolved legal issues

Regulatory approval, in particular, would be an issue in many developing countries. Also, legal problems would be created. There are presently extensive discussions concerning the potential risks and complex legal problems associated with telemedicine health care services provided to patients from remote locations using telecommunication and this will impact on the practice of telepathology. Legal problems relate generally to problems concerning the privacy of identifiable health information, and the reliability and quality of health data, as well as medical liability. Since telemedicine in developing countries is mainly practised across state borders, providers must be aware of the potential risks concerning medical liability in the respective countries where the patients are located. There is a need for developing countries to adopt rules and regulations to address legal aspects involved in the use of telemedicine in order to safeguard the rights of patients. Matters that need to be considered include mainly safeguards about data forwarding, security of the patient's data (including images), confidentiality and the responsibilities of health workers involved.

7. Future developments

Majority of the people living in developing countries do not have access to modern diagnostic services due to a host of factors. So the impact of telepathology in diagnostic work, education or second opinions remains to be fully felt. In this respect, the growth of telepathology in the developing world had been rather slow for reasons which are beyond the control of healthcare providers. These include the low telephone penetration, inadequate and expensive national Internet bandwidth and lack of skilled manpower.

On a positive note, the number of institutions that have embraced telepathology in the developing countries is increasing, and there is already an attempt to integrate the technique into the healthcare system in some of these low resource nations. If this growth is sustained, then the practitioners would also have to grapple with the problems associated with managing rapidly growing telepathology networks in future. Hopefully, the net increase in the numbers should provide the impetus to standardize the practice of telepathology through technological solutions that are well adapted to the local environments. Until now, establishing telepathology services in the low income countries had been mainly hampered by the high implementation costs. The identification and implementation of proven low-cost technology approaches would therefore optimize telepathology services.

Virtual pathology holds a great promise but poor communications facilities and epileptic power supply are some of the greatest challenges to it. Future technical improvements may assist telepathology links, but simple technology like the store-and-forward e-mail system would probably continue to play a leading role. Notably some successful models in remote areas are based only on an email account with an Internet service provider and the local-rate telephone call charges. In future we could see more innovative use of web applications such as Skype or MSN or even mobile phones with built-in cameras in telepathology. This sort of telepathology networks in the developing world may not necessarily provide the quality of service obtained in the industrialized countries now or in the foreseeable future. However, if used by healthcare workers trained to follow simple photographic and email procedures they can improve specialist access in remote areas.

A yet unharnessed benefit of telepathology is in clinical research. The technique could also be mutually advantageous to the extent that while local pathologists stand to benefit from the professional interactions, mentoring, education and access to improved research facilities while consulting experts also get special opportunities to review unusual or rare pathological entities. Apart from tele-consultation, what has proved to be especially effective in many low-resource nations is tele-education. Numerous examples of this can be cited, but valid concerns remain that if telepathology is used on a larger scale it may stifle the development of local resources and lead to a culture of dependence on Western expertise. However, if properly managed these rare educational opportunities may prove to be the catalyst for developing telepathology services in the developing world.

A still unresolved issue is the cost effectiveness of telepathology. In South Africa, apart from the common problems relating to the technical and organizational challenges of introducing telemedicine another area of concern was the relatively low usage of the telemedicine system, which raised questions about its cost-effectiveness (Gulube & Wynchank, 2001). Rough calculations suggested that only about 0.1% of the potential telemedicine demand from the developing world was being met (Wootton, 2008).

An important research question is how best to scale up telepathology projects for greater benefit to the people in low-resource countries? Further studies are needed especially to define the minimal technical and ethical implications of introducing telepathology in individual developing countries. Also more studies focusing on telepathology outcomes should be conducted to confirm its clinical benefits and cost-effectiveness. These would ensure acceptance, economic viability and effectiveness, as well as sustainability.

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Edited by Georgi Graschew and Theo A. Roelofs

Innovative developments in information and communication technologies (ICT) irrevocably change our lives and enable new possibilities for society. Telemedicine, which can be defined as novel ICT-enabled medical services that help to overcome classical barriers in space and time, definitely profits from this trend. Through Telemedicine patients can access medical expertise that may not be available at the patient's site. Telemedicine services can range from simply sending a fax message to a colleague to the use of broadband networks with multimodal video- and data streaming for second opinioning as well as medical telepresence. Telemedicine is more and more evolving into a multidisciplinary approach. This book project "Advances in Telemedicine" has been conceived to reflect this broad view and therefore has been split into two volumes, each covering specific themes: Volume 1: Technologies, Enabling Factors and Scenarios; Volume 2: Applications in Various Medical Disciplines and Geographical Regions. The current Volume 2 is structured into the following thematic sections: Cardiovascular Applications; Applications for Diabetes, Pregnancy and Prenatal Medicine; Further Selected Medical Applications; Regional Applications.

ISBN 978-953-51-6425-8

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