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Clinical Trials in Vulnerable Populations

Edited by Milica Prostran

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Notice

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Meet the editor

Professor Milica Prostran MD, Ph.D., graduated from the School of Medicine, University of Belgrade, Serbia. She obtained a Master of Science degree in Cardiology and a Ph.D. in (Molecular) Pharmacology. Professor Prostran, is the president of the Pharmaceutical Medicine Section of the Serbian Medical Association, and was a member of several important governmental bodies. She has published more than 200 *in extenso* papers in peer-reviewed journals indexed in CC/SCI, as well as over 50 chapters in international and national books. Professor Prostran serves as a member (and referee) of the Editorial Board of several highly respected journals including *Frontiers in Ageing Neuroscience*, where she is an Associate Editor, and F*rontiers in Pharmacology, Current Medicinal Chemistry*, as well as several national scientific and professional journals.

Contents

Preface

The book Clinical Trials in Vulnerable Populations has 12 chapters divided in four sections:

- Minority patients
- Women
- Medically compromised patients and
- Clinical trials.

More than 30 authors came from different countries of the world, from Serbia to Turkey. The editor of this book is Professor Milica Prostran MD, Ph.D. Professor Prostran is a pharmacologist as well as a clinical pharmacologist with a subspecialty in clinical pharmacology - pharmacotherapy. This editorial task was due to her vast experience with publishing in respected international journals. She has published more than 200 *in extenso* papers in international journals indexed in CC/SCI, and over 50 chapters in international and national books. Professor Prostran serves as a member (and referee) of the Editorial Board of several highly respected international journals - *Frontiers in Ageing Neuroscience*, where she is an Associate Editor, *Frontiers in Pharmacology*, *Current Medicinal Chemistry*, as well as several national scientific and professional journals.

"Vulnerable subject - a subject who is at risk (from trialist rather than from disease). Examples include patients with very serious diseases and with high expectations of the benefits of a new product, subjects who have a working relationship with investigators (medical students, nurses, employees of pharmaceutical companies, etc." (Day, 2007).

Some authors make a distinction between a vulnerable population and a special research population.

A vulnerable population includes children and minors, pregnant women, fetuses and human *in vitro* fertilization. Also, cognitive impaired persons and prisoners are included in this group.

On the other hand, a special population includes students, residents, employees, terminally ill patients and minorities (Prostran et al., 2012, Prostran et al., 2016).

The potential reader is shown the modern approach to clinical trials in vulnerable populations, from different points of view (Medič et al., 2016). The chapters deal at length and clarity with their topics. Finally, I believe that this book I edited and reviewed with dedication will capture the attention of many readers, from medical students to practicing doctors and pharmacists. All of them must consider this very important field of medicine: clinical trial in vulnerable patients. Also, I believe that the answers to their questions may be found in this book and may make their practice at least more bearable.

Last but not least, I want to express my gratitude to Ms. Diana Olloni from InTechOpen, for her constant help during the editing of this book.

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References

[1] Day S. Dictionary of clinical trials, 2007.2nd edition, John Wiley & Sons, Ltd, Chichester.

[2] Prostran M, et al. Bioethics in clinical trials: vulnerable subjects. In: Bioethics and pharmacology: ethics in preclinical and clinical drug development, eds. Z Todorović, Milica Prostran and Karel Turza, 2012, 87-100.

[3] Prostran M, et al. Pharmacotherapy of pain in the older population: the place of opioids. Frontiers in Aging Neuroscience, 2016, 8, 144.

[4] Medić B, et al. Evaluation of novel biomarkers of acute kidney injury: the possibilities and limitations. Current Medicinal Chemistry, 2016, 23, 1981-1997.

Section 1

Minority Patients

Chapter 1

Scientific and Ethical Considerations for Increasing Minority Participation in Clinical Trials

Julius M. Wilder

Additional information is available at the end of the chapter

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Abstract

Since its inception, a major weakness in clinical trial research has been an inability to recruit diverse populations into clinical trials. These under-represented populations are mostly comprised of the poor, the elderly, children, women, and racial/ethnic minorities (African Americans and Hispanics). This fundamental weakness is further exacerbated by the fact that these same groups are often disproportionately affected by the diseases being studied in clinical trials. There are various patient specific, provider specific, and policy related causes for the existence of these disparities. Regardless of the cause, the lack of participation of these groups in clinical trials raises important questions about the quality and ethics of clinical research. The goal of this document is to discuss the evidence and reasons behind disparities in clinical trial participation. We also provide a discourse on potential mechanisms to address disparities in clinical trial accrual including the ethical considerations of financial incentives, the impact of a more stringent policy and review process for product approval from the Food and Drug Administration (FDA) including a diversity mandate with an associated population black box warning.

Keywords: African American, hispanic, clinical trials, underrepresented, health disparities, food and drug administration (FDA)

1. Introduction

Since its inception, a major weakness in clinical trial research has been an inability to recruit diverse populations into clinical trials. These under-represented populations are mostly comprised of the poor, the elderly, children, women, and racial/ethnic minorities (African Americans and Hispanics). This fundamental weakness is further exacerbated by the fact that these same groups are often disproportionately affected by the diseases being studied in clinical trials. There are various patient specific, provider specific, and policy related causes for the existence

of these disparities. Regardless of the cause, the lack of participation of these groups in clinical trials raises important questions about the quality and ethics of clinical research. The goal of this document is to discuss the evidence and reasons behind disparities in clinical trial participation. We also provide a discourse on potential mechanisms to address disparities in clinical trial accrual including the ethical considerations of financial incentives, the impact of a more stringent policy and review process for product approval from the Food and Drug Administration (FDA) including a diversity mandate with an associated population black box warning.

2. Evidence of disparity among racial/ethnic minorities

The composition of minorities in clinical trials has historical been low. Between 1996 and 2002, blacks represented on average 9.3% of the total number of enrollees in cancer clinical trials [1]. That number peaked at 11% in 1996 and steadily declined to 7.9% in 2002 [1]. Similarly, Hispanics on average represented on average 3.1% of the total number of enrollees in cancer clinical trials between 1996 and 2002 [1]. Not only are minorities under-represented in clinical trials, but the overall racial and ethnic composition of clinical trials is not reported at an acceptable rate. Between 1990 and 2000, only 35.1% of treatment studies among cancer clinical trials reported race/ethnicity [2]. This number increased to 51.6% from 2001 thru 2010, but the percentage of blacks included in the analysis for the second decade decreased by 42% [2]. The lack of diversity goes beyond race and ethnicity. Similar trends are found in women, where they only represented 26.5% of the population in prevention studies between 2001 and 2010 [2].

The disparity in clinical trial participation is not limited to cancer clinical trials and the scientific impact can be significant in terms of outcomes. African Americans are disproportionately affected by hepatitis C virus (HCV) in the United States and HCV infection is the leading cause of cirrhosis and hepatocellular carcinoma and the most common indication for liver transplantation in the United States [3]. Although African Americans comprise approximately 13% of the US population, they make up approximately 23% of Americans with hepatitis C [4]. The rate of a positive HCV antibody test was higher in blacks than in whites (3.2% versus 1.5%) and black men had higher rates of infection, with the highest prevalence rate (9.8%) among black men ages 40–49 years [5, 6]. HCV treatment has undergone a rapid evolution in treatment with the first generation protease inhibitors released in 2011 and now multiple direct acting antivirals regimens with amazing outcomes [7, 8].

We performed a meta-analysis of clinical trials on hepatitis C treatment between January 2000 and December 2011 [9] to evaluate the participation of African Americans in hepatitis C clinical trials given the tremendous burden of that disease within this population. We reviewed 588 randomized controlled clinical trials on hepatitis C treatment with interferon 2a or 2b between January 2000 and December 2011. Of the 588 reviewed, 314 (53.4%) fit inclusion criteria [9]. This meta-analysis showed that of the 314 RCT's that met search criteria, only 123 (39.2%) actually reported race. We evaluated clinical trials in North American and Europe, and found significant differences. The clinical trials performed in North America were more likely to report racial data than European trials, although racial reporting overall increased

over time in North America and Europe. Our main outcome was the rate of African American/black participation in North American HCV clinical trials [10]. There was a statistically significant difference among the expected and observed participation of African Americans in HCV clinical trials in North America based on the prevalence of this disease within the population. The observed rate was 0.148 (95% CI, 0.126–0.174). Therefore, among those clinical trials reporting race, African Americans were significantly under-represented, especially given the disproportionate burden of hepatitis C within this population [9].

3. Reasons for the disparity

The persistent disparity in minority clinical trial participation is a result of a combination of historical, demographic, and socioeconomic factors. These complex issues combine to create barriers preventing clinical researchers from reaching communities and barriers preventing communities from engaging in clinical trial research.

Socioeconomic status (SES) is a major contributor to disparities in minority clinical trial participation. The mechanism through which SES impacts minority trial accrual is *primarily* through individual patient level access to resources associated with clinical trial participation. Lower levels of education and income are known to correlate with a lack of insurance and underinsurance. Previous estimates have shown that up to 30% of the US population is underinsured or uninsured [11]. While the "Patient Protection and Affordable Care Act, 2010" will significantly improve access to health insurance, the impact on clinical trial participation will need to be studied given the lack of uniformity in implementation across the individual states in the US. Low SES presents issues with transportation as well [12]. Hence, patients with limited transportation resources are more likely not to be able to logistically make the follow up appointments associated with participation in a clinical trial [1, 12]. The cost of transportation and clinical trial research participation goes beyond typical costs such as fuel and mileage. Many patients of lower SES cannot afford to miss the time from work required for clinical trial visits as well. A lack of education and awareness of cancer and clinical trials has been shown to contribute to reduced participation in clinical trials [12–15] due to a lack of knowledge concerning the cancer diagnosis, treatment options, and precisely what is clinical research. One's SES is often reflected in the neighborhood that they live. Unfortunately, living in lower SES neighborhoods (be they urban or rural) reduces the likelihood of one having access to clinical trial research [12].

Cultural issues related to race and ethnicity also contribute to disparities in clinical trial participation. The race of one's provider can impact access to clinical trials. Under-represented minorities are more likely to receive healthcare from a physician who is also a minority [1, 16]. Few minority physicians are engaged in clinical research and this thus reduces opportunities for the minority populations they serve to be engaged in clinical research. A lack of culturally appropriate educational materials targeting individuals with diverse cultural backgrounds and in whom English is their second language contributes to an inability to recruit individuals of Hispanic and other ethnic backgrounds [12, 17–19].

Provider characteristics also contribute to the lack of diversity within clinical trials. Provider attitudes towards a patients age, comorbidities [20, 21], physician perception of mistrust of researchers [21, 22], and lack of physician awareness of clinical trials [21, 23] all contribute to disparities in clinical trial research. Furthermore, studies targeting under-represented minorities (Hispanics and blacks) have found that provider miscommunication including lack of compassion, lack of respect, and perceived mistrust have all contributed to minorities hesitating to engage in clinical trial research [21]. The legacy of the Tuskegee Syphilis experiment still resonates among blacks in the United States when confronted with issues around clinical trial research. The Tuskegee study involved 400 African American males with syphilis who were systematically denied treatment from 1932 to 1972 even though a known treatment existed [24, 25]. This was the longest nontherapeutic experiment on human beings in medical history [25]. These men were largely illiterate and uninformed about the risks and benefits of this study despite the existence of US policy to protect clinical research subjects [24]. The social and political significance of the US Public Health Service performing unethical research on African Americans following the Civil Rights Movement of the 1960s was monumental and continues to contribute to the mistrust among African Americans for clinical research today [24, 25].

4. Addressing disparities in clinical trial accrual

Policy initiatives have been implemented in an attempt to address a lack of diversity in clinical trials. The National Institute of Health (NIH) Revitalization Act of 1993 created a mandate for the appropriate inclusion of minorities in all NIH-funded research projects [26]. Twenty years following the implementation of this act, the accrual and reporting of minorities within clinical trials remains inadequate. A recent review shows that the reporting of race/ethnicity ranged from 1.5% to 58% with only 20% of RCT's in high impact journals reporting subgroup analyses by race/ethnicity [27]. The failure of the 1993 Revitalization Act to address disparities in minority clinical trial accrual may be related to it only impacting NIH funded studies. From 1990 to 2000, a period that includes implementation of the 1993 NIH Revitalization Act, 61.5% of cancer clinical trials only used funding from NIH or other federal funding resources [2]. During this same time period, the percentage of trials only using pharmaceutical funding was 13.2% [2]. However, in the next decade (2001–2010), the percentage of cancer clinical trials relying solely on NIH or federal funding decreased to 35.9% and the percentage of trials relying solely on pharmaceutical funding increased to 50.4% [2]. Therefore, the research landscape has changed with respect to primary funding resources. Any policy attempting to impact how research is done must consider the primary source of funding for clinical trial research today.

The 1997 Food and Drug Administration Modernization Act (FDAMA) [28, 29] is an example of policy recognizing funding sources and utilizing it to implement positive change in accrual for clinical trials. This law included a "Pediatric Exclusivity Provision" which provided an additional 6 months of patent protection, or marketing exclusivity in return for performing studies specified by the FDA [28]. The provision for economic incentives was then extended by the "Best Pharmaceuticals for Children Act of 2002" [28, 30]. Following this, "The Pediatric Research Equity Act" in 2003 allowed the FDA to require pediatric studies of certain drugs

and biological agents [31]. The purpose of these laws was to provide financial motivation for pharmaceutical companies to engage in pediatric clinical research. Children, similar to minorities the elderly, the poor, and women, were a group often not included in clinical trials. In return for their willingness to provide drug labeling information on children and increase delivery of biologics for children to the market, pharmaceutical companies received financial benefits. These laws resulted in critical changes in drug labeling for pediatric patients because unique pediatric dosing is often necessary because of the growth and maturational stages of pediatric patients [31]. Furthermore, since the implementation of these incentive programs, a majority of biologics (vaccines, anti-toxins, and insulin) approved include pediatric information in their labeling [32].

A major reason for concern with financial incentives for pharmaceutical companies to engage in pediatric clinical research is monetary. There is concern that PHARMA could reap great financial reward from the patent extensions, and many question the ethics of this in return for doing what is deemed to be the morally correct thing to do [28]. Complicating the debate is the fact that the financial data is mixed. Li et al. [28] performed a cohort study of nine drugs granted pediatric exclusivity. They found that exclusivity did not guarantee a financial windfall with the distribution of net economic return for 6 months of exclusivity varying widely [net return ranged from (−)$8.9 million to (+)$507.9 million] [28]. However, at times, it appears that the financial incentives provided are disproportionate to the cost of the research being done because the profit ratio for certain blockbuster medications (anti-hypertensives), can be as high as 17:1 [28, 33–35].

Within 10 years of implementation of the Pediatric Exclusivity Act in 1997, there were more than 300 studies conducted and more than 115 products with labeling changes to account for pediatric use [31, 33, 34]. However, many of the drugs studied were not considered important targets among the pediatric population [33, 34]. The pediatric exclusivity studies have also tended to focus on more profitable drugs and the drugs most frequently studied are more likely to be important targets for the adult population [33, 34, 36]. The literature also raises important concerns related to the quality of the clinical trials conducted under the exclusivity act [37]. The extensions for patents under the exclusivity act are granted regardless of the quality or outcome of the clinical trial and many of the results of studies done under the exclusivity act are not published [38].

The data on the use of financial incentives to increase clinical trial diversity is mixed with evidence of success in terms of new drug labeling and evidence of failure in terms of poor research quality and financial gains for industry. However, financial incentives to increase diversity in clinical trials may be a viable and aggressive means of eliminating these health disparities if implemented in a thoughtful and ethical way. Men make up more than two-thirds of the population in clinical tests of cardiovascular devices [10]. African Americans and Hispanics respectively make up 12% and 16% of the US population. However, African Americans and Hispanics respectively make up only 5% and 1% of clinical trial participants [10]. There are clear benefits and costs associated with the use of financial incentives. These must be carefully considered and weighed when implementing any policy concerning financial incentives to increase clinical trial diversity.

An alternative to financial incentives to improve clinical trial diversity would be a stronger stance by governing and regulating bodies such as the NIH and FDA. The FDA recently implemented the "Food and Drug Administration Safety and Innovation act" (FDASIA). Section 907 of this act directs the FDA to investigate how well demographic subgroups (sex, age, race and ethnicity) in applications for medical are included in clinical trials; and if subgroup-specific safety and effectiveness data are available. While this does not create a mandate for inclusion like the NIH revitalization act of 1993, it is an important step forward in improving clinical trial accrual of under-represented populations. But, given the size of the disparity, a more aggressive stance is required. Laws implemented by the NIH and FDA 10 years ago would have had potentially significant effects on diversity within clinical trials because the government (NIH) was the major funder of clinical trials at that time. However, the major funder of clinical trials in the United States today is the pharmaceutical industry. If the goal is to create policies to change research behaviors in clinical trials today, those policies must take a stronger stance in terms of requirements for new drug approval or creatively and ethically consider what is valued by the main funder of clinical trials; industry. The literature has previously discussed in great detail the issue of financial incentives to increase clinical trial diversity. Now is the time to begin a discourse on the role of an FDA mandate on clinical trial diversity.

A mandate on diversity by the FDA would be a powerful motivational factor for the pharmaceutical industry to increase clinical trial diversity. A FDA mandated minimum level of diversity (or diversity benchmark) within clinical trials could be applied to research within areas of medicine where there are known issues in terms of health disparities (hepatitis C, cardiovascular disease, diabetes). Through the creation of an expert panel, the need for specific emphasis on diversity within certain populations could be assessed. For example, an FDA or industry appointed expert panel on cardiovascular disease could mandate that phase 3 clinical trials on hypertension medications need to establish a minimum level of diversity in terms of African American participation, given the disparities that exist in hypertension control among African Americans. Those trials who successfully reach the diversity benchmark could be eligible for an expedited approval process and those that do not reach the benchmark would receive the equivalent of a black box warning concerning the lack of data in diverse populations. Exceptions could be made in those scenarios where earnest attempts at accruing diverse populations were attempted but unsuccessful.

The benefits and risks of improving diversity by any mandate or benchmark would have to be weighed. There is a potential for impeding clinical research due to the time required to achieve diversity. Furthermore, financial resources would be required to invest in the accrual of diverse populations. The expertise of thought leaders would be key to identifying those clinical trials which should have to reach diversity benchmarks as well as what precisely those diversity benchmarks should be. But achieving a consensus on what types of clinical trials require diversity benchmarks and what those benchmarks should be would require close collaboration between regulatory entities (FDA) and the pharmaceutical industry. Although there would be pros and cons with the implementation of such a policy, previous policies which have taken a less assertive stance have not addressed this important issue and the pharmaceutical industry has not shown a propensity for addressing the issue on their own.

Finally, a core ethical issue in clinical research is justice. The lack of diversity in clinical trial participation represents an injustice. The clinical trial population should reflect the population of people who are affected by the disease being studied. Not doing so risks the possibility new therapies are only efficacious and safe in a small proportion of the population at risk for the disease. Or worse, as has historically been the case in hepatitis C, clinical trials could lack a reasonable representation of those individuals at greatest risk for the disease and who have the worse outcomes (African Americans). This system creates lower quality research and the knowledge gained from these clinical trials has less value when compared to novel findings in a clinical trials that truly reflected the genetic diversity of the disease process being studied.

As has been the case in US history, to address social injustices, we must implement an aggressive policy to ensure that significant and positive progress is achieved. Here, we have discussed the potential for financial incentives as well as a FDA mandate in conjunction with appropriate product labeling to increase diversity in clinical trials. We urge a discourse on these issues because industry is now the major funder of clinical trials today and previous policies to address diversity in clinical trials have failed. Any cost associated with financial incentives or an FDA mandate pales in comparison to the cost of life lost because of unjust and inferior clinical research trials.

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References

[1] Colon-Otero G, Smallridge RC, Solberg LA, Jr., Keith TD, Woodward TA, Willis FB, et al. Disparities in participation in cancer clinical trials in the United States: A symptom of a healthcare system in crisis. Cancer. 2008;**112**(3):447-454

[2] Kwiatkowski K, Coe K, Bailar JC, Swanson GM. Inclusion of minorities and women in cancer clinical trials, a decade later: Have we improved? Cancer. 2013;**119**(16):2956-2963

[3] Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. The Lancet Infectious Diseases. 2005;**5**(9):558-567

[4] Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Annals of Internal Medicine. 2006;**144**(10):705-714

[5] NIH consensus statement on management of hepatitis C: 2002. NIH Consensus and State-of-the-Science Statements. 2002;**19**(3):1-46

[6] Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. The New England Journal of Medicine. 1999;**341**(8):556-562

[7] Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. The New England Journal of Medicine. 2011;**364**(25):2405-2416

[8] Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. The New England Journal of Medicine. 2011;**364**(13):1195-1206

[9] Wilder J, Saraswathula A, Hasselblad V, Muir A. J Natl Med Assoc. 2016 Feb;**108**(1):24-9. doi: 10.1016/j.jnma.2015.12.004

[10] (OMH) FsOoMH 2013; http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm347896.htm2013

[11] Schoen C, Doty MM, Collins SR, Holmgren AL. Insured but not protected: How many adults are underinsured? Health Affairs (Millwood). 2005;Suppl Web Exclusives: W5-289-W5-302

[12] Ford JG, Howerton MW, Lai GY, Gary TL, Bolen S, Gibbons MC, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: A systematic review. Cancer. 2008;**112**(2):228-242

[13] Advani AS, Atkeson B, Brown CL, Peterson BL, Fish L, Johnson JL, et al. Barriers to the participation of African-American patients with cancer in clinical trials: A pilot study. Cancer. 2003;**97**(6):1499-1506

[14] Lara PN, Jr., Paterniti DA, Chiechi C, Turrell C, Morain C, Horan N, et al. Evaluation of factors affecting awareness of and willingness to participate in cancer clinical trials. Journal of Clinical Oncology. 2005;**23**(36):9282-9289

[15] Trauth JM, Jernigan JC, Siminoff LA, Musa D, Neal-Ferguson D, Weissfeld J. Factors affecting older African American women's decisions to join the PLCO Cancer Screening Trial. Journal of Clinical Oncology. 2005;**23**(34):8730-8738

[16] Komaromy M, Grumbach K, Drake M, Vranizan K, Lurie N, Keane D, et al. The role of black and Hispanic physicians in providing health care for underserved populations. New England Journal of Medicine. 1996;**334**(20):1305-1310

[17] Mandelblatt J, Kaufman E, Sheppard VB, Pomeroy J, Kavanaugh J, Canar J, et al. Breast cancer prevention in community clinics: Will low-income Latina patients participate in clinical trials? Preventive Medicine. 2005;**40**(6):611-618

[18] Moinpour CM, Atkinson JO, Thomas SM, Underwood SM, Harvey C, Parzuchowski J, et al. Minority recruitment in the prostate cancer prevention trial. Annals of Epidemiology. 2000;**10**(8 Suppl):S85-S91

[19] Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: Race-, sex-, and age-based disparities. JAMA. 2004;**291**(22):2720-2726

[20] Kimmick GG, Peterson BL, Kornblith AB, Mandelblatt J, Johnson JL, Wheeler J, et al. Improving accrual of older persons to cancer treatment trials: A randomized trial comparing an educational intervention with standard information: CALGB 360001. Journal of Clinical Oncology. 2005;**23**(10):2201-2207

[21] Howerton MW, Gibbons MC, Baffi CR, Gary TL, Lai GY, Bolen S, et al. Provider roles in the recruitment of underrepresented populations to cancer clinical trials. Cancer. 2007;**109**(3):465-476

[22] Pinto HA, McCaskill-Stevens W, Wolfe P, Marcus AC. Physician perspectives on increasing minorities in cancer clinical trials: An Eastern Cooperative Oncology Group (ECOG) Initiative. Annals of Epidemiology. 2000;**10**(8 Suppl):S78-S84

[23] Nguyen TT, Somkin CP, Ma Y. Participation of Asian-American women in cancer chemoprevention research: Physician perspectives. Cancer. 2005;**104**(12 Suppl):3006-3014

[24] McCarthy CR. Historical background of clinical trials involving women and minorities. Academic Medicine. 1994;**69**(9):695-698

[25] Thomas SB, Quinn SC. The Tuskegee Syphilis Study, 1932 to 1972: Implications for HIV education and AIDS risk education programs in the black community. American Journal of Public Health. 1991;**81**(11):1498-1505

[26] United States. Congress. House. Committee on Energy and Commerce. Subcommittee on Health and the Environment. NIH Revitalization Act : hearing before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, One Hundred Third Congress, first session, on H.R. 4, a bill to amend the Public Health Service Act … February 3, 1993. Washington: U.S. G.P.O.: For sale by the U.S. G.P.O., Supt. of Docs., Congressional Sales Office; 1993

[27] Chen MS, Jr., Lara PN, Dang JH, Paterniti DA, Kelly K. Twenty years post-NIH Revitalization Act: Enhancing minority participation in clinical trials (EMPaCT): Laying the groundwork for improving minority clinical trial accrual: Renewing the case for enhancing minority participation in cancer clinical trials. Cancer. 2014;**120**(Suppl 7): 1091-1096

[28] Li JS, Eisenstein EL, Grabowski HG, Reid ED, Mangum B, Schulman KA, et al. Economic return of clinical trials performed under the pediatric exclusivity program. JAMA. 2007;**297**(5):480-488

[29] United States. Food and Drug Administration. Food and Drug Administration Modernization Act of 1997 : FDA Plan for Statutory Compliance. Rockville, MD: FDA; 1998

[30] Administration. USFaD. Best Pharmaceuticals for Children Act of 2002. Rockville, MD: FDA; 2002

[31] Rodriguez W, Selen A, Avant D, Chaurasia C, Crescenzi T, Gieser G, et al. Improving pediatric dosing through pediatric initiatives: What we have learned. Pediatrics. 2008;**121**(3):530-539

[32] Field MJ, Ellinger LK, Boat TF. IOM Review of FDA—Approved biologics labeled or studied for pediatric use. Pediatrics. 2013;**131**(2):328-335

[33] Kesselheim AS. Using market-exclusivity incentives to promote pharmaceutical innovation. New England Journal of Medicine. 2010;**363**(19):1855-1862

[34] Luo J, Kesselheim AS. Underrepresentation of older adults in cancer trials. JAMA. 2014;**311**(9):965-966

[35] Baker-Smith CM, Benjamin DK, Jr., Grabowski HG, Reid ED, Mangum B, Goldsmith JV, et al. The economic returns of pediatric clinical trials of antihypertensive drugs. American Heart Journal. 2008;**156**(4):682-688

[36] Boots I, Sukhai RN, Klein RH, Holl RA, Wit JM, Cohen AF, et al. Stimulation programs for pediatric drug research—Do children really benefit? European Journal of Pediatric. 2007;**166**(8):849-855

[37] Benjamin DK, Jr., Smith PB, Jadhav P, Gobburu JV, Murphy MD, Hasselblad V, et al. Pediatric antihypertensive trial failures: Analysis of end points and dose range. Hypertension. 2008;**51**(4):834-840

[38] Benjamin DK, Jr., Smith PB, Murphy MD, Roberts R, Mathis L, Avant D, et al. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. JAMA. 2006; **296**(10):1266-1273

Chapter 2

The "Obese Asthma" in Children as a Distinct Clinical Phenotype: Review

Andjelka Stojkovic, Aleksandra Simovic,
Vesna Velickovic and Katerina Dajic

Additional information is available at the end of the chapter

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Abstract

Asthma, obesity, and irrational use of antibiotics early in a life can be considered to be the three epidemics of modern times, which encourage one another and whose base is the loss of bioavailability. Disruption of the intestinal microbiome early in the life is the basis for the development of metabolic diseases, allergic immunological diseases, and high mortality rate due to infection with resistant strains of bacteria. During the irrational use of penicillin and macrolides postnatally, the composition of the intestinal microbiota and its functions change 12–24 months after the antibiotics treatment, the settlement of advantage intestinal flora with probiotic microorganisms is delayed, the maturation of the intestinal mucosa is compromised. Respiratory and systemic inflammation is strongly influenced by the rich adipocyte metabolism so that the treatment of these children is complex, and their asthma often remains only partially controlled. The phenotype "obese asthma" is characterized by a steroid and bronchodilator resistance. Therapeutic solution could be the body weight reducing, vitamin D3 substitution, and antileukotriene application. The prophylactic therapy of this asthma, using macrolides for a long time, should be supported, mandatory, with the substitution of probiotic/synbiotic during, and at least 6–9 months after discontinuation of therapy with macrolide.

Keywords: asthma, overweight, macrolide, prophylaxis, probiotic

1. Introduction

Pediatricians are nowadays increasingly more convinced by the data reported in the medical literature that the crucial time for the inception of asthma and obesity is during the childhood. What is it that happens during the 1st years of a child's life that produces changes in the lung and immune system, which predisposes the child to a lifetime of chronic symptoms related

to the "obese asthma" phenotype? This phenotype has previously been discussed [1, 2] as a unique, but today we are closer to the opinion that there is a distinct phenotype. Each of these diseases, asthma and obesity, is complex per se, modified by multiple factors, followed by complex inflammatory and immunological interactions, and often shared comorbidities; and, both diseases share similar lifestyle factors [1]. Until recently, many authors have explored a number of hypotheses about the mechanisms of their association including inflammation, gastro-esophageal reflux, and mechanical factors. Nowadays, we can consider the one more mechanism to be responsible for their association, i.e., the significant influence of irrational use of antibiotics (penicillin, macrolides) in the youngest children under 3 years of age [3, 4]. It is known that children of this age predominantly suffer from viral and atypical respiratory infection, which is, in practice, often treated with macrolides.

Macrolides, particularly, modify the microbiota and their functions, as well as the antibiotic resistance of the intestinal microbiota, and they are the strongest drive of interindividual differences in microbiota composition even 12–24 months after the course, as well as the drive of microbiota richness and maturity [4]. The recent study [4] has shown that, in all macrolide users, some advantage orders of germs (*Lactobacillus*, *Bifidobacterium*, *Collinsella*, *Anaerostipes*, unassigned *Coriobacteriaceae*) were reduced within 12–24 months while the number of side/undesirable orders of germs increased (*Lactobacillales*, *Bacteroides*, *Parabacteroides*, *Proteobacteria*, *Enterobacteriaceae*, *Eubacterium*, *Clostridium*, *Dorea*). It is known that the depletion of *Lactobacillus* and *Bifidobacterium* with intestinal microbiota deviations and low biodiversity, in early life, contributes to an increased risk of the allergic disease [5]. The composition of CD4 T lymphocytes and responsiveness of invariant natural killer T (iNKT) cells on many inflammatory cytokines in the intestinal mucosa affect the composition and diversity of the gut microbiota [6], especially during early life, and this may influence susceptibility to asthma later in life [7]. The commensal microbiota, achieving two mechanisms (positive-antigenic drive and negative-cytolytic depletion by CD8+T cells) profoundly depletes the iNKT cell compartment [7], plays an important epigenetic role in distinguishing individuals throughout life and contributes to the host immune status. The restricted gut flora followed with decreased microbial stimulation leads to the delayed immune maturation (Th2 and T regulatory) and impaired immune regulation with Th2-skrewing early in life, which precedes asthma at school age [8]. The infant microbiome (gut microbiota and its corresponding genes) is undergone dynamic changes during the first 3 years of life when an adult-like microbiome is reached [9]. In the research with mice, it was found that the penicillin, also, led to the ileal atrophy associated with the generally decreased expression of genes involved in intestinal immune responses, with numerous consistencies across gender, i.e., reducing population of CD4 IL17 or IL22 in the ileum and colon [10].

Besides this, poor intestinal microbiota cannot provide adequate activity of the bile-salt hydrolase so there is no reduction in the host body weight, insulin resistance, and blood cholesterol [4].

2. The mechanisms of association between asthma and obesity

The pathogenesis of asthma in obese children and, vice versa, the obesity in asthmatics are poorly understood and, until recently, labeled as a pathogenesis of "obese asthmatics" [2].

Today, we know that the obesity had its origin in utero [1, 8]. Suboptimal nutrition in utero during the first two trimesters (despite normal postnatal nutrition and followed by catch-up growth in the first several years of life) causes obesity and consequently metabolic syndrome in children [8, 11]. Frey et al. [12] concluded that the children born with a low and high birth weight have an almost same increased risk of obesity later in life.

According to one hypothesis, the first risk factors for obesity in childhood asthma and "non-pure eosinophilic childhood asthma" [1, 13] are younger gestational age at birth and higher infant weight gain. For the "obese asthma," there is no sufficient evidence of a noneosinophilic pattern of inflammation, with subgroup of asthmatics demonstrating IL8-driven neutrophilic airway inflammation [13]. In such cases, there is a high mitogen-activated protein kinase (MAPK) and 8-isoprostane level, which all together correlate with increased leptin, increased Th 1 cytokines (IL2, tumor necrosis factor (TNF)-alpha, IL6, INF-gamma, and IL1-beta, IL8), increased tryptase, expressed leptin and adiponectin receptors in bronchial and alveolar epithelial cells, and simultaneously, they correlate with low adiponectin, decreased Th2 cytokines (IL4, IL5, and IL13), decreased Treg cells, decreased eosinophils, and decreased M2 macrophages [14]. Leptin and TNF-alpha establish a positive feedback mechanism. Leptin promotes activation toward Th1 phenotype, increases production of interferon (INF)-gamma, and promotes monocytes and alveolar macrophage activation, but decreases Th2 cytokines production. Simultaneously, leptin exhibits antiapoptotic properties on neutrophils via NF-kB and MEK1/2 MAPK pathway, and so it promotes neutrophil survival. These, all together, immunological occasions could modify airway function and lead to asthma with special airway inflammation [1, 13], accompanied, in the same time, with a low-level chronic systemic inflammation [14]. The systemic inflammation in obesity upregulates the asthmatic pathway, and this is modified by adipokines and other systemic inflammatory markers [14]. Increased TNF-alpha is responsible for airway hyperresponsiveness although data suggest little association with obesity [15]. However, other authors [16] consider that the adipocytes diameter is in a positive correlation with TNF-alpha. The subcutaneous adipocytes may be more important for glucose/insulin regulation than visceral fat in obese children and women [6, 16, 17]. The low insulin sensitivity is followed by high exhaled breath condensate levels of malondialdehyde, high exhaled nitric oxide, and low glutathione, which are some asthma markers [18, 19].

At the same time, leptin promotes angiogenesis and airway remodeling via vascular endothelial growth factor (VEGF) (released from airway muscle cells). However, metabolism of leptin can only partly explain the relationship that exists in the phenotype of asthma in obese children [13]. The next adipokine, called adiponectin, decreases in the obese, increases with weight loss, i.e., inversely correlates with body mass index (BMI), and can inhibit the production of pro-inflammatory cytokines (IL6, TNF-alpha), can promote the production of anti-inflammatory cytokine IL1 receptor antagonist and IL10, and so can attenuate allergen-induced airway inflammation [13].

Furthermore, some researchers observed the intergeneration aggregation (transgeneration transmission) of obesity and metabolic dysfunction [11, 12]. The gestational programming with metabolic abnormalities leads to the changes to the epigenomics and shifts toward obesity and metabolic syndrome. This should be taken with caution because the epigenetic gene modifications may be reversible [11, 12]. Surely, the epigenetic alterations are induced by suboptimal maternal nutrition/endocrine factors and include several factors (deoxyribonucleic

acid (DNA) methylation, histone modifications, chromatin remodeling, and/or regulatory feedback by microRNAs) that have the ability to modulate gene expression and promote the metabolic syndrome phenotype [13]. DNA methylation prevents gene access to transcription factors into mRNA and promotes other epigenetic changes. Epigenetic modification of genes in immune cells responsible for disease/disorder is launched by diet, microbiome, and environmental exposures, and can have long-lasting effects on immune responses related to allergic disease. We should not forget that prenatal exposures can have the potential to modify the development of atopic diseases during childhood.

Moreover, the possible reason for obesity in early childhood is a genetic polymorphism (Arg16, Gln 27, 308-G/A, and NR3C1) [13]. Polymorphism of gene Gln27 for beta-2-adrenergic receptors is associated with obesity and poor bronchodilator response. Polymorphism of 308-G/A of gene for TNF-alpha is also associated with both obesity and asthma. Gene ADRB2 codes the activity of adrenergic beta-2-receptor and is located on chromosome 5q31-q32. Thus, Arg16 polymorphism of this receptor may be associated with some asthma phenotypes (nocturnal, response to long-acting beta-2-agonists). Polymorphism of gene NR3C1 is followed by the resistance of glucocorticoid receptors and difficult-to-control asthma. Polymorphism of gene on chromosome 11q13 contributes to variation of obesity phenotypes in general population. Moreover, it is known that single nucleotide polymorphisms within several genes influence the development of both obesity and asthma at the genetic level [13]. We should not forget that chromosome 12q contains genes (12q13) for variants in vitamin D receptors and inflammatory cytokines in obese asthmatics [13, 14].

Atopy significantly mediates the effect of adiposity on asthma outcomes (**Figure 1**). However, the exact role of atopy or allergic airway inflammation in the "obese asthmatic" phenotype is currently unclear [13]. Periyalil et al. [14] found that adipocytes, macrophages, and mast cells secrete inflammatory cytokines, which in turn lead to systemic inflammation and negative effects of target organs. Allergic asthma may be followed by obesity when the children are

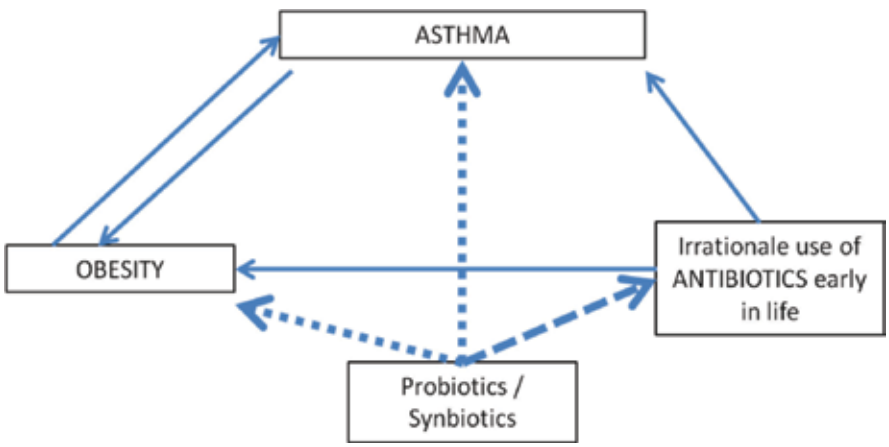

Figure 1. Associations among asthma, obesity, irrational use of antibiotics and effects of probiotics/synbiotics. The solid arrows indicate undesirable effects. The dashed-line arrows indicate desirable effects.

younger than 12 years and suffer from early-onset asthma and/or atopic eczema and/or food allergy in infants, that all together lead to excessive consumption of food and to modified asthma phenotype called "obese asthmatic" phenotype [13]. As the metabolism of adipocytes is rich, and the estrogen enhances eosinophil function and modulates IL4 and IL13 production by monocytes, the "obese asthma" phenotype is noted predominantly in prepubertal boys and girls, and premenopausal women, established the sex and age dependency [15–17].

According to another hypothesis, both asthma and obesity are associated with the increased airway oxidative stress and systemic inflammation, which is followed by lung restriction, reduced tidal volume (Vt), reduced cyclic loading and unloading impulses, less production of adenosine triphosphate (ATP) for uncoupling, i.e., unlocking of actin-myosin latch so that the airway smooth muscles are in stiff state, the bronchoconstriction is very strong and without bronchodilator response [19, 20]. This is accompanied with changes in the mechanics of breathing [21] with low volume at end of normal expiration (FRC), especially when in supine position, and low the expiratory reserve volume (if BMI higher than 35), the tidal volume (Vt) closed to residual volume. Low forced expiratory volume in 1 second (FEV1), low forced vital capacity (FVC), and the ventilation/perfusion ratio mismatch are followed by barrelhocked chest and possible atelectasis; lung compliance is reduced, and the airway resistance rises so that oxygen uptake is greater (VO_2) with high respiratory rate and work of breathing. Recent research study [21] has found that, within obese patients in supine position, the airway resistance during tidal breathing increases, but there is a difference between those with and without ventilatory failure. This change is mostly correlated with the visceral adipose tissue mass and the small airways. In effect, the authors [21, 22] argue that mass loading affects respiratory mechanics by other mechanisms such as altering chest wall compliance directly by restricting expansion and causing the respiratory system to operate on a less compliant part of the pressure-volume curve.

According to the third hypothesis, the obese children often have gastroesophageal reflux disease [23], which can worsen their asthma and vice versa. The stomach acid goes back into the esophagus, spills over the larynx, causes injury to the lining of the throat, airways, and lungs, which makes inhalation difficult and often causes a persistent cough on extraneous content, or acid enters the esophagus, triggers the afferent nerve reflex of coughing, causes the narrowing of airways in order to prevent the acid from entering, and the consequence is the shortness of breath [24]. Neural connections between esophagus and airway through the transient receptor potential may contribute to that [24]. Microaspirations of small amounts of acidic content, over time, contribute to chronic cough and reduce laryngeal mechanosensitivity to air stimuli, increasing the risk of aspiration thereby, as in a vicious circle [24].

3. The pathogenesis of asthma in children who are not obese

Unlike the obese children suffering from asthma, the asthmatic children with normal body weight (nBW) have a different immunopathogenesis of asthma. Asthma in children with nBW is predominantly allergic, especially if it is associated with eczema, food allergy, and allergic rhinitis. Allergic asthma can begin during the 1st year and disappear by the 3rd year of life. In this

case, it is called infantile asthma. Immunopathogenesis of infantile allergic asthma [25] often is not typical (mediated by increased immunoglobulin E (IgE) production of IgE and eosinophilic airway inflammation). Postnatal sensitization to perennial inhalant allergens and frequent viral infections of the lower respiratory tract occur in this age. The most common trigger factors of the asthmatic attacks are viruses and atypical bacteria, so the asthma is accompanied by mixed (eosinophil/neutrophil) inflammation of the airways. In children older than 3 years with nBW, allergic asthma usually has a typical immunopathogenesis, with the increased IgE production, eosinophilic inflammation of the airways, and type I hypersensitivity response.

Certainly, in children suffering from asthma with nBW, undermined tissues integrity of the airways and/or defective function of the respiratory epithelial barrier allow penetration of allergens, viruses, bacterial toxins, and other harmful noxae, which activate the immune system (**Figure 2**) and direct toward chronic airway inflammation [25, 26]. Activation of epithelial cells and the release of pro-inflammatory cytokines and chemokines (TNF-alpha, IL13, thymic stromal lymphopoietin (TSLP), IL31, and IL33) lead to Th2 cell response (IVb type immune response). After that the apoptosis of the epithelial cells and their peeling with a supporting release of IFN-gamma, TNF-alpha, and IL32 follow. Chemokines attract inflammatory cells that interact with the target tissue cells. Akdis found that innate lymphoid cell type 2 (ILC2) plays a key role in the activation and collection of T and B cells, i.e., they are early providers of Th2 immune response followed by the release of IL5, IL9, and IL13 when stimulated with IL25, IL33, and TSLP (released from epithelial cells of mucous membranes in response to protease allergens) [25, 26].

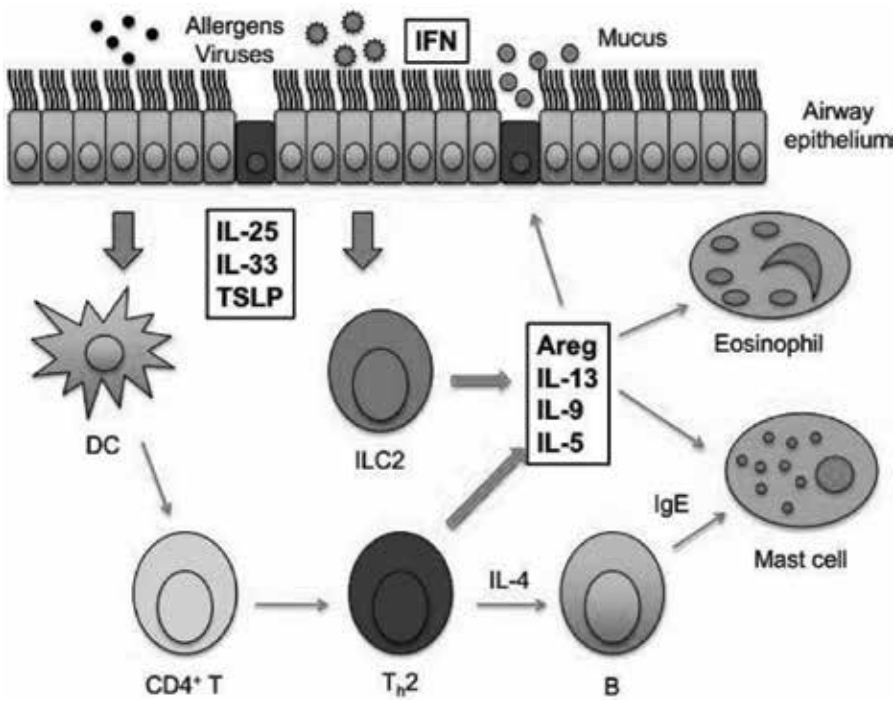

Figure 2. Pathogenic mechanisms in asthma.

It is known that certain interleukins (IL5, IL25, and IL33) induce eosinophilia and eosinophilic airway inflammation, and other interleukins (IL4 and IL13) induce local and systemic IgE production [25, 26]. In the phase of sensitization of a patient, FcεRI binds the allergen-specific IgE [25] on the surface of mast cells and basophil cells. During the repeated contact with the same allergen, subsequent degranulation of mast cells and basophils, which release the mediators of type I hypersensitivity reactions (histamine, prostaglandin D2 (PGD2), PAF, LTC4, LTD4, LTE4, IL3, IL4, IL5, IL13, chemokines), occurs. Effector T cell subpopulations (TH9, Th17, and TH22) play a partial role in inflammation, mucus production, and the tissue healing. Bronchial hyperreactivity, smooth muscle spasm, and activation of myofibroblasts are controlled by a number of cytokines (IL4, IL9, IL13, IL25, and IL33). Subsequently, collection of inflammatory cells and increased inflammatory cascade are induced by chemokines and the molecules of the metabolic pathway of arachidonic acid. Angiogenesis is a sign of chronic inflammation and is accompanied by an increased production of VEGF and IL32. Survival, reactivation of migratory inflammatory cells and their interaction with tissue cells are mediated by IL2 and IL4 [26]. The type 2 innate lymphoid cells also produce amphiregulin to induce airway remodeling (**Figure 2**).

IL33 is a cytokine and a biomarker of innate immune response. It is expressed by epithelial cells, endothelial cells, eosinophils, smooth muscle, myofibroblasts, dendritic cells (DC), macrophages, and mast cells, and contributes to Th2 inflammation and bronchial hyperreactivity in asthma, and involves in T cell differentiation. IL33 is one of the sensing cytokines, thus signals to the allergen-presenting dendritic cells to take up incoming allergens and bring them to lymph nodes.

In the course of the immune response to a viral antigen, the signaling of factor 3 of the interferon gene regulation is defective in a child suffering from allergic asthma, which is accompanied by a reduced or absent INF-beta production, causing the absence of apoptosis and inhibition of the virus replication [25–27]. Since the cellular immunity is defective, viral nucleic acid cannot activate the toll-like receptors (TLR3, TLR5, and TLR7) that lead to the virus survival, its replication, and the cytotoxic destruction of epithelial cells, which release the mediators that cause the exacerbations with mixed neutrophil/eosinophilic inflammation. The final result of INF-beta deficiency is an increase of transforming growth factor (TGF)-beta, which contributes to the deregulation of Treg lymphocytes, an early proliferation and remodeling of the airways [27]. At the same time, FcεRI action on the precursors of dendritic cells is amplified, so the virus can be easily attached via a light chain of the Fab fragment of IgE. Recent research findings suggest that the iNKT cells promote sensitization to ubiquitous inhalant allergens [28], contribute to *in vivo* Th2 inflammatory response of the airways facilitating the activity of dendritic cells, i.e., acting as adjuvants for the enhance of Th2 inflammatory cell response [29] and thereby contribute to the development of asthma and other allergic diseases. What else, activated DCs traffic to lymphoid organs to initiate T cell responses to the viruses or allergens and so contribute to further disease pathogenesis.

Th2 molecular asthma phenotypes are determined by identifying the clinical characteristics and biomarkers (eosinophilia and serum periostin, the concentration of exhaled nitric oxide) and sometimes by identifying specific molecular pathways [30]. However, non-Th2 phenotypes of asthma, often asthma in obese children and sometimes infantile asthma, are still

poorly defined and their biomarkers (modified natural inhibitor of inducible nitric oxide synthase, asymmetric dimethylarginine in the blood) are still not routinely measured. Identifying phenotypes of asthma in children and adults is important so we could provide the appropriate treatment. Most children suffering from allergic asthma with nBW are successfully treated according to the recommendations of the Global Initiative for Asthma [31]. Most children suffering from the asthma with the nBW have a good response to inhaled steroids (ICS) and/or antileukotrienes. In a small number of children, asthma is severe and requires the treatment with high-dose of ICS. Poor response to ICS can have children with difficult to treat asthma, asthma induced by viruses and "obese" asthma so the treatment of these patients is complicated.

4. The obese and asthmatic children treated with antibiotics

The children of the youngest age predominantly suffer from viral and atypical respiratory infection, which is, often, mistakenly treated with antibiotics, actually, very often with macrolides. This applies, furthermore, in the children suffering from asthma with accompanying obesity because their asthma exacerbation, very often, triggered with virus and followed by the fever, is often considered to be a respiratory infection with bronchial obstruction and is hitherto mistakenly treated with antibiotics.

The overweight cases, the asthmatics, and the children treated with penicillin or macrolide (one or more times) have the microbiota with the abundance of side bacteria and long-term reduction in microbial richness [4] (**Figure 1**). For example, one of the macrolides, the azithromycin, reduces biomarkers of not only environmental enteropathy and pathogenic intestinal bacteria [32, 33], but also commensal and advantage bacteria, which makes restricted (poor) flora. The gut microbiota with restricted flora is mediated by cytolytic CD8+ T cells with depleted iNKT cells that contribute to epigenetically modulating of specific host immune traits (defense and immunoregulation) [6]. It is known that CD8+ T cell responses are elicited by certain microbiota, including Listeria and Salmonella and followed by the local enteric mucosal stress response, which is associated with striking increases in certain chronic inflammatory and autoimmune diseases [6]. Besides that azithromycin inhibits ribosomal translocation, leading to the inhibition of bacterial protein synthesis, acts bacteriostatic but may be bactericidal at high concentrations, modulates differentiation and lipopolysaccharide (LPS) induces maturation in dendritic cells but decreases transcription and activity of histone deacetylation-2 promoter, which results in gene repression [32]. After macrolide [3, 4, 32, 33], the microbiota slowly recovers so that it establishes persistence of the antibiotic-associated microbiota composition, which contributes to the persistence of metabolic changes and compromises the development of a healthy immune system, so that the consequences are early manifestations of asthma and obesity. The mentioned effect of macrolides is not dependent on the age of the child [4].

The impression is that use of antibiotics during early life, linked with poor gut microbial diversity, drive to "preponderance" of side over advantage effects of antibiotics (macrolides and penicillin) [3, 4, 32, 33]. Pronouncedly, in the case of irrational use of antibiotics during early life, the restricted gut flora is followed by a decreased microbial stimulation, which

leads to the delayed immune maturation (Th2 and T regulatory) and the impaired immune regulation with Th2-skrewing early in life, which precedes asthma at school age [3, 4, 8] and obesity early in life [10, 11, 14]. This consideration has no intention of diminishing the desired effects of azithromycin (attenuates Th-1 responses following LPS or INF-gamma stimulation of macrophages, shifting polarization of activated macrophages toward the alternative/anti-inflammatory M2-phenotype (which plays a role in directing Th-2 responses), inhibits IL17-induced IL8 and 8-isoprostane release)—but pointing out the need for its rational application, the "balanced" therapy, new therapeutic modality, especially in the children suffering from wheezing, respiratory infections and obesity.

In the mentioned period of 12–24 months, the macrolide use is associated with the increased risk of asthma and it predisposes children to the antibiotic-associated weight gain. The macrolides impact on the intestinal microbiota should be considered with mandatory prescribing probiotics [4], which would prevent compromising of a healthy immune system and metabolism development. It has been proven that "good" probiotic bacteria and "good" probiotic fungi in the mouth and intestines, sufficiently represented, are necessary to compensate destroyed intestinal flora during and after antibiotic therapy and for the health of children [5] (**Figure 1**). We have, also, confirmed that the use of synbiotics in the optimal period of time of 3–6 months can achieve adequate control of respiratory infection and allergic wheezing diseases in children younger than 5 years [34]. Nevertheless, we have found that the time necessary for the restitution of the immune balance between immunoglobulin A and immunoglobulin E was 9 months in the youngest children [34]. Now, we can add a logical setting as hypothesis that should have been assessed in clinical trials, that the everyday application of synbiotic (during several months) after antibiotic using would likely prevent the obesity.

In favor of this Million's findings [35], the probiotics affect the microbiota directly by modulating its bacterial content and indirectly through bacteriocins produced by the probiotic bacteria, as well as, *L. plantarum* and *Lactobacillus gasseri* (formerly named *L. acidophilus*) strains, which has an anti-obesity effect in overweight/obese people in terms of reductions in abdominal adiposity, body weight, and other measures. Adding a probiotic strain Bacteroidetes can be essential for the body weight loss in obese patients, because Bacteroidetes overgrows the undesirable gut strain named Firmicutes [35].

It is known that the trillions of the side microbial cells in the intestinal microbiota can contribute to obesity by increasing energy extraction or by altering metabolic signaling and inflammation [36], and thus occupy a central role in the pathogenesis of, so far seemingly unrelated systemic auto-inflammatory and metabolic disorders. As a matter of fact that the condition of basal immune and metabolic homeostasis is mainly controlled by the bacterial microbiome.

5. The inflammation in the "obese asthma" phenotype and the possibility of the treatment

Inflammation is the goal in the treating of childhood asthma accompanied by obesity, but here, inflammation is neutrophilic, with elevated leptin levels in the plasma and airways, predominately Th-1-related inflammation (IL8 driven) [13, 21], potential and IL-17-related

inflammation, enhanced inflammatory/oxidative response to leptin and decreased airway eosinophils. The high level of leptin stimulates the synthesis of TNF-alpha, IL6, and prostaglandins, which is the basis for a low-grade inflammatory process that leads to the atherogenesis process and early development of metabolic syndrome. The leptin receptors are reduced in the airways but they are represented in the visceral fat, which enables metabolic influence on bronchial hyperreactivity [20, 37]. Increased oxidative stress and decreased physiologic nitric oxide are due to low L-arginine/asymmetric dimethylarginine ration, which overall contributes to bronchoconstriction [20, 21, 38, 39]. This metabolic function of smooth muscle in the airways contributes to a poor response to bronchodilators, poor asthma control, and low pulmonary function. In the "obese asthma" phenotype, increased airway oxidative stress and systemic inflammation are followed by reduced cycling loading and unloading impulses, the less production of adenosine triphosphate for uncoupling, i.e., unlocking of actin-myosin latch [19, 20], so that the smooth muscles airways are in a stiff state, the bronchoconstriction is very strong and without bronchodilator response, i.e., the resistance to short-acting beta-agonists exists.

Both conditions, asthma and obesity, associated, act to aggravate the degree of bronchodilatation after a deep inhalation, which is a mechanical airway dysfunction [37]. The mechanical airway dysfunction in an "obese asthma" phenotype is a consequence of restriction or reduced the total lung capacity, decreased expiratory reserve volume and there is a ventilation/perfusion mismatch. In obese asthmatics, it is associated with increased airway inflammation indices. At the same time, body mass index (BMI) more than 30 was associated with a 10-fold increase in odds for developing methacholine responsiveness [37, 38]. Anyhow, early onset of asthma is a potential risk factor for the weight gain. In the early onset category, BMI increased linearly for every year of having asthma since diagnosis [37]. It is still not clear whether obesity, preceding or following asthma, influences the severity of asthma and asthma control.

A special problem in the treatment of this asthma phenotype is the steroid resistance. The response to inhaled steroids is different according to BMI categories [39]. The oxidative stress contributes to the activation of MAPK, baseline TNF-alpha in peripheral blood mononuclear cells and bronchoalveolar lavage cells, so that the response, for example, to dexamethasone is poor or does not exist. The TNF-alpha is in a positive correlation with the adipocyte diameter, with which metabolism is rich. Doubtless, we can always try to treat this asthma phenotype in the form of fixed combinations of low doses of inhaled steroid and long-acting beta 2 agonist.

The second reason for the steroid resistance in the "obese asthma" phenotype is, often, a low vitamin D level that is inversely related to BMI [40, 41]. Vitamin D performs the upregulation of IL-10 by CD4 Treg lymphocytes, thus it exceeds steroid resistance [37] and inhibits the activity of DCs across the decreased LPS activation, inhibits the proliferation and fibroblasts activation and inhibits the inflammatory cytokines and the airway remodeling mediators secretion by the smooth muscle cells in airway, reduces the secretion of extracellular matrix, acts anti-proliferatively on smooth muscles, improves the immune function in the lungs, upregulates the antimicrobial proteins (cathelicidin, beta-defensin), acts anti-inflammatory, reduces the pulmonary hyperplasia, inhibits the eosinophils recruitment, promotes the immune tolerance [41], and reduces the IL-17A and IL-22 cytokine levels [42].

The antileukotriene treatment can be successful at the certain asthmatics with the phenotype "obese asthma" because it controls the release of INF-gamma and producing of myofibroblasts types I and II well [31].

The antineutrophil drugs, such as macrolides and dapsone (diaminodiphenyl sulfone), did not give the expected results for the "obese asthma" phenotype control [31]. Furthermore, the advantage of anti-inflammatory role of macrolides is in conflict with its side, already commented, effects on intestinal mucosa in young children. Because of this, we must find other drugs to treat the "obese asthma" phenotype in the youngest children, such as, perhaps, anticytokines or biological agent [12]. However, the anti-TNF-alpha therapies have not yet been approved for children, but only for adults [38]. The bariatric surgery is the only aggressive attempt.

6. Conclusion

Well-known and safe recommendations for the "obese asthma" phenotype control are, without doubt, the cutoff of the vicious cycle of childhood obesity/asthma, which should be reached with more physical activity and less desire for food [43, 44]. Afterward, the substitution of D3 vitamin may be decisive in the treatment of the asthma with a distinct phenotype "obese asthma." The treatment of this asthma phenotype in children, always, involves an attempt with antileukotriene or/and a fixed combination of low dose of inhaled steroid and long-acting beta 2 agonist. The current use of some macrolides, as an anti-inflammatory drug for asthma, is under question now, because it is necessary to make a new assessment of benefit and harm, or establish a new treatment modality with a combination of macrolides and probiotics/synbiotics.

We expect that, in the future, the indications for macrolides, as an anti-inflammatory drug (e.g., for infantile and asthma in childhood), will be accompanied by a recommendation on mandatory, simultaneous, and the concomitant application of probiotics or synbiotics, especially in the youngest children (**Figure 1**). The duration of substitution with probiotics or synbiotics during and after discontinuation of macrolides should be determined in future studies. From our current perspective and findings, and bearing in mind the long-term disruption (24 months) of the intestinal microbiota, we suggest a period of, at least, 9 months of probiotics or synbiotics supplementation, which is necessary time for the restitution of immune balance between immunoglobulin A and E, in the youngest children [34, 44]. We join the recommendation, to avoid all antibiotics, in particular macrolides, for the "irresponsible" treatment of viral infections in the youngest children, or several times a year, or longer than the prescribed time and doses for macrolides [45] and penicillin [46]. All antibiotics should be avoided for one more reason—it is the exclusive way to avoid the intestinal microbiota disruption, disorder of the genetic material within the intestinal microbial niches (microbiome), metabolic alterations, obesity, immunological imbalance, and early onset of asthma.

We and many other authors worldwide did not end the research for the treatment of asthma in obese children, for the "balanced" treatment of the youngest children during respiratory

infections, for the overcoming the side effects of some antibiotics in early childhood, for a new therapeutic modality, especially in children suffering from wheezing/asthma, respiratory infections and obesity, simultaneously, but this is our future research goal.

Abbreviations

iNKT	invariant natural killer T cells
Th	T helper cells
IL	interleukin
TNF-alpha	tumor necrosis factor-alpha
INF	interferon
nBW	normal body weight
TSLP	thymic stromal lymphopoietin
ILC2	innate lymhoid cells type 2
DC	dendritic cell
IgE	immunoglobulin E
FcεRI	Fc epsilon RI, the high-affinity receptor for the Fc region of IgE
PGD2	prostaglandin D2
PAF	platelet-activating factor
TGF	transforming growth factor
MAPK	mitogen-activated protein kinase
MEK1	mitogen-activated protein kinase kinase 1
MEK2	mitogen-activated protein kinase kinase 2
NF-kB	nuclear factor kappa B
VEGF	vascular endothelial growth factor
Areg	amphiregulin
mRNA	messenger RNA
DNA	deoxyribonucleic acid
RNA	ribonucleic acid
TLR	toll-like receptor

ICS	inhaled steroids
Vt	tidal volume
ATP	adenosine triphosphate
FRC	functional residual capacity
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
VO_2	oxygen consumption
LPS	lipopolysaccharide

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References

[1] Stojkovic A, Velickovic V. The clinical implications of asthma in obese children: Review. Pediatru.ro. 2015;**39**(3):18-20

[2] Papadopoulos NG, Arakawa H, Carlsen K-H, Custovic A, Gern J, Lemanske R, et al. International consensus on (icon) pediatric asthma. Allergy 2012; DOI: 10.1111/j.1398-9995.2012.02865.x

[3] Nobel RY, Cox ML, Kirgin FF, Bokulich AN, Yamanishu S, Teitler I, et al. Metabolic and metagenomic outcomes from early-life pulsed antibiotic treatment. Nature Communications. 2015;**6**:74-86. DOI: 10.1038/ncomms8486

[4] Korpela K, Salonen A, Virta LJ, Kekkonen RA, Forslund K, Bork P, de Vos WM. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. Nature Communications. 2016;**7**:10410. DOI: 10.1038/ncomms10410

[5] Haahtela T, Holgate S, Pawankar R, Akdis CA, Benjaponpitak S, Caraballo L, et al. The biodiversity hypothesis and allergic disease: World allergy organization position statement. World Allergy Organization Journal. 2013;**6**:3-41. DOI: 10.1186/1939-4551-6-3

[6] Wingender G, Stepniak D, Krebs P, Lin L, McBrides S, Wei B, et al. Intestinal microbes affect phenotypes and functions of invariant natural killer T cells in mice. Gastroenterology. 2012;**143**(2):418-428. DOI: 10.1053/j.gastro.2012.04.017

[7] Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. Science. 2016;**352**(6285):539-544. DOI: 10.1126/science.aad9378

[8] Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. Clinical & Experimental Allergy. 2014;**44**(6):842-850. DOI: 10.1111/cea.12253

[9] Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. Nature. 2012;**486**:222-227. DOI: 10.1038/nature11053

[10] Cox ML, Yamanishi S, Sohn J, Alekseyenko VA, Leung MJ, Cho I, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell. 2014;**158**(4):705-721. DOI: 10.1016/j.cell.2014.05.052

[11] Desai M, Jellyman JK, Ross MG. Epigenomics, gestational programming and risk of metabolic syndrome. International Journal of Obesity. 2015;**39**(4):633-641. DOI:10.1038/ijo.2015.13

[12] Frey U, Latzin P, Usemann J, Maccora J, Zumsteg U, Kriemler S. Asthma and obesity in children: Current evidence and potential systems biology approaches. Allergy. 2015;**70**:26-40. DOI:10.1111/all.12525

[13] Ali Z, Ulrik SC. Obesity and Asthma: A coincidence or a causal relationship? A systemic review. Respiratory Medicine. 2013;**107**(9):1287-1300. DOI: 10.1016/j.rmed.2013.03.019

[14] Periyalil AH, Gibson GP, Wood GL. Immunometabolism in obese asthmatics: are we there yet? Nutrients. 2013;**5**:3506-3530. DOI: 10.3390/nu5093506

[15] Maffeis C, Manfredi R, Trombetta M, Sordelli S, Storti M, Benuzzi T, et al. Insulin sensitivity is correlated with subcutaneous but not visceral body fat in overweight and obese prepubertal children. The Journal of Clinical Endocrinology & Metabolism. 2008;**93**(6):2122-2128. DOI: 10.1210/JC.2007-2089

[16] Boulet LP. Asthma and obesity. Clinical & Experimental Allergy. 2013;**43**(1):8-21. DOI: 10.1111/j.1365-2222.2012.04040.x

[17] Vieira VJ, Ronan AM, Windt MR, Tagliaferro AR. Elevated atopy in healthy obese women. The American Journal of Clinical Nutrition. 2005;**82**(3):504-509 [PubMed: 16155260]

[18] Forno E, Acosta-Pérez E, Brehm JM, Han YY, Alvarez M, Colón-Semidey A, Canino G, Celedón JC. Obesity and adiposity indicators, asthma, and atopy in Puerto Rican children. Journal of Allergy and Clinical Immunology. 2014;**133**(5):1308-1314. DOI: 10.1016/j.jaci.2013.09.041

[19] Jimenez SJ, Espinet HJF, Garrido MMJ, Antonio RJ, Mayor PS, Boira PdelMM, Comas RA, Martinez BA. Asthma and insulin resistance in obese children and adolescents. Pediatric Allergy and Immunology. 2015;**25**:699-705. DOI: 10.1111/pai.12294

[20] Wechsler ME, Kunselman SJ, Chinchilli VM, Bleecker E, Boushey HA, Calboun WJ, et al. Effect of beta2-adrenergic receptor polymorphism on response to long acting beta2

agonist in asthma (LARGE trial): A genotype-stratified, randomised, placebo-controlled, crossover trial. Lancet. 2009;**374**(9703):1754-1764. DOI: 10.1016/S0140-6736(09)61492-6

[21] Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. Chest. 2006;**130**(3):827-833 [PMID: 16963682]

[22] Dattani RS, Swerner CB, Stradling JR, et al. Exploratory study into the effect of abdominal mass loading on airways resistance and ventilatory failure. BMJ Open Respiratory Research. 2016;**3**:e000138. DOI: 10.1136/bmjresp-2016000138

[23] Gaude SG. Pulmonary manifestations of gastroesophageal reflux disease. Annals of Thoracic Medicine. 2009;**4**(3):115-123. DOI: 10.4103/1817-1737.53347

[24] Mitrovic S. Terminology, diagnostics and therapy of laryngopharyngeal reflux—A glimpse into the past. Vojnosanitetski Pregled. 2014;**71**(6):608-610. DOI: 10.2298/VSP1406608M

[25] Akdis M. The pathogenesis of asthma. In: Global Atlas of Asthma. European Academy of Allergy and Clinical Immunology; 2013. pp. 28-30

[26] Akdis CA. The underlying mechanisms in allergy. In: Global Atlas of Allergy. European Academy of Allergy and Clinical Immunology; 2014. pp. 39-42

[27] Bordon Y. Asthma and allergy: TGFβ—Too much of a good thing? Nature Reviews Immunology. 2013;**13**(9):618-619. DOI: 10.1038/nri3519

[28] Wingender G, Rogers P, Batzer G, Lee MS, Bai D, Pei B, et al. Invariant NKT cells are required for airway inflammation induced by environmental antigens. Journal of Experimental Medicine. 2011;**208**(6):1151-1162. DOI: 10.1084/jem.20102229

[29] Nie H, Yang Q, Zhang G, Wang A, He Q, Liu M, et al. Invariant NKT cells act as an adjuvant to enhance Th2 inflammatory response in an OVA-induced mouse model of asthma. PLoS One. 2015;**10**(4):e0119901. DOI: 10.1371/journal.pone.0119901

[30] Wenzel S. Phenotypes & endotypes: Emerging concepts on asthma heterogeneity. In: Global Atlas of Asthma. European Academy of Allergy and Clinical Immunology; 2013. pp. 34-35

[31] Global Initiative for Asthma (GINA), National Heart, Lung and Blood Institute, National Institute of Health. GINA Report. Global Strategy for Asthma Management and Prevention. Bethesda: National Institute of Health; Updated 2016. Available from: www.ginasthma.org

[32] Parnham JM, Eraković Haber V, Giamarellos-Bourboulis JE, Perletti G, Verleden MG, Vos R. Azithromycin: Mechanisms of action and their relevance for clinical applications. Pharmacology & Therapeutics. 2014;**143**(2):225-245. DOI: 10.1016/j.pharmthera.2014.03.003

[33] Bishai WR. Macrolide immunomodulatory effects and symptom resolution in acute exacerbation of chronic bronchitis and acute maxillary sinusitis: A focus on clarithromycin. Expert Review of Anti-infective Therapy. 2006;**4**(3):405-416. DOI: 10.1586/14787210.4.3.405

[34] Stojkovic A, Simovic A, Bogdanovic Z, Bankovic D, Poskurica M. Optimal time period to achieve the effects on synbiotic-controlled wheezing and respiratory infections in young children. Srpski Arhiv za Celokupno Lekarstvo. 2016;**144**(1-2):38-45. DOI: 10.2298/SARH1602038S

[35] Million M, Lagier C-J, Yahav D, Paul M. Gut bacterial microbiota and obesity. Clinical Microbiology and Infection. 2013;**19**:305-313. DOI: 10.1111/1469-0691.12172

[36] Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal ZW, Strowig T, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature. 2012;**482**:179-185. DOI: 10.1038/nature10809

[37] Litonjua AA, Sparrow D, Celedon JC, DeMolles D, Weiss ST. Association of body mass index with development of metacholine airway hyperresponsiveness in men: The normative aging study. Thorax. 2002;**57**(7):581-585. DOI:10.1136/thorax.57.7.581

[38] Szefler JS. Advances in pediatric asthma in 2014: Moving toward a population health perspective. Journal of Allergy and Clinical Immunology. 2015;**135**:644-652. DOI: http://dx.doi.org/10.1016/j.jaci.2014.12.1921

[39] Baffi WC, Winnica ED, Holguin F. Asthma and obesity: Mechanisms and clinical implications. Asthma Research and Practice. 2015;**1**:1-7. DOI: 10.1186/s40733-015-0001-7

[40] Xystrakis E, Kusumakar S, Boswell S, et al. Reversing the defective induction of IL10 secreting regulatory T cell in glucocorticoid resistant asthma patients. Journal of Clinical Investigation. 2006;**116**(1):146-155. DOI: 10.1172/JCI21759

[41] Gupta A, Sjoukes A, Richards D, Banya W, Hawrylowicz C, Bush A, Saglani S. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. American Journal of Respiratory and Critical Care Medicine. 2011;**184**:1342-1349. DOI: 10.1164/rccm.201107-1239OC

[42] Nanzer MA, Chambers SE, Ryanna K, Richards D, Black C, Timms MP, et al. Enhanced production of IL-17A in patients with severe asthma inhibited by 1alfa,25-dihydroxyvitamin D3 in a glucocorticoid-independent fashion. Journal of Allergy and Clinical Immunology. 2013;**132**:297-304. DOI: 10.1016/j.jaci.2013.03.037

[43] Moreira A, Bonini M, Garcia-Larsen V, Bonini S, Del Giacco RS, AgacheI, Fonseca J, Papadopoulos GN, Carlsen HK, Delgado L, Haahtela T. Weight loss interventions in asthma: EAACI Evidence-based clinical practice guideline (part I). Allergy. 2013;**68**(4):425-439. DOI: 10.1111/all.12106

[44] Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-Year follow-up of a randomised placebo-controlled trial. Lancet. 2003;**361**(9372):1869-1871. [PMID: 12788576]

[45] Macrolides. BNF for Children 2014. Vol. 15. London, UK: BMJ Group, Pharmaceutical Press. pp. 283-286. Available from: www.bnf.org

[46] Penicillins. BNF for Children 2014. Vol. 15. London, UK: BMJ Group, Pharmaceutical Press. pp. 261-269. Available from: www.bnf.org

Chapter 3

Good Clinical Practice in Children and Adolescents

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Additional information is available at the end of the chapter

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Abstract

Good clinical practice (GCP) is a series of systematically developed ethical and quality standard of designing, registering, running, recording, and reporting of the clinical trials. Good clinical practice is very important regarding the trials usually performed on the vulnerable populations especially children and adolescents. The sensitivity of the issue is even higher in the children with psychiatric disorders. Usually, these children have little legal protection. Hence, the safety of interventions and the ethical considerations are among the most important issues in this field. The purpose of this chapter is to deal with above problems and globally applicable standards for the conduct of clinical trials on the under legal age subjects especially those with psychiatric disorders. Selection of trial subjects, ethical principles, regulatory requirements, protection of trial subjects, monitoring (compliance with the protocol), responsibilities of the investigator, and other requirements to perform a clinically and ethically sound clinical trial in children and adolescents will be discussed in this chapter.

Keywords: children and adolescents, ethics, good clinical practice, monitoring

1. Introduction

While new medical products (drugs and vaccines) are being developed and asking for registration, their efficacy and safety should be assessed in a well-designed clinical trial, ultimately on human beings [1]. This process is costly, and ethical considerations are controversial. The history of developing of good clinical practice (GCP) goes back to the end of World War 2 following the Nuremberg trials on war victims. In Nuremberg Nazi, physicians were accused for performing inhumane trials on human beings in the name of medical research. After the

war, two American doctors who were present in Nuremberg invented a set of research ethics principles including 10 points which are in compliance to the human rights. These principles are known as Nuremberg Codes [2, 3].

Later in 1964, the elected medical representatives came from all over the world, attended the 18th General Assembly of the World Medical Association in Helsinki. They decided to improve the points asserted in the Nuremberg Code and create a more formal statement of ethical principles. Its attitude was to provide detailed directions for medical science researchers to conduct the trials on human subjects with scientifically sound methods and in accordance with basic ethical principles. This statement is known as the "Declaration of Helsinki," and until now, several revisions have been released [4].

This history formed the basis for developing good clinical practice.

2. Good clinical practice definition

Good clinical practice is an internationally accepted scientific and ethical standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials on human subjects which provides assurance that the reported results are credible and accurate; the rights, integrity, and confidentiality of trial subjects are protected [3].

The good clinical practice is a quality assurance system for the conduct of clinical trials. It is a legal requirement accepted by health systems in many countries. Hence, a new product will not be licensed by regulatory authorities if the rules of good clinical practice are not followed [5].

3. Selection of trial subjects

Patient selection for any clinical trial is a very critical point. When choosing the inclusion criteria, the researcher should think that what factors are important to the research question and include the main characteristics of target population. The researcher should be careful that excessive exclusion may degeneralize the study. The caseness of pediatric subjects should be confirmed by a pediatrician. When working on pediatric psychiatric patients, the sensitivity is much more, the eligibility of subjects must be clearly defined in the inclusion and exclusion criteria. Furthermore, the diagnosis must be confirmed by a child and adolescent psychiatrist based on the latest version of diagnostic and statistical manual of mental disorders (DSM). In psychiatry trials, documentation and history of the diagnosis are usually required [6, 7].

4. Protection of trial subjects

Childhood period comes with rapid growth and development and ends with puberty. Unfortunately, sometimes it is accompanied by harsh diseases like infection diseases, allergies, cancers, and psychiatric disorders. So, many advanced vaccines and medicines are

needed to be developed for children and adolescents. Furthermore, some supplements are targeted for this group of population [8–10]. Hence, performing clinical trials on children and adolescents is a critical mission sometimes inevitable. Children are vulnerable population in medical research; hence, inclusion of children in clinical trials always is a matter of great concern for parents, researchers, and ethic committees. Children and adolescents who will attend in the clinical trials should be selected carefully by a qualified physician. The physician should be qualified by sufficient education, training, and experience and should be in charge for optimum health of the participants. All diagnosis should be supported by the latest clinical guidelines [11]. Furthermore, inclusion and exclusion criteria should be carefully set on the basis of study objectives and previous studies. The processes of medical care and every decisions made here should be based on evidence and guarantee the maximum safety of the patients in a way that the rights and well-being of the children would be protected. Blood sampling in children is not ethical if the benefits of the study do not exceed the harms for children. When a specific group of children directly benefit from blood sampling or blood sampling is necessary for diagnosis, the documents should be presented to the institutional ethics committee and benefits should be described to the parents or legal guardians. The subjects or his/her parent or legal guardian should be adequately informed about the processes of research, the rights and responsibilities. The aims and methods of the research should brightly be described to them. Furthermore, the subjects and their legal guardian must be aware of anticipated benefits and potential hazards of the intervention. Then, informed consent must be signed by the parents or legal guardian of the subjects below the legal age. Moreover, the subjects should ascent to participate. Then, after obtaining sufficient ethical approvals and consent forms, blood sampling could be gathered by a trained client under the guidance of existing guidelines [12, 13]. In clinical trials on pediatric psychiatry, a team-based approach involving the laboratory physician would help the quality assurance of examination, diagnosis, and reporting, as well as patient safety [14, 15].

5. Safety reporting

In trials with the main objective of efficacy assessment, the safety assessment is usually the secondary objective. One of the responsibilities of the researcher is to carefully monitor the adverse effects and record immediately when a participant experiences any side effect [16]. Then, the investigator should report it in a suitable way. Furthermore, in respecting the privacy, the researchers should guarantee the confidentiality of records that could identify the subject. Another duty of the researcher is to provide best possible care available and follow until complete disappearance of adverse effect. Sometimes, it is necessary to stop the trial to protect one or more subjects. Sometimes, the subjects or the legal guardian themselves decide to stop medication. In pediatric psychiatry, loss to follow-ups happens due to adverse effects of the intervention, stigma, and lack of parent's knowledge about medicinal psychotherapy [17]. So, the researcher should conduct a thorough investigation and find the exact reason of each loss to follow-up and report it. Usually, identifying the barriers and reducing them would be helpful. Educating the parents and legal guardians to help reduce the stigma of referring to psychiatrist and fear of tacking psychiatry medications may support the children health [18].

6. Develop informed consent form

Consenting is the process by which participant voluntary confirms his/her willingness to participate in the trial. The medical researchers should be careful and pay special attention when obtaining consent from vulnerable subjects, including children, the elderly, and psychiatric patients. Subjects with low perception may feel unable to make use of their right to judge the profits or hazards of the intervention and decide whether to consent or not. Child and adolescent psychiatrists should be careful about the decisional capacities of children and the role of the parents in medical decision making. Hence, obtaining informed consent form from the legal guardian of the subjects under legal age and the patients with severe psychiatric disorder is crucial. In addition, obtaining oral ascents from the subjects with low perception or children who will participate in the medical research is essential. Full procedures, rights and responsibilities, potential hazards, and benefits should be described to each participant and the legal guardian. Then, informed consent must be dated and signed by the legal guardian before the subject participates into the trial. Then, a copy of informed consent form and related information should be delivered to the parents or guardian. The original informed consent must be kept in the investigator's file [19].

7. Ethical approval

The researcher should submit the sponsor-provided protocol document to the Institutional Review Board (IRB) or Research Ethics Board (REB) for approval before recruiting any case into the trial. The investigator should also submit consent forms and assessment tools, including questionnaires. During specific intervals, the researcher must report the progress of the trial and request re-approval of the research by the IRB/REB. The IRB/REB will ask for a summary of trial progress [20]. The responsibility of the ethics committee is to guarantee the protection of the rights and well-being of human subjects enrolling into clinical trials. The ethics board decisions are in line with the latest revision of the declaration of Helsinki and local pertinent regulations [21].

8. Quality of data

Every research study needs to have a written protocol which includes the plan of the study as detailed as possible. The design and method of the trial should be well-thought-out, and the protocol must be well-written and approved by a faculty council. Protocol includes the trial information in detail and should consist of the trial title, the name of the main investigator, supervisor/s and sponsor/s, literature review, materials and methods, characteristics of intervention, dosage, duration, randomization, blinding, allocation concealment, inclusion criteria, exclusion criteria, project schedule (Gantt chart), and budget of the project [22].

In trials performing on children and adolescents, the investigators should be trained and interested in the scientific aspect and ensure that the study meets the needs of patient's health.

The researchers must also review up-to-date information, ensure the confidentiality of the data, and provide confidentiality agreement to sponsor. Furthermore, proper facilities, location, equipment, laboratory, product storage, and archive must be provided prior to study initiation [22, 23].

9. Resources

One of the requirements of good clinical practice is that the researcher has adequate access to resources to carry out a sound clinical trial. Resources include not only sufficient budget and materials, but also the ability to recruit adequate numbers of research subjects. Furthermore, the research team members must have adequate information about their specific roles, and they should have adequate time to deal with subjects and conduct the trial. In trials being conducted in children and adolescents, at least one of the team members should be specialized or trained previously to deal with the subject on this age span [24].

10. Randomization

Single-arm trials with historical controls for comparison may be biased by differences in subject characteristics (age, sex, prior therapy, phase of disorder, and supplemental care). Still, when matched controls can be selected, unknown confounding factors may be haphazardly distributed between two groups.

Designing a two-arm trial with distributing the subjects between two groups using randomization can help to minimize potential bias caused by unknown confounding factors. However, a placebo-controlled trial may be ethically defensible when the use of placebo would not add any risk or serious harm to the subjects. Sometimes, crossover design is more ethical and adheres to the principle of good clinical practice. In crossover studies, the subjects are randomly allocated to the treatment or control groups, after the first phase ends, the subjects will change the groups. In this design, all subjects receive all treatments. Of course, the priority of treatments should not harm the subjects.

When an uneven distributed factor between groups recognized, then controlling by statistics method at the analyses level may be considered. One strategy is to stratify the variable and discuss the results at different levels of the variable. A better solution is stratification process at the time of randomization using the permuted blocked randomize allocation. In this method, randomization will be performed using different age and sex blocks. Hence, the subjects will distribute evenly between treatment arms.

In a randomized clinical trial to control for the placebo effect and minimize the study bias, the subjects and researchers should be blinded using placebo, coding, and allocation concealment. In the case of a blinded trial, the protocol must declare who and in what conditions is allowed to break the codes (for example, the supervisor and in emergencies). Breaking the codes must be justified and must be reported [21].

11. Reports

Moving in accordance with protocol allows its accurate reporting, interpretation, monitoring, and verification of the trial. Furthermore, it assures the quality of every aspects of the trial. The data obtained from the trial must be handled, analyzed, synthesized, and reported in a sound approach. In addition, the sponsor or the research institute should be able to carry out on-site inspections of the validity of reported results. Hence, brilliant documentations and reporting are very important as well as the monitoring processes. For this purpose, the research institute should have easy access to all patient files and raw data during the trial [21].

12. Monitoring

Monitoring is an important part of good clinical practice. Monitoring is the process of auditing the trial based on compliance to the approved protocol, ethics, and regulation in a way that guarantee the optimum health and rights of the subjects, as well as timely submission of high-quality data. The objectives of monitoring are to prevent, detect, and correct careless errors, neglect, fraud/misconduct, and violations. Monitoring will guarantee the quality of medical care, quality of data, quality of trial, and quality of product. The monitor is a person who has been chosen by the sponsor or research institute for the monitoring and reporting of progress of the trial and for the confirmation of data. The monitor should have enough medical, scientific, and/or pharmaceutical qualifications, and clinical trial experience [21].

12.1. Monitor's responsibilities

Monitor's responsibilities are listed below:

- To act as a soother between the sponsor and the investigator

  The inspector is chosen by sponsor and is responsible for corresponding between sponsor and investigator.

- To help the investigators on all aspects

  Helping investigators in providing supplies and solving problems is among the responsibilities of the inspector.

- To help protection of study subjects

  Confirming obtain of informed consent for all subjects prior to their participation in the trial is one of the monitors responsibilities.

- To verify adequacy of trial resources

  Monitor check for adequacy investigators, staff, and facilities before and throughout the study period.

- To verify supply, control, storage, and disposition of investigational product/s

  Turning back additional materials after the trial is finished is one of the inspector's duties.

- To verify adherence to the approved protocol/amendments

  Adherence to the approved protocol ensures that data are correctly gathered and reported. Any changes to the protocol should be documented and reported.

- To verify adherence to good clinical practice and standard operating procedures

  Standard operating procedure (SOP) is a standard comprehensive framework for administration of clinical trials.

- To monitor recruitment rate, safety evaluation, and compliant observations

  Validity and quality of data gathered and safety of patients are monitored by the inspector during the trial.

- To check the accuracy and completeness of all trial data and case report forms

  Case report form is a paper-based or computer-based sheet that is used to record and gather the data on each trial subject during the trial, as defined by the protocol. The documentation should allow easy access for verification, audit, and inspection.

- To discuss study plan and problems with main investigator and staff

  Monitors are trained in clinical trial and medical research and may collaborate to improve the quality of trial. They may also verify that trial documents are complete and up-to-date [25].

13. Monitoring visits

13.1. Pretrial monitoring visit

During prestudy visit, the monitor ensures feasibility of trial in the center and interest of the investigator. Also he/she makes sure that the investigator understands the required "trial procedures" and sufficient site staff, proper facilities, location, equipment, laboratory, product storage, and archive exist to support the study.

The inspector may discuss with investigator(s) about

- The protocol in detail
- Consent form
- Assenting children (if present)
- Case report form and documentation of findings including adverse effects, standard operating procedures

The audit may clarify any issues that remain uncertain, regulatory requirement and fulfills the sponsor expectations. He/she may document any changes in the protocol to eliminate practical defects.

13.2. Trial initiation visit

Deliver study material, documents, and products, and make sure the investigational team understands the protocol and good clinical practice requirements.

The responsibilities of the inspector in trial initiation visit are listed below:

- Revise team training
- Ensure understanding of protocol
- Ensure understanding of case report form
- Ensure ethical requirements
- Ensure safety reporting procedure

Discuss in detail:

- Enrollment and exclusion criteria
- Endpoints
- Patients safety
- Criteria for grading adverse effects
- Handling of patient samples
- Handling of test product
- Standard operating procedures

13.3. Monitoring visit

In approach to help the investigational team in solving problems, the trained audits would make sure that the study is conducted in accordance with the requirements of the protocol and good clinical practice principles. Also they make sure that investigators are available during the visits.

Discuss:

- Problems
- Modifications
- Obtaining informed consent from legal guardian
- Obtaining assent from the children and adolescents (process by which patient/subject voluntarily confirms his/her willingness to participate)

- Protocol compliance: strictly follow protocol procedures, alteration
- Sponsor approval

13.4. Close-out visit

Make sure the investigator file is archived properly and collects back all unused materials, documents, or products.

14. Responsibilities of the investigators after approvals

- Sign the final copy of protocol

  The main investigator should sign and hereby accept the responsibility of trial.

- Submit the requested document

  The main investigator should provide the requested form including budget, Gantt chart, and consent forms to the sponsor, the research institute and ethics committee.

- Registering the protocol of the trial in one of the clinical trial registries

  Now most high-quality journals necessitate researchers to submit their work in one of clinical trial registries before patient's enrollment into the trial and provide its code at the time of submission to the journal. He/she must also agree with publication policy of journal and publisher.

- Work according to the protocol and good clinical practice guidelines

  The investigator must ensure that he/she acts in accordance with the sponsor-approved protocol and globally accepted standard of GCP.

- Collaborate with monitor

  The investigator should collaborate in on-site inspections and in corresponding.

15. Responsibilities of the investigators during study

- Adherence to the protocol and good clinical practice principles

  The investigator should adhere to the inclusion and exclusion criteria mentioned in the approved protocol. He/she has overall responsibility for ensuring the accuracy and completeness of data gathered.

- Adhering to administrative and regulatory requirements

  Local regulations and administrative requirements should also be respected by the investigators.

- Compliance with ethics

  Give adequate information to the subjects and legal guardians about study procedure, harms, and benefits of the intervention. Also, give adequate information to the subjects and legal guardians about responsibility and rights of each side. Then, obtaining freely signed informed consent form from legal guardian.

- Obtaining oral assent from the children and adolescents

  The researcher should also spend sufficient time for participants and allow participants themselves to decide.

- Unbiased selection/randomization, blinding, and allocation concealment

  The investigator should ensure that the subjects are correctly diagnosed and reduce the known kinds of biases including random bias and selection bias with adhering to clinically sound diagnosis, randomization, blinding, and allocation concealment. These processes are discussed before.

- Be sure that dosage and instruction for use are correct

  The main objective of performing a clinical trial is usually assessing the effectiveness of a product at a specific dose. But, the phase II clinical trials are dominantly aim at the determination of appropriate or safe dose ranges. Hence, determining appropriate dose and timing of product intake based on previous studies and literature is very important.

- Correspondence

  The main investigator is responsible to correspond with the sponsor, ethics committee, and research institute.

- Monitoring and follow-up potential side effects

  Adverse effects must be reported and monitored until its removal.

- Trial data documentation

  The researcher must make sure that the participant's identification, trial observations, findings, and also side effects are recorded correctly and completely in a paper-based or computer-based case report form (CRF). Furthermore, the investigator should fill and maintain investigator's file.

- Laboratory quality assurance/quality control (normal lab values)

  Laboratory values within or outside the normal reference ranges, if possible together with the specificity and sensitivity of the methods used, should always be recorded on the CRF or be attached to it.

- Secured storage and limited access to data

  Suitable place for archiving and confidentiality of the data should be guaranteed by the investigator.

- Preparing the final report

  The project should be based on the Gantt chart and the sponsor-approved budget. Then, the final report of the trial should be prepared as defined in the protocol. The report should be signed by the sponsor, monitor, and investigator(s) as well as the responsible statistician, in accordance with the relevant regulations.

16. Conclusion

Clinical trial in children and adolescents as a vulnerable population is a great concern to the legal guardians, medical investigators, and ethics committees. These trials must be planned, set up, conducted, documented, and reported in a great standard named good clinical practice. The data should be collected, synthesized, and documented with accuracy and consistency. Furthermore, researches involving humans especially those with low perception including psychiatric patients and children, and adolescents should be scientifically sound and conducted in accordance with high ethical standards. Obtaining written freely signed informed consent form from parents or legal guardians is mandatory in clinical trials performing on children and adolescents. Additionally, obtaining oral assent from the subject itself is essential too. Institutional ethics committees are responsible for approving the trial methodology and safety in a way that ensure protecting of patient's rights and health. Meanwhile, monitoring would help to guarantee the maximum quality of data and well-being of subjects. Monitoring the clinical trial is the process of auditing trials based on the sponsor-approved protocol and the standard of good clinical practice. In all, the concept of good clinical practice in children and adolescents necessitates medical researchers a binding statement: "Performing the trial with best possible standards and optimum health of my patient will be my first consideration."

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References

[1] Acosta CJ, et al. Implementation of good clinical practice guidelines in vaccine trials in developing countries. Vaccine. 2007;**25**(15):2852-2857

[2] Kious BM. The Nuremberg code: Its history and implications. Princeton Journal of Bioethics. 2001;**4**:7-19

[3] Vijayananthan A, Nawawi O. The importance of good clinical practice guidelines and its role in clinical trials. Biomedical Imaging and Intervention Journal. 2008;**4**(1):e5

[4] The World Medical Association. Declaration of Helsinki [Internet]. 2004. Available from: http://www.wma.net/e/policy/b3.htm

[5] Ray S, et al. Maintaining good clinical practice: Publication of outcomes and handling of outliers. Heart. 2016;**102**(19):1518-1519

[6] Stein DJ, Lund C, Nesse RM. Classification systems in psychiatry: Diagnosis and global mental health in the era of DSM-5 and ICD-11. Current Opinion in Psychiatry. 2013;**26**(5):493-497

[7] Bathgate F, et al. Good practice guidelines for clinical psychologists working in paediatric cochlear implant teams. Cochlear Implants International. 2013;**14**(Suppl 4):S32-34

[8] Mostafavi SA, et al. Role of melatonin in body weight: A systematic review and meta-analysis. Current Pharmaceutical Design. 2016;**22**. (E-pub Ahead of Print) DOI: 10.2174/1381612822666161129145618

[9] Mostafavi A, et al. Melatonin decreases olanzapine induced metabolic side-effects in adolescents with bipolar disorder: A randomized double-blind placebo-controlled trial. Acta Medica Iranica. 2014;**52**(10):734-739

[10] Mohammadi MR, et al. Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: A randomized double blind clinical trial. Iranian Journal of Psychiatry. 2012;**7**(2):87-92

[11] Zimlichman E, Meilik-Weiss A. Clinical guidelines as a tool for ensuring good clinical practice. Israel Medical Association Journal. 2004;**6**(10):626-627

[12] Howie SR. Blood sample volumes in child health research: Review of safe limits. Bulletin of the World Health Organization. 2011;**89**(1):46-53

[13] Loebstein R, Koren G. The ethics of multiple blood sampling in children for research. Therapeutic Drug Monitoring. 1997;**19**(3):251

[14] Asai S, Miyachi H. Good practice of clinical physiology examination for patient safety with a team-based approach: Quality practice in ultrasonographic examination. Rinsho Byori. 2015;**63**(7):847-854

[15] Ezzelle J, et al. Guidelines on good clinical laboratory practice: Bridging operations between research and clinical research laboratories. Journal of Pharmaceutical and Biomedical Analysis. 2008;**46**(1):18-29

[16] Good efficacy and safety profile in clinical practice. MMW Fortschritte Der Medizin. 2015;**157**(20):66-67

[17] Mohammadi MR, Mohammadzadeh S, Akhondzadeh S. Memantine versus methylphenidate in children and adolescents with attention deficit hyperactivity disorder: A double-blind, randomized clinical trial. Iranian Journal of Psychiatry. 2015;**10**(2):106-114

[18] Gust DA, et al. Risk factors for non-adherence and loss to follow-up in a three-year clinical trial in Botswana. PLoS One. 2011;**6**(4):e18435

[19] Neilson G, Chaimowitz G. Informed consent to treatment in psychiatry. The Canadian Journal of Psychiatry. 2015;**60**(4):1-11

[20] Kawar LN, Pugh DM, Scruth EA. Understanding the role and legal requirements of the institutional review board. Clinical Nurse Specialist. 2016;**30**(3):137-140

[21] Idanpaan-Heikkila JE. WHO guidelines for good clinical practice (GCP) for trials on pharmaceutical products: Responsibilities of the investigator. Annals of Medicine. 1994;**26**(2):89-94

[22] Goodarzynejad H, Babamahmoodi A. Project management of randomized clinical trials: A narrative review. Iranian Red Crescent Medical Journal. 2015;**17**(8):e11602

[23] Stevens W. Good clinical laboratory practice (GCLP): The need for a hybrid of good laboratory practice and good clinical practice guidelines/standards for medical testing laboratories conducting clinical trials in developing countries. Quality Assurance. 2003;**10**(2):83-89

[24] Devine S, et al. Good clinical practice and the conduct of clinical studies in pediatric oncology. Pediatric Clinics of North America. 2008;**55**(1):187-209, xi-xii

[25] Grainger A. Clinical audit: Shining a light on good practice. Nursing Management (Harrow). 2010;**17**(4):30-33

Women

Chapter 4

Clinical Trials in Pregnant Women with Preeclampsia

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Abstract

Preeclampsia (PE) is the leading cause of preterm birth by medical indication when associated with premature detachment of placenta normoinserta, and Intrauterine growth restriction (IUGR) is associated with high perinatal morbidity and mortality and long-term sequelae. The main problem of PE is threefold: the diagnostic difficulty, the complicated interrelationship of the pathophysiological processes, and the vulnerability of the maternal-fetal binomial to the therapeutic interventions. The approach for management with PE is preventing its late occurrence in pregnancy. The key to preventing PE is knowledge of the factors that trigger the pathophysiological processes that culminate in the presentation of PE. Understanding the developmental characteristics of the placenta in pregnancy at high risk for PE is essential for understanding the pathophysiology and developing strategies for prevention. When deciding that the population of study is a group of pregnant women, the first ethical criteria that need to be reviewed are those aimed at the protection of the fetus. There are no specific guidelines on how to assess fetal well-being during pregnancy routinely in the clinic, and this deficiency is shifted to clinical research with pregnant women.

Keywords: preeclampsia, eclampsia, pregnancy induced-hypertension, complications in pregnancy women

1. Introduction

Preeclampsia (PE) is the leading cause of preterm birth by medical indication when associated with premature detachment of placenta normoinserta, and IUGR is associated with high perinatal morbidity and mortality and long-term sequelae. It has been described that standardization in the management of health services and the use of clinical practice guidelines is associated with a reduction in adverse outcomes, and a fundamental part of the management of severe PE includes a complete evaluation of the mother and the fetus. Despite the advances in medicine, the frequency of this syndrome has not changed, and globally its incidence ranges between 2 and 10% of pregnancies. The World Health Organization (WHO) estimates that the incidence of PE is seven times higher in developing than in developed countries (2.8–0.4%). In Mexico, it is estimated that PE is a major cause of maternal and perinatal morbidity and mortality. In Jalisco alone, maternal deaths increased to 57.14% from 2011 to 2014, placing this state in fourth place at the national level in terms of maternal deaths, during 2015 [1]. Because it is a heterogeneous associated idiopathic syndrome to endothelial damage, so far there is no effective treatment that reduces the morbidity and mortality of this pathological entity, so it is necessary to reinforce prevention. In this area, only the use of calcium supplements and acetylsalicylic acid (ASA) appears to be a recommendation, albeit with controversial results [1, 2].

The main problem of PE is threefold, the diagnostic difficulty, the complicated interrelationship of the pathophysiological processes, and the vulnerability of the maternal-fetal binomial to the therapeutic interventions.

2. Pregnant women, scientifically complexed population

There are various concepts about the characteristics of vulnerable populations; however, it is generally accepted that a vulnerable group is one whose ability to protect their own interest or grant their consent is physically, psychologically, or socially compromised. Since the development of ethical principles in research, children, psychiatric patients, prisoners, and pregnant women have been included in this group; however, in recent years it has been intended to remove pregnant women from this group. The National Institutes of Health (NIH) through the Office of Research on Women's Health recommended as early as 2010 that pregnant women should be considered as a scientifically complex rather than vulnerable group, this being for the reason that this group has the same capacity and autonomy for decision making as its nonpregnant counterparts, including the decision of whether or not to participate in a clinical trial [3].

Scientific complexity arises from the special physiological conditions of pregnancy and from the ethical considerations of the balance between maternal well-being and fetal well-being.

Pregnancy is accompanied by important physiological changes and their knowledge is an element of great value for the proper management of the obstetric patient. Practically, all the body's system of the pregnant woman is adapted to house the product, among them are changes at the ocular, musculoskeletal, skin and mucous, hepatic, hematological, renal, and gastrointestinal levels. The most relevant changes occur at the uterine level, systemic vascular

resistance is reduced due to high flow and low resistance circuit in the uteroplacental circulation. In pregnancy, uterine blood flow significantly increases to allow perfusion of intervillous placental spaces and fetal development. The trophoblast invades the uterine spiral arteries; vascular smooth muscle cells are lost and replaced by the fibrinoid material, converting them into large dilated blood vessels allowing greater perfusion of the placenta [4]. These changes pose a challenge for the researcher as they make it very difficult to define not only the possible therapeutic results of an intervention, but also to adapt the intervention to these new changes that are not present in nonpregnant women. In a pathological condition such as preeclampsia, this may represent a greater challenge, because of restrictions on research in a physiological pregnancy, ignorance or doubts about the effects of the intervention on the organism, or pathological adaptations that may affect the intervention that is intended to be performed are greater.

The ethical complexity is established in the possibility that the intervention applied in key phases causes a teratogenic risk or that affects the adaptation of the product to extrauterine life, and more worrying, the possibility of long-term toxicity. This is why it is necessary that preclinical teratogenicity studies have been completed prior to the intervention in pregnant women. Also, it is recommended to start the new interventions after the 12th week of gestation, when the organogenesis is finished and finally, it is recommended to follow the fetus and newborn [5]. However, these special considerations do not seem to be sufficient, as there are currently two forms of research in the group of pregnant women: the first consists of interventions unrelated to pregnancy that may benefit only the mother [3]. It seems that the previous recommendations were formulated with this type of research, since the use of thalidomide has contemplated the possibility of developing drugs that may attenuate different discomforts during pregnancy. The clinical investigation currently has to verify that the pharmacological interventions do not cause damage to the product and not only benefit the mother. The second type of research concerns interventions that may potentially benefit the mother and her fetus [3]. This aspect is more related to the development of pharmacological interventions for pathologies in pregnancy, specifically speaking of preeclampsia, the treatments are not indicated at the same time for the mother and for the fetus. Betamimetics used to prevent preterm birth are not intended to treat the mother and may even complicate maternal health. In contrast, depending on the severity of hypertension, the drugs could have a toxic effect on the fetus. These two aspects should be considered when deciding to experiment with a new therapeutic product or scheme [5].

3. Fetal well-being in the clinical trial

When deciding that the study population is the group of pregnant women, the first ethical criteria that need to be reviewed are those aimed at the protection of the fetus. Generally, investigations of pregnant women involving an intervention or experimental procedure such as in PE cases, should not expose the embryo or fetus to a greater risk than the minimum, except when the use of the intervention or procedure is justified for saving the life of the mother. However, in addition to a deep and sufficient knowledge of the intervention that is proposed to apply, there is no strategy to evaluate during the course of research the side effects on the

product. Although maternal-fetal medicine is currently a fact, with several diagnostic imaging and biochemical resources, with established therapeutic procedures, there is no consensus on what tests are necessary to perform and monitor the product during investigations in pregnant women. Even experts do not dare to indicate any fetal diagnostic procedure, within the clinic in the management of pathological pregnancies, but it is at the discretion of the attending physician the use of some diagnostic or therapeutic techniques [6].

There are six most generalized methods to know and evaluate fetal well-being [7]:

1. Maternal evaluation of fetal activity. It consists of the count by the mother of the number of times fetal movement occurs. Although the fetal movement count is a recommendation that is made to every pregnant woman, there is no cutoff point when abnormal movement is considered abnormal, some clinicians mark the alarm in less than 10 fetal movements perceived per day, others when no movements are perceived within 2 h. This form of assessment of fetal well-being presents a false-positive rate, since it depends on the subjectivity of the mother.
2. Test without stress. It consists of the evaluation of fetal heart rate in relationship to uterine contractions. Although it has a low false-negative rate (0.19–1%), its high rate of false positives (55%) makes it a test with minimal benefits, and its counterpart, the stress test, in which it is administered by infusion intravenous oxytocin, is contraindicated in high-risk situations.
3. Biophysical profile. It is a test composed of the evaluation of five parameters, fetal heart activity, fetal respiratory movements, fetal thick movements, muscle tone, and volume of amniotic fluid. Although its false-negative rates are very low (0.07%), its false-positive rate is only lower than that of the stress-free test, and has not shown any difference in terms of fetal death, cesarean indication, and under Apgar score. In addition to being a dependent operator test, factors that may alter outcomes include hypoxemia, gestational age, steroid administration, magnesium sulfate administration, and labor; five factors that occur frequently in pregnant women with PE.
4. Modified biophysical profile. It is the combination of the stress-free test with the biophysical profile. Although it requires less time and experience for its realization, makes its result more reliable, its false-positive and -negative rates are similar to the two tests separately.
5. Fetal Doppler ultrasound. The evaluation consists in measuring by ultrasound the velocity of blood flow in the fetal vessels, usually the umbilical artery. Out of all of the above, Doppler has been evaluated with the most rigorous clinical trials and although it does not show a benefit in terms of fetal death in high-risk pregnancies, it has become an effective test in the reduction of fetal morbidity and mortality in high-risk pregnancies, being this an indication for its use. The use of Doppler in pregnant women with high risk of PE can be a predictive tool combined with serum biomarkers; this strategy is still being validated but promising.
6. Evaluation of fetal lung maturity. It consists the evaluating the presence of surfactant factor in the amniotic fluid. It is a useful evaluation when it is necessary to determine the best time to interrupt the pregnancy when the risk of continuing it is greater. Due to the fact

that in PE the treatment consists of the interruption of pregnancy, to be able to prolong it until reaching the fetal maturity, becomes one of the most difficult aspects of the management to avoid the fetal morbidity-mortality, reason why it is to make sure that the fetus counts with pulmonary maturity to resist extrauterine life has become essential.

Although these tests and diagnostic interventions are the most used in the clinic, the amount of imaging tests, serum markers, and procedures with maternal-fetal medicine is higher; however, many of the tests have not shown their value, they could be useful and applicable reason why they require to be studied, especially those that allow predicting the presentation of complications or diseases such as PE. Among the currently available tests are the evaluation of both fetal DNA and the cells that make up the placenta, even in an experimental way, it is possible to attenuate or increase gene expression through miRNAs, not only for diagnostic purposes, but also for possible therapeutic applications in the future.

The American Congress of Obstetricians and Gynecologists states that the evaluation of fetal well-being may be appropriate for pregnancies with an increased risk of fetal involvement; however, there are no comprehensive trials demonstrating the benefit of all tests and their potential indications. On the other hand, experts recommend carrying out tests of fetal well-being in cases of diabetes, uterine growth restriction, and hypertension [7].

As we can see that there are no specific guidelines on how to evaluate fetal well-being during pregnancy routinely in the clinic, and this deficiency is translated into clinical research with pregnant women. As mentioned before, although one of the principles of research in pregnancy is to maintain the integrity of the product, there are neither guidelines nor recommendations on which tests to apply and when to ensure the safety of the fetus. From the above, we can infer that most clinical trials involving pregnant women have not been able to guarantee or know with certainty the fetal well-being. So how is it possible to monitor fetal well-being in a clinical trial? How can we evaluate adverse effects on the product? And if there is no strategy to assess at least fetal well-being, is it ethical to allow the participation of pregnant women in clinical trials? It is up to the researcher to decide the degree of safety with which he plans to conduct his research, and in the absence of additional tests to ensure fetal well-being, using those available is the most reasonable. However, we should not be satisfied with the analysis of the structural function to guarantee the innocuousness of an intervention, it is necessary to find strategies that in fact allow to evaluate not only the welfare, structural integrity, and fetal vitality, but also to value the whole range of possible adverse effects, both acute and chronic, that may be occurring as a result of new pharmacological interventions or procedures.

4. Clinical research in women pregnant with PE

Pregnancy is a physiological condition inherent in almost all species and life; however, it is one of the lesser known states and a field of research that just begins to grow, because at the beginning of research with pregnant women, a series of events occurred that negatively marked research in this population.

Research is now making its way into the subject of pregnancy and its pathologies in order to have a better understanding of physiological processes and to reduce maternal-fetal morbidity and mortality. However, despite the intentions and efforts of researchers, little is known. In the context of PE, it has been possible to trace its origin to the inadequate invasion of the trophoblastic villi on the vascular bed of the uterine spiral arteries, little is known about the cause of this inadequate adaptation of the uteroplacental vascular system [8]. Moreover, we are in complete disbelief about why some women develop PE and others do not. There is no effective diagnostic test to predict who will have PE, the best biomarkers have poor predictive power, the best chance to achieve prevention so far arises from the combination of Doppler ultrasound with some of the serum markers, which have been implemented, nevertheless, only demonstrate efficacy once the first evident changes of PE are presented, when it is no longer possible to avoid the development of the disease [9]. A real opportunity for prevention of PE would arise from a marker that would allow us to know with great certainty, which women are at risk of having PE, even before the pregnancy is carried out. The best predictive tool we have are the risk factors that have been determined by both prospective and retrospective studies, but are only able to predict 30% of women who develop PE [9], there is even a larger group of the population that develops PE with no previous risk factors. On the other hand, from the group of women who develop PE, one part shows severe PE and another group develops eclampsia, and again it is not possible for the treating doctors to determine who and how they evolve to more serious stages.

In women with severe PE, who present it before fetal viability, maternal stabilization is recommended before interruption of pregnancy. Once treatment is established, close monitoring is required to identify the presence of serious complications of PE. Despite efforts to treat PE, treatment is symptom-based and focused on controlling blood pressure. In regard to the time of delivery, gestational age should transfer to the maximum possible. However, in severe PE, in addition to antihypertensive treatment, termination of pregnancy is recommended if it is greater than 34 weeks. If the pregnancy is less than 34 weeks and the mother and product are stable, the pregnancy should be continued with administration of corticosteroids. Currently, there are multiple criteria for better management of PE, but the only cure for PE is termination of pregnancy. This results in a difficult decision for the physician and the mother because of the psychological burden, and the social and economic morbidity [8].

The results of medical interventions have failed to significantly decrease the morbidity and mortality of PE. The main reason for this failure could be the multifactorial origin of pathogenic processes that lead to the development of PE. Therefore, the approach for management of patients with PE is preventing its late occurrence in pregnancy. The key to prevention of PE is knowledge of the factors that trigger pathophysiological processes that culminate in the presentation of the PE. However, efforts to understand the origin of these processes are still poorly or incompletely understood. There is a lack of knowledge because the approach to study this population may be unethical compared with diseases of nonpregnant women [10]. The multifactorial origin of PE and difficulty of carrying out an investigation in the early stages of pregnancy, because it can endanger the mother and fetus, have made research difficult. Understanding the developmental characteristics of the placenta in pregnancy at high risk for PE is essential for understanding the pathophysiology and for developing strategies of prevention [8].

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5. Current state of research about PE

There are currently 236,008 clinical trials registered in clinicalTrials.gov, from which only 3% are focused on pregnancy, and among them 6.4% are about PE. Of all clinical trials dedicated to PE, 47.9% focus on strategies to improve treatment, 22.2% of the clinical trials aim to improve the diagnosis or its establishment in the early stages, and 16.7% aim to establish the utility of new biomarkers, for both diagnostic and monitoring. Finally, only 10.7% of the clinical trials registered until February 1, 2017 are focused on the prevention of PE (**Figure 1**).

Another aspect that should be taken under consideration is that more than half of the clinical trials directed to PE are carried out in regions classified as first world such as Europe and North America, whereas research in the rest of the world only constitutes 40%, despite the fact that developing countries are the ones that bear the greatest burden of morbidity and mortality caused by this disease (**Figure 2**).

In our times, PE has a worldwide relevance and it has been increasing over the years. Clinical trials with the objective of reducing the morbidity and mortality of this pathology have also increased over time. The previous chart denotes some of the terminated trials registered in clinicaltrials.gov, many of which have certain limitations that we were able to observe (**Table 1**).

In the study titled, "L-arginine and antioxidant vitamins during pregnancy to reduce preeclampsia", there is little coherence between the objective and the design of the study. Although

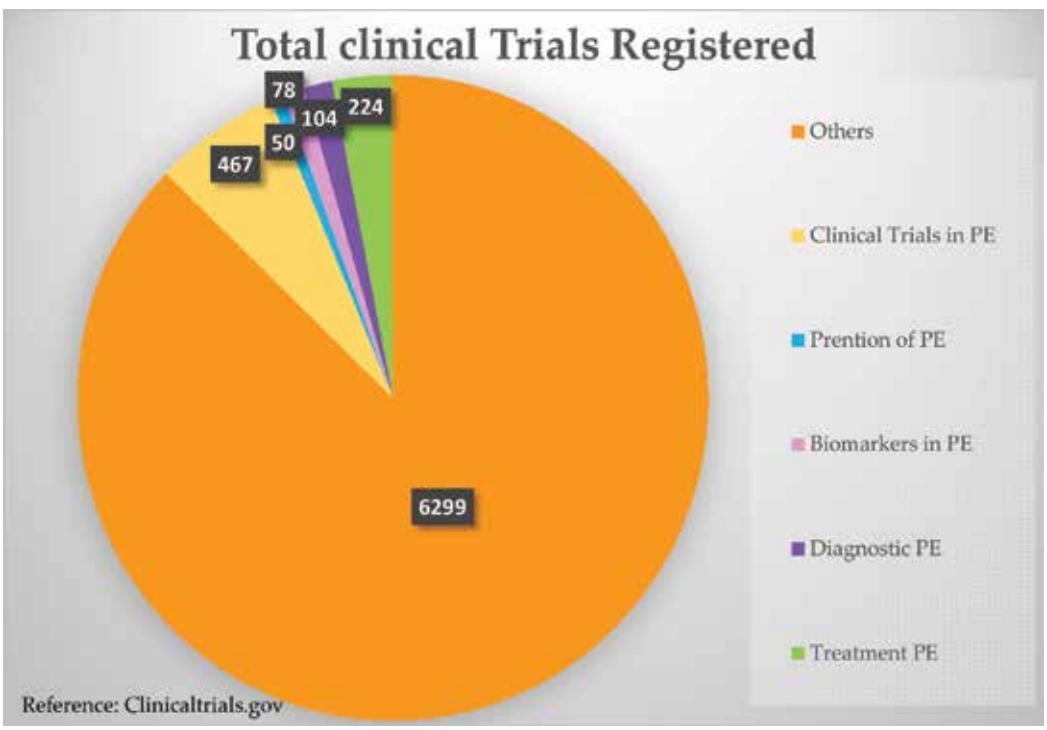

Figure 1. Clinical trials registered until February 1, 2017. Data from: clinicaltrials.gov.

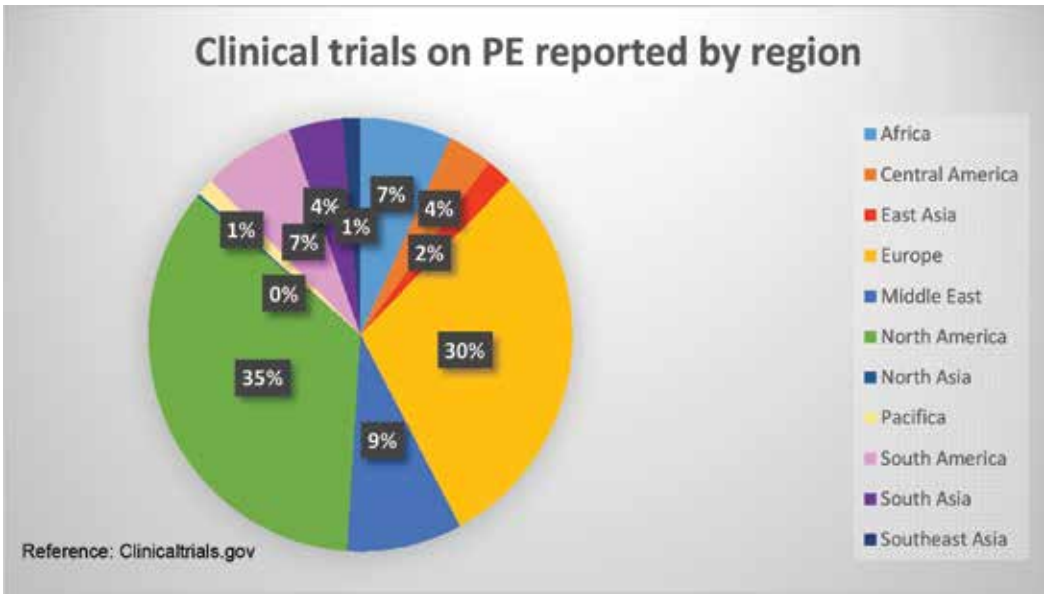

Figure 2. Clinical trials on PE reported by region.

it is known that the production of nitric oxide and L-arginine as the main substrate of nitric oxide synthase is involved in the pathophysiology of PE, the study design is directed at the effect of L-arginine that has on the development of PE; however, levels of L-arginine are not evaluated at any moment, neither its nitrates nor nitrites, being the reason why this design cannot help reach the hypothesis. In addition, the main inclusion criteria appeared to be having a high-risk profile for developing PE; however, high-risk factors such as diabetes, autoimmune diseases, and hypertension in pregnancy and kidney diseases are not considered as inclusion criteria, and these factors combined with a history of risk of developing PE in previous pregnancies, increase up to nine times the risk of developing PE. Another mistake that can be found in their design is noted when analyzing the main conclusion and the way the intervention was carried out, the conclusion states that the supplementation of L-arginine and vitamins reduces the incidence of PE; nevertheless, in the results it can appreciated that the group that only received the food-bar containing the vitamins did not have a significant reduction in the risk of developing PE. Meaning that the mayor contributing factor for the reduction of PE was indeed L-arginine and not the combination of L-arginine/vitamins, and these would have been more notorious if a supplementation group taking only L-arginine was added [11].

In the study titled "Usefulness of Extracorporeal Removal of sFLT-1 in Women with Very Early Severe Preeclampsia (ADENA)", at first instance we are lead to appreciate that the primary outcome of the study is about early severe PE; however, later, we appreciate that the intention is improving perinatal death as the primary outcome. The first comment worth mentioning is that using words such as "improving" in an investigation study may be to imprecise, it is better to use terms such as "reducing" for this instance. Moreover the levels of sFLT-1 are not per say an inclusion criteria for deciding whether or not to perform apheresis, even by being quantified before and after the intervention, those women with high levels of sFLT-1 could perhaps have a

Title	Hypothesis	Population	Intervention	Conclusions
L-Arginine and Antioxidant Vitamins during Pregnancy to Reduce Preeclampsia	To test that a relative deficiency of L-arginine, precursor of *nitric oxide* (NO) by the enzyme NO *synthase* (NOS), reduces the development of preeclampsia in high-risk pregnancies	Pregnant women with a history of a previous pregnancy complicated by preeclampsia, or preeclampsia in a first degree relative, whom are deemed to have an increased risk of recurrence of the disease, were studied from 14 to 32 weeks of gestation and followed until delivery	Supplementation with: medical food-bars containing L-arginine plus antioxidant vitamins, antioxidant vitamins alone or placebo	Supplementation during pregnancy with a medical food containing L-arginine and antioxidant vitamins reduced the incidence of preeclampsia in high-risk pregnancy
Usefulness of Extracorporeal Removal of sFLT-1 in women with very early severe Preeclampsia (ADENA)	The removal of s-Flt1 improves perinatal death in women with very early severe preeclampsia	Women with singleton pregnancy having severe preeclampsia at 23–25 6/7 weeks of gestation	Apheresis for extracorporal removal of sFlt-1	Does not have a result
Oral Progesterone and Low Dose Aspirin in the Prevention of Preeclampsia	Low-dose aspirin combined with progesterone will decrease the risk of preeclampsia in pregnant women with history of preeclampsia in a previous pregnancy	Pregnant patients with a previous history of preeclampsia in the immediate prior pregnancy	Aspirin 81 mg once a day orally, progesterone 200 mg twice daily	Does not have a result
Safety and Efficacy of RLX030 in Pregnant Women with Preeclampsia	Part 1: To assess the safety and tolerability of different doses of RLX030, when given to pregnant women with preeclampsia. Part 2: To assess whether an optimal dose of RLX030 can prolong pregnancy in women with preeclampsia	Pregnant women in 28 weeks (0 days) and 33 weeks (+4 days) of gestational age with a diagnosis of preeclampsia or superimposed preeclampsia requiring hospitalization	RLX030 15 μg/kg/day IV for 72 h	Not enough information was provided to analyze because the study was stopped after three patients were enrolled
CPAP in Preeclampsia	To assess the effects of nasal CPAP in pregnant women (24–37 gestational weeks) with preeclampsia	Women with 24–37 weeks of pregnancy with Singleton pregnancy, primiparous and primigravid diagnosis of preeclampsia	Continuous Positive Airway Pressure Ventilation (CPAP)	Does not have result

Source: Clinicaltrials.gov [11].

Table 1. Current state of clinical trials about PE.

greater benefit, reason why stabilizing grades at first instance could help the obstetrician make a better clinical decision. Finally, although its justifiable not using a control group, this type of design (before and after), not having a reference group, leads to a lower internal validity [11].

In the study titled "Oral Progesterone and Low Dose Aspirin in the Prevention of Preeclampsia", the main inclusion criterion is having a history with preeclampsia. Nevertheless, other factors of high risk were not taken account. Even though the study propounds that a deficiency of progesterone could lead to PE and in consequence, supplementation with progesterone could reduce the incidence of PE, serum values as an indicator to identify patients whom could benefit with progesterone supplementation were not taken into account. The comparison between before and after instead of vs the placebo group is also an inconvenient [11].

In the study titled "Oral Progesterone and Low-Dose Aspirin in Preeclampsia Prevention," the main inclusion criterion is the antecedent of PE in previous pregnancies; however, as in the previous study, other factors that increase the risk are not taken into account. The study assumes that a deficiency of progesterone could be the cause of PE, this argument seems to be the rationale to reduce the incidence of PE using supplementation with progesterone; but in the study, they did not take serum values in consideration as a marker to indicate which patients could benefit from supplementation. This study, as the previous one, also lacks the comparison against a placebo group, creating the same limitations [11].

In the study entitled "Safety and Efficacy of RLX030 in Pregnant Women with Pre-Eclampsia" proposed by the company NOVARTIS did not have sufficient information to perform an analysis, because of premature termination of the study [11].

In the study entitled "CPAP in Preeclampsia", the main objective is the evaluation of fetal well-being using nasal continuous positive airway pressure (CPAP) as a basis to increase fetal oxygenation; however, monitoring fetal movements is a scarce strategy to evaluate fetal well-being and it could be enhanced, according to the advances in fetal medicine to allow us to get closer to knowing the well-being of the fetus. The study did not make a distinction on the severity of PE, and if a clinical benefit of using CPAP is demonstrated, a distinction on the severity might be useful for clinical decisions. Therefore, the rationale to use CPAP is not clear [11].

In several studies, narrowing gestational age as inclusion criteria perhaps increases internal validity; however, the results cannot be extrapolated to other groups [11].

It is worth noting that the protocols registered in clinical trial go through variations during the study, which go unnoticed.

6. Transference of scientific knowledge to clinical practice persist in LAG

One of the most important advantages of basic research is the possibility to transfer knowledge to improve clinical practice. However, in the case of PE, new information

regarding new biomarkers and new opportunities of intervention emerge every year, but these are not implemented by the treating physicians. Moreover, clinical practice guidelines are lagging too, and many years pass before a new intervention reaches the level of recommendation within them. On the one hand, this occurs because the information that is generated seems to be isolated and fragmented, there is no body or work team or expert committee that focus their efforts on trying to solve the problem or on generating a line of research on the subject. Another part of the transforming knowledge problem is that for this to be carried out it is necessary that the information obtained may be applicable to different populations at different times and with different characteristics, this is very complex to achieve in the first place because, as mentioned previously, there is no focus group to this and separated efforts generate a bias in the study population. Another bias that impedes transfer is that the risk factors presented by each population are different in the developed countries than those in the developing world, so information generated on the one side is not necessarily applicable in other parts of the world. Because the origin of PE is not well understood, the approaches with which the different studies are developed differ, while some may determine that the cause is oxidative stress, some others may argue that the cause is genetic. The truth is that so far it is considered multifactorial and because of this the international guidelines are more discreet about which recommendations to accept, in the sense of being able to verify which actions will have an evident weight in clinical practice.

Finally, one of the most worrying aspects that delay the transfer of knowledge is the lack of medical update on the subject. A very obvious example is that in practice, physicians do not intentionally seek pregnancies with a high risk of PE, and when a patient is classified with high risk, the first action of the doctor is an expectant management, without any intervention, although in the guidelines of clinical practice the administration of acetylsalicylic acid, calcium, and L-arginine is recommended, this happens because evidence of acetylsalicylic acid's efficacy in reducing the risk is contradictory, while calcium intake is reserved for those women with low risk and low calcium intake, and L-arginine, although it is part of the Canadian guide, no dosage or time is specified.

Other evidence in the lack of management of the subject in some specialists is the lack of communication they generate with patients who are at high risk. Patients are not informed of their situation and expectant management "poor surveillance" continues even after the patient develops PE, which is when the symptomatic management begins, and it seems that the physicians are waiting for a complication to occur, to make the decision of taking a more active management. It is true that during the 1st weeks of the PE, there are not many recommendations, and that most focus on the final stages in which fetal viability can be achieved, but this same reason should be what drives medical doctors to have a closer monitoring in research opportunities and new information to improve the outcome of the pregnancy, remembering that once PE is presented, there is no curative treatment, beyond the interruption of pregnancy. Efforts should be directed at preventing the occurrence of PE or, failing at that, occurring late in pregnancy.

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References

[1] Atención integral de la preeclampsia en el segundo y tercer nivel de atención: secretaría de salud. 2008

[2] Campos A. O papel da AAS na prevenção da Pré-Eclâmpsia: Estado da Arte. Acta Médica Portuguesa. 2015;**28**(4):517-524

[3] American College of Obstetricians and Gynecologists. Ethical considerations for including women as research participants. Committee Opinion No. 646. Obstetrics and Gynecology. 2015;**126**:e 100-e107

[4] Ojeda-González JJ, Rodríguez-Älvarez M, Estepa Pérez JL, Piña-Loyola CN, Cabeza-Poblet BL. Cambios fisiológicos durante el embarazo. Su importancia para el anestesiólogo. Medisur. 2011;**9**(5):484-491

[5] Viada-González CE, Ballagas-Flores C, Blanco-López Y. Ética en la investigación con poblaciones especiales. Revista Cubana de Investigaciones Biomédicas. 2001;**20**(2):140-149

[6] Geaghan SM. Fetal laboratory medicine: On the frontier of maternal-fetal medicine. Clinical Chemistry. 2012;**58**(2):337-352

[7] O´Neill E. Thorp J. Antepartum evaluation of the fetus and fetal well being. Clinical Obstetrics and Gynaecology. 2012;**55**(3):722-730

[8] García Benavides L, Hernandez Molina D, Barajas Vega JL, Totsuka Sutto SE, Ramírez Lizardo EJ, et al. New pharmacological opportunities for prevention of preeclampsia. Journal of Clinical and Experimental Cardiology. 2016;**7**:457

[9] Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: Systematic review of controlled studies. British Medical Journal. 2005;**330**(7491):565

[10] Reglamento de la ley general de salud en materia de investigación para la salud [Internet]. 2014. Available from: http://www.ordenjuridico.gob.mx/leyes.php [Accessed: January 13, 2017

[11] https://clinicaltrials.gov

Section 3

Medically Compromised Patients

Chapter 5

Dental Implants in the Medically Compromised Patient Population

Ayşe Sümeyye Akay and Volkan Arısan

Additional information is available at the end of the chapter

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Abstract

As a result of the increase of the life expectancy, elder people live with diverse diseases or conditions like systemic disorders, immune-related disorders, and psychiatric issues. Consecutively, practicing clinicians are faced with serving dental implant treatments in such a population comprised of medical and demographic characteristics. Most commonly, implant therapy is performed among patients above middle ages; therefore, clinicians often encounter medically compromised patients. The patients are usually with adverse conditions like bleeding disorders, bone diseases, cardiovascular disease (CVD), and/or immunologic conditions like cancer therapy, steroid or immunosuppressive or antiresorptive medication, alcoholism, smoking, and many others. Nevertheless, only few conditions could be stated for contraindication to dental implant therapy. Besides the broad range of the mentioned dental implant comorbidities smoking seems less prevalent compared to the general population. Dental implants in smoking patients are certainly affected in relation to the failure rate, marginal bone loss, and some other risks of postoperative complications. Hence, smoking or other similar conditions could be accounted as a chronic systemic disorder just like diabetes mellitus or drug usage. Briefly, it seems that establishing the medical and demographic conditions prior to implant therapy along with controlling the systemic diseases or disorders may be more important than the presence of compromise.

Keywords: systemic diseases, dental implant success, contraindication

1. Introduction

Dental implant (DI) is broadly considered to be the ideal treatment of the tooth loss, which is mostly required in the aged population [1, 2]. The prevalent age-range for implant therapy has been reported above 40 years [2] or between 51 and 60 years [1], thus the patients who required

dental implant therapy are usually associated with systemic comorbidities. For both patients' and clinicians' benefit, systemic comorbidities of the patient should be well-diagnosed before DI therapy. Besides, treatment plan and patient selection should be carried out with reference to the clinical evidence. Patients should be ensured to inform thoroughly about the risks and precautions.

2. Systemic disorders and compromised conditions

2.1. Elderly population

Aging has an effect on biological activity via altering the inflammatory, regenerative, and remodeling phases of healing process. First, it makes inflammatory phase prolonged by promoting the release of inflammatory mediators. Second, it decreases new tissue formation in the regenerative phase by reducing angiogenesis and the number of mesenchymal stem cells, which are the progenitors of new bone formation. Last, it causes an imbalance in bone remodeling by changing cell activity, level of matrix metalloproteases, apoptosis, and collagen turnover [3]. Therefore, it may not be wrong to consider that aging causes a delay on osseointegration of dental implants.

In the literature, there are eligible studies that have been conducted for long-term time periods and the survival rate (SR) of dental implants is about 90% (**Table 1**). Furthermore, in a recent meta-analysis, SR has been reported to be 91.2% for up to 10 years [4]. On the other hand, considering the peri-implant pathology and bone level changes, studies have unsatisfactory results. According to the aforementioned meta-analysis [4], there is only one prospective clinical study that reports peri-implant marginal bone loss (MBL) after 10 years as 1.5 mm [5]. Additionally, another reviewer states that peri-implant mucositis and peri-implantitis are observed more commonly in totally edentulous patients, which are mainly ≥65 years old [3].

2.2. Tobacco smoking

Tobacco consumption is one of the main considerable patient-related systemic conditions for the patients who require DI. Though smoking is not a contraindication for DI therapy, there have been a lot of studies that report negative effects on DI outcomes.

According to the clinical studies (**Table 2**), there is a tendency to consider that implant failure is correlated with smoking habits. Most of the studies confirm the association between smoking and increased failure rate of implants in both short- and long-term periods. Besides, tobacco smoking has been proved to increase the failure rate of DI from 2.5- to 3-fold [9, 12]. However, there is only one study that has showed a higher survival rate of DI in smoker patients [13].

People who consume 10–20 cigarettes daily are often counted as heavy smokers in clinical studies. And despite a small number of studies that reveal the effect of the number of cigarettes on failure, it has been demonstrated that consuming the 6–15 cig/day doubled the risk of implant failure [9].

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Moy et al., 2005, Retrospective cohort [6]	2–20 years	541 subjects are aged >60 years (1140 total)	ND (4680 total)	82% (for aged >60 years)	–	Patients who are aged >60 years have higher risk for implant failure (RR = 2.24)
Manor et al., 2009, Retrospective cohort [7]	6 years	194 (2 equal groups for evaluating early and late failures)	294	–	Assigned as minor/ moderate/major MBL	Old age may be a risk factor for late failures and risk is also more likely for men and posterior of jaws
Lee et al., 2010, Prospective [8]	2.7 years (mean)	35 subjects are >70 aged geriatric MCP with controlled systemic disease	118	–	MBL: 0.27 mm	Old age is not a risk factor for peri-implant MBL ($p = 0.484$)
Busenlechner et al., 2014, Retrospective [9]	8 years	2632 subjects are >50 years (61% out of 4316 total)	ND	95.3% for the age >70 years	–	Old age over 70 years is not associated with long-term implant success
Becker et al., 2015, Prospective [10]	7 years	31 aged subjects	84	94.6% for 13 patients with 40 implants	MBL: 0.1 mm (difference of 0–7 years' follow-up) PD: 2.6 mm	DI is successful in aged population, and MBL changes are comparable with the younger populations
Neves et al., 2016, Retrospective [2]	7.3 years (mean)	528 subjects are aged >40 years (721 total MCP subjects with the age range of 20–87)	ND (3998 total)	92.7% for the age <40, 85.3% for age >40, and 86.5% is overall SR (patient based)	33.8% of patients and 12.7% of implants have pathology	>40 age is a risk factor of implant loss (risk is higher for more than two times than <40 age), but is not a risk for peri-implant pathology
Prasad et al., 2016, Retrospective cohort [11]	5.7 years of mean	Approximately the half of 1091 total subjects is aged >60 years	ND (1918 total)	96.4% (implant based), 94.6% (patient based)	–	Age over 65 years is shown to have an increased risk of implant failure
Hoeksema et al., 2016, Prospective comparative [5]	10 years	(1) 52 subjects with age range of 35–50 years (2) 53 subjects with age range of 60–80 years	(1) 104 (2) 106	(1) 97.1% (2) 93.4%	MBL: 0.1 mm (1st year), 0.7 mm (5th year), 1.5 mm (10th year) PD: 3 mm for both groups at 10th year	Mandibular two-implant OD is equally successful in older patients compared with the younger patients without significant differences of the parameters
Srinivasan et al., 2016, Sys. Rev., meta-analysis [4] (includes 11 prospective studies)	1–10 years	206 subjects are aged ≥65 years	480	97.7% (1st year), 96.2% (5th year), 91.2% (10th year)	MBL: 0.1–0.3 mm (1st year), 0.7 mm (5th year), 1.5 mm (10th year)	Age alone should not be a limiting factor for DI therapy Reported complications are found inadequate for a meta-analysis

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Mean/total of values/subjects and considerations	1–20 years	4765 patients above middle ages	>1082	SR is 90% for long-term period	0.1 mm in the 1st, 1.7 mm in the 5th, and 1.5 mm in the 10th year follow-ups (out of 3 in available 8 studies)	Implant therapy is a successful treatment in the medically compromised patient

MCP, medically compromised patients; DI, dental implant; SR, survival rate; MBL, marginal bone loss; BoP, bleeding on probing; RR, risk ratio; ND, no data available; OD, overdenture.

Table 1. Studies that indicate dental implant outcomes in the elderly population.

Regarding the MBL, smoking seems to have a destroying effect by increasing the annual rate of MBL by 0.164 mm/year [14], and MBL is about 1.4 mm after 3 years with a statistically significant difference from people who do not smoke tobacco [15, 16].

As a result, tobacco smoking alone is not contraindicated for DI, and DI survival is about 90% for a long time period. On the other hand, smokers are under a higher risk of implant failure compared to the nonsmokers. Thus, clinicians should take into account other concomitant systemic factors which could increase the risk of failures.

2.3. Alcohol consumption

There is no evidence to suggest that alcoholism is a contraindication for DIs. SR of DI is similar to healthy population with a reasonable alcohol consumption. Nevertheless, alcoholism is claimed to increase the risk of complications for DI because it may cause many systemic disorders like liver disease, bleeding disorders and osteoporosis (OP), and it may impair immune response and some nutritional elements like folate and B vitamins, and it is often associated with tobacco smoking [28].

It is reported that consumption of >10 g of alcohol increases the MBL and decreases DI survival in humans [15]. Despite there are few studies available (**Table 3**) concerning the DI outcomes in patients who consumed high level of alcohol, further clinical studies with well-defined subjects are required for clarifying the relation.

2.4. Cardiovascular diseases

Cardiovascular disease (CVD) compromises the blood flow which may restrict oxygen or nutrients in the osseous tissue, thus is hypothesized to have higher risk of osseointegration failure [29–31]. Clinical studies and reviews demonstrate no evidence of contraindication related to DI success in patients with CVD (**Table 4**), and this disease is registered as a relative complication due to the risk of infective endocarditis. Antibiotic prophylaxis is necessary prior to the surgery [31] according to the guidelines of the American Heart Association's last publish [32, 33].

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Ekfeldt et al., 2001, Retrospective controlled study [17] (half of subjects lost at least half of their implants)	8 years	54 total (half part is smoker, and 9 of them defined as heavy smokers who consumed ≥10 cig/day)	ND	31 DI loss in 7 heavy smokers (at least half of their implants)	6% of implants had infection during healing in smokers	Except from instability associated with bad bone quality, implant losses mostly occur in patients with heavy smoking habits or bruxism. It is more prominent in post-loading period (22 implants had lost after loading in 7 patients of heavy smokers)
Moy et al., 2005, Retrospective [6]	2–20 years	173 smoker	ND	79.77% for smokers	–	There is a correlation between smoking and increased failure rate (RR = 1.56)
Galindo-Moreno et al., 2005, Prospective [15]	3 years	63 smoker	ND (514 total)	–	MBL is 1.36 mm in smokers	MBL is significantly related to tobacco smoking
Alsaadi et al., 2007, Retrospective [18]	Up to the abutment connection	ND (2004 total)	6946 total (343 heavy smoker who consumed >20 cig/day)	92.95% for heavy smokers	–	Smoking of >20 cig/day is shown significantly higher early implant failure when compared to no smoking groups
Holahan et al., 2008, Retrospective chart review [19]	5 years	24 smoker	83 in smokers	88% for smokers	–	Implants placed in smokers are 2.6 times more likely to fail than implants placed in nonsmokers
Sverzut et al., 2008, Retrospective [20]	<1 year	76 smoker (out of 650 total)	197 in smokers (1628 total)	97.19% for smokers, 96.68% for nonsmokers	–	Tobacco use alone cannot be considered as a factor for risk related to early implant failures
Alsaadi et al., 2008, Retrospective [21]	2 years	22 (>20 cig/day)	93 implants in patients who consumed >20 cig/day	93.94%	–	Smoking does not seem predominant player for late implant loss
Alsaadi et al., 2008, Prospective [22]	<1 year	90 smoker	95 in smokers	94.44%	–	Tendency for more early implant failures is noticed in smokers
Lee et al., 2011, Retrospective [23]	5 years	ND (95 total)	ND (249 total)	ND	ND	Implant failures are correlated with smoking
Cakarer et al., 2014, Retrospective [24]	5 years	ND	246 in smokers		–	Smoking is not affected the DI survival

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
				97.5% (6 failed out of 246 implant)		
Busenlechner et al., 2014, Retrospective [9]	8 years	1726 smoker	ND (13147 total)	76.5% for smokers (overall SR is 97%)	–	Smoking increases the failure rate by 3-fold 6–15 cig/day doubles the risk of implant failure
Tran et al., 2016, Retrospective chart review [12]	10 years	215 smoker	(2729 total)	–	–	Smoking increases the failure rate by 2.6-fold
Krennmair et al., 2016, Prospective cohort [16]	3 years	9 smoker (out of 44 total)	ND	–	1.45* mm in smokers	Smoking is risk factors for MBL (OR: 8.9)
Neves et al., 2016, Retrospective [2]	7.3 years of mean	476 smoker	ND	85.1% (patient based)	36.6% pathology rate (patient based)	Smoking is not associated with higher risk of implant failure and peri-implant pathology (>4 mm pocket depth with BoP or MBL)
Pedro et al., 2017, Analytical, observational, longitudinal study [25]	2–4 years	ND (18 total)	ND (57 total)	–	ND	Smoking has an influence on both mesial and distal bone loss (p = 0.037)
Niedermaier et al., 2017, Retrospective cohort [13]	7 years	141 smoker (out of 380 total)	ND (2081 total)	98.6% for smokers, 96.1% for nonsmokers	–	Smokers have a significantly higher DI survival rate than nonsmokers
Clementini et al., 2014, Systematic review and meta-analysis [14]	>1 year	478 smoker and 1207 nonsmoker	ND	ND	Smoking increases the annual rate of MBL by 0.164 mm/year	Smoking has a harmful effect on peri-implant bone loss. However, the level of evidence for oral implant therapy in patients with systemic conditions is very low
Mean/total of values/subjects	1–20 years	3520 patients with smoking habits (13 out of 17 available studies)	1057 implants in smokers (6 out of 17 available studies)	SR is about 90% for smokers	Apprx. 1.4 mm MBL after 3 years	Smoking has a negative impact on the success and survival of dental implants

Statistically significant difference with healthy groups.DI, dental implant; SR, survival rate; MBL, marginal bone loss; BoP, bleeding on probing; OR, odds ratio; RR, risk ratio; ND, no data available.

Table 2. Studies that indicate dental implant outcomes in patients with smoking habits.

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Galindo-Moreno et al., 2005, Prospective [15]	3 years	23 alcohol users	ND	–	MBL: 1.66 mm	MBL is significantly related to a daily consumption of >10 g of alcohol
Gander et al., 2014, Retrospective [26]	20 months	33 (29 patients with SCC, 24 underwent mandibular reconstruction)	136 total	92.7% (at 1st year), 87.5% (after 20th month)	–	In head and neck oncology patients alcohol ($p = 0.001$) is associated with higher implant failure rate
Scully et al., 2007, Review [27]	ND	ND	ND	Similar to healthy population	–	May not be a risk for DI
Diz et al., 2013, Review [28]	ND	ND	ND	Similar to healthy population	–	May be at increased risk of complications for DI

MBL, marginal bone loss; ND, no data available; SR, survival rate; SCC, squamous cell carcinoma; DI, dental implant.

Table 3. Studies that indicate dental implant outcomes in patients with alcohol abuse.

DI surgery is suggested as a legitimate procedure for the patients at high risk for IE (such as aortic or mitral valve replacement or cyanotic congenital malformation) which under prophylactic antibiotic regime of 2 g amoxicillin orally at 1 hour preoperatively [34]. There is also evidence suggesting that this regimen significantly reduces failures of DIs though it is still unknown whether postoperative antibiotics are more beneficial, and which antibiotic is the most effective [33]. Reviewers stated the importance of concomitant bleeding or cardiac ischemia which could develop during DI insertion, therefore, procuring medical advice is recommended prior to the implant surgery [28]. As a matter of fact, recent myocardial infarction, stroke, and cardiovascular surgery are well-known contraindications for performing DI surgery [35].

According to the current literature, CVD does not hinder the osseointegration of DI [36, 37] and is not associated with higher risk of implant failure (**Table 4**). SR is about 89% up to 20 years (**Table 4**). However, the number of the studies that reports peri-implant health condition is insufficient. Unlike the other studies available, one study revealed that CVD has risk factors for peri-implant bone loss with the mean value of 1.38 mm after 3 years [16]. Further studies are needed in this respect.

2.5. Diabetes

As being the most prevalent endocrine disease, diabetes mellitus is a metabolic disorder that is generally diagnosed by the characteristic symptoms of polydipsia, polyuria, and polyphagia in correlation with exceeded blood glucose levels more than 200 mg/dL. It causes hyperglycemia due to a defect of insulin secretion [39], that insulin has an effect on the regeneration of bone matrix. In a diabetic patient, hyperglycemia reduces clot quality, number of osteoclasts, and collagen production, which are the keys of bone regeneration [30].

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Moy et al., 2005, Retrospective cohort [6]	2–20 years	1140 total (202 with hypertension, 106 with CVD, 75 with pulmonary disease)	ND (4680 total)	85% for hypertension, 85% for CVD	–	There is no correlation between hypertension, coronary artery disease, pulmonary disease and increased failure rate of DI
Alsaadi et al., 2007, Retrospective [18]	Up to the abutment connection	ND (2004 total)	ND (6946 total)	ND	–	Cardiac disease is not associated with increased incidence of the early failures
Alsaadi et al., 2008, Retrospective [21]	2 years	19 subjects with CVD	76 in subjects with CVD	90.79%	–	Cardiac problem does not seem a predominant player for late implant loss
Neves et al., 2016, Retrospective [2]	7.3 years of mean	222 subjects with CVD	ND	89.2% (patient based)	32% (patient based)	Cardiac disease is not associated with higher risk of implant failure and peri-implant pathology (>4 mm pocket depth with BoP or MBL)
Nobre et al., 2016, Retrospective [38]	5 years after loading	70 total (CVD subjects: 38 patients; non-CVD subjects: 32 patients)	352	CVD: 86.7%; non-CVD: 93.8%	MBL at 1st and 5th year is 0.95–1.52 mm in CVD; 0.78–1.54 mm in non-CVD group	Implant rehabilitations represent a valid treatment for diabetic patients with or without coexisting CVD, with a good risk/benefit ratio (nonsignificant differences between the groups)
Krennmair et al., 2016, Prospective cohort [16]	3 years	19 subjects with CVD (out of 44 total)	ND	–	1.38 mm in CVD*	CVD is risk factors for bone loss. (OR: 5.1)
Pedro et al., 2017, Analytical, observational, longitudinal [25]	2–4 years	ND (18 total)	ND (57 total)	–	ND	Heart diseases are not a contraindication for DI bone loss
Niedermaier et al., 2017, Retrospective cohort [13]	7 years	95 subjects with CVD (380 total)	ND (2081 total)	97.8%	–	DI survival in patients with cardiovascular problems does not differ from the healthy control subjects
Mean/total of values/ subjects	2–20 years	1533 patients with CVD (in 6 out of 8 available studies)	428 (in 2 out of 8 available studies)	Approx. 89% SR	0.95 mm at 1st year 1.38 mm at 3rd year 1.52 mm at 5th year	CVD may not pose a risk for dental implants

Statistically significant difference with healthy groups.CVD, cardiovascular disease; RD, rheumatic disorders; OR, odds ratio; MBL, marginal bone loss; ND, no data available; SR, survival rate.

Table 4. Studies that indicate dental implant outcomes in patients with cardiovascular diseases.

A decreased bone density is observed around the titanium implants in animal subjects, and implant survival is slightly reduced in poor metabolic control [28] with an average rate of 89% (**Table 5**). Yet no clinical evidence exists to establish an association of glycemic control with implant failure because of the insufficient identification and reporting of glycemic control in most of the published studies [40].

Though diabetes is not a contraindication for DI therapy, evaluating the HbA1c level of the patient and chlorhexidine mouth wash and antibiotic prophylaxis are recommended in order to reduce the relative risk of infection associated with diabetes [28, 30].

2.6. Bleeding disorders

There is no evidence to suggest that bleeding disorders (BDs) are contraindication for placement of DIs [28] or a contraindication for implant survival/success [31]. Since the risk of thromboembolism of interrupting or changing the antiplatelet therapy is higher than the risk of hemorrhage caused by dental implant surgery, invasive dental procedures including dental implant surgery are suggested to perform normally [42].

Considering the oral anticoagulant therapy (OAT), DI is not contraindicated in patients under an OAT [28, 31]. Minor DI surgery (that does not involve autogenous bone grafts, extensive flaps, or osteotomy preparations extending outside the bony envelope) is asserted to be safe regarding the risk of hemorrhage in patients who have an INR value of 2–4, and local hemostatic agents are suggested enough for these patients [43, 44]. On the other hand, it should be noted that some medications that are commonly used in dental practice (like metronidazole, erythromycin, and clarithromycin) may increase the anticoagulant effect of warfarin [31].

There are some additional precautions for the patients with inherited BDs such as taking medical advice previously, the replacement of deficient coagulation factor to reach a minimum level of 50% before surgery, slow injection of local anesthesia with vasoconstrictor, the use of antifibrinolytic agents (oral tranexamic acid and/or 5% tranexamic mouthwash) up to 7 days postsurgically, and the use of topical antiseptics (chlorhexidine or povidone iodine) in order to reduce the risk of local infection. Sinus lifting and bone graft procedures are recommended to be avoided, and consulting for the use of nonsteroidal anti-inflammatory drugs is advised as they may increase the risk of a dangerous hemorrhage [31].

Studies that analyze the bleeding risk and DI success after invasive DI surgeries are lacking (**Tables 6** and **7**). Studies are also required for evaluating whether anticoagulants have an effect on DI therapy negatively or which is the optimum drug or regimen.

2.7. Thyroid disorders

Thyroid hormones of triiodothyronine (T3) and thyroxine (T4) have been demonstrated to have influence on cortical bone healing than cancellous bone around titanium implants [47]. Thus, thyroid hormones-related disorders could be regarded as the considerable issues for evaluating the success of dental implants.

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Moy et al., 2005, Retrospective cohort [6]	2–20 years	48 diabetic	ND	68.75% in diabetic patients	–	There is a correlation between diabetes and increased failure rate (RR = 2.75)
Alsaadi et al., 2007, Retrospective [18]	Up to the abutment connection	ND	ND	ND	–	Controlled diabetes type 2 is not associated with increased incidence of the early failures
Alsaadi et al., 2008, Retrospective [21]	2 years	9	33	100%	–	Diabetes type 2 does not seem predominant player for late implant loss
Busenlechner et al., 2014, Retrospective [9]	8 years	185 (4.3% out of 4316 total)	ND	95.1% for diabetes (overall 97%)	–	Diabetes is not associated with long-term implant survival (p = 0.928)
Neves et al., 2016, Retrospective [2]	7.3 years (mean)	56 diabetic	ND	92.9% (patient based SR)	26.8% patient based	Diabetes is not associated with higher risk of implant failure and peri-implant pathology (>4 mm PD with BoP/MBL)
Niedermaier et al., 2017, Retrospective cohort [13]	7 years	9	ND	91.9%	–	DI survival in diabetic patients does not differ from the healthy control subjects
Shi et al., 2016 Meta-analysis [41] (abstract available)	ND	252	587	ND	–	There is no difference between the failure rates of the patients with uncontrolled and well-controlled diabetes
Diz et al., 2013, Review [28]	ND	ND	ND	Slightly reduced in bad metabolic control	–	Evaluating the HbA1c level for patient selection, avoiding hypoglycemia, using chlorhexidine and antibiotic prophylaxis are recommended for diabetic patients
Oates et al., 2013, Review [40]	Unrestricted	–	–	Implant failure rates ranging from 0 to 9.1%	–	Clinical evidence is lacking for the association of glycemic control with implant failure, because the identification and reporting of glycemic control are insufficient or lacking in most of the published studies
Mean/total of values/subjects	2–20 years	559 diabetic patients (in 6 out of 7 available studies)	620 (in 2 out of 7)	Approx. 89% SR		Diabetes may interfere with the SC and SR pf implants

DI, dental implant; BoP, bleeding on probing; MBL, marginal bone loss; ND, no data available; SR, survival rate; RR, risk ratio; PD, pocket depth.

Table 5. Studies that indicate dental implant outcomes in patients with diabetes.

Author, year, study design	Objective of the study	No of patients	Conclusion related to surgical risks of DI
Clemm, 2016, Clinical comparative study [45]	Postoperative bleeding risk of patients continuing their anticoagulation therapy (antiaggregant, vit-K inhibitors, vitamin-K inhibitor withdrawal bridged with heparin, direct oral anticoagulants) and undergoing implant surgery and advanced bone grafting procedures	564 patients	**1.** No thromboembolic complication occurred **2.** The postoperative bleeding risk after implant surgery and/or bone grafting procedures is very low in patients continuing the anticoagulant therapy **3.** The invasiveness of the surgical procedure had no statistically significant effect on bleeding frequencies **4.** Patients taking vit-K inhibitors had a significantly higher risk of a postoperative bleeding compared to patients without any anticoagulant **5.** Most of the postoperative bleedings are easily controllable via local hemostatic measures

Table 6. Hemorrhagic risks in patients undergoing advanced implant surgery and bone grafting procedures.

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Markovic et al., 2016, Randomized study [46]	1 year	20	80	100% for both groups	–	There is no difference between healing of the hydrophilic and hydrophobic TiZr implant surface. OAT influences the bone healing by resulting in lower ISQ at 3rd month in comparison with baseline values, although without compromising implant stability

OAT, oral anticoagulation therapy; ISQ, implant stability quotient; SR, survival rate.

Table 7. Studies that indicate dental implant outcome in patients with bleeding disorders or under an anticoagulant therapy.

Concerning the peri-implant pathology, thyroid disorders are reported to have the lowest potential risk compared to the other systemic disorders, in a recent clinical study [2] (**Table 8**). Due to the limited number of clinical studies that report DI outcomes in patients with thyroid disorders, it is hard to deduce a suggestion. Therefore, there is a certain need for further studies about the thyroid disorders.

2.8. Hepatitis

Concerning the dental implantology, hepatitis is one other disease which has not been studied widely yet. These infectious diseases impair immune system, increase oxidative stresses induced by the viral proteins, and cause virus-associated organ damage including liver fibrosis, steatosis, or hepatocellular carcinoma [48].

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Alsaadi et al., 2008, Retrospective [21]	2 years	25 Hypo-6 Hyper-	111 Hypo-22 Hyper-	93.69% Hypo-86.36% Hyper-	–	Hypo- or hyperthyroidism does not seem a predominant player for late implant loss
Neves et al., 2016, Retrospective [2]	7.3 years of mean	37	ND	86.5% (patient based SR)	18.9% (patient based)	Thyroid disorders are associated with neither higher risk of implant failure nor peri-implant pathology (>4 mm PD with BoP or MBL)
Mean/total of values/subjects	Up to 7 years	68	133 (in one study available)			Further studies are required

BoP, bleeding on probing; MBL, marginal bone loss; ND, no data available; SR, survival rate; PD, pocket depth.

Table 8. Studies that indicate dental implant outcomes in patients with thyroid disorders.

Being one of the most spread and dangerous human pathogens, hepatitis C is shown to affect the oral conditions by increasing decays, gingival bleeding, and pocket depth due to the evident change in salivary flow [49].

Though hepatitis was indicated only as a possible risk factor previously [50], a present report is registered that hepatitis is the only risk factor for peri-implant pathology among the other systemic compromising factors such as cardiac diseases, thyroid disorders, diabetes, rheumatologic disorders, HIV infection, and smoking [2] (**Table 9**).

2.9. Bone diseases

Being the most frequent bone disorder, osteoporosis (OP) affects both bone mass and density. The effect is also more prominent in cancellous bone and in women [30].

Clinical studies have demonstrated that a SR of DIs in the patients with the diagnosis of OP is about 94% (**Table 10**). Despite a small number of studies that report peri-implant conditions, one study has presented a high rate of peri-implantitis in patients with OP (76.1%), but this rate does not differ from the healthy population or the patients with osteopenia [51]. Regarding the peri-implant MBL, one recent study has reported a mean value of 0.11 mm at first

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Neves et al., 2016, Retrospective [2]	7.3 years of mean	12 with hepatitis	ND	83.3% (patient based)	66.7% (patient based)	Hepatitis is not associated with higher risk of implant failure but it is a risk factor for peri-implant pathology (OR = 3.74) (>4 mm PD with BoP or MBL)

OR, odds ratio; BoP, bleeding on probing; MBL, marginal bone loss; ND, no data available; PD, pocket depth.

Table 9. Studies that indicate dental implant outcomes in patients with hepatitis.

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Alsaadi et al., 2007, Retrospective [18]	Up to the abutment connection	ND	ND	ND	–	OP is found significantly associated with early implant failures (OR: 2.88)
Alsaadi et al., 2008, Retrospective [21]	2 years	19 subjects with OP	68	86.76%	–	OP does not seem predominant player for late implant loss
Holahan et al., 2008, Retrospective chart review [19]	5 years	41 with OP (21.4% of 192 total), 57 with OPN (29.7% of total)	ND	ND	–	OP or OPN is not a contraindication to DI. No association between BMD T-score and DI survival is found
Busenlechner et al., 2014, Retrospective [9]	8 years	151 subjects with OP (3.5% out of 4316 total)	ND	94.4% for OP-subjects (overall rate is 97%)	–	OP is not associated with long-term implant survival ($p = 0.661$)
Dvorak et al., 2011, Cross-sectional study [51]	6 years	47 subjects with OP, 16 with OPN, 140 are healthy controls	ND	81% for OPN, 87% for OP, 87% for the control	Peri-implantitis rates: 75% in the OPN, 76.1% in OP group, 76.5% in the control	There is no relation between (neither OPN nor OP) bone status and peri-implantitis or implant loss
Siebert et al., 2015, Comparative prospective [54]	1 year	24 women (the half was under iv. 5 mg zoledronic acid once-yearly, others without OP)	120	100%	ND	The mean MBL is similar for both groups. Immediate implant osseointegration can be successful in patients who received iv. zoledronic acid
Chow et al., 2016, Prospective [53]	5 year	79 subjects with OP	158	98.7%	MBL 0.65 mm BOP 49.6% PI 47.4%	OP is not a contraindication for DI, and reduced skeletal BMD is not associated with increased MBL. BOP is found significantly correlated with MBL
Niedermaier et al., 2017, Retrospective [13]	7 years	7 subjects	ND	94.1%	–	OP under the medication with BF seems to be a risk factor for success of DI
Temmerman et al., 2017, Prospective nonrandomized controlled multicenter [52]	1 year	20 subjects with OP, 28 control subjects	63 in OP-patients, 85 in control	98.4% is for OP group, 100.0% is for control group	MBL: 0.11 ± 0.49 mm for OP group; 0.05 ± 0.52 mm for control group (implant based)	DI in patients suffering from OP/OPN is a reliable treatment compared to healthy patients. Long-term follow-up is necessary

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Mean/total of values/subjects	1–8 years	388 (in 8 out of 9 available studies)	409 (in 4 out of 9 available studies)	94% SR in patients with OP	Mean MBLs are 0.11 mm at 1st year and 0.65 mm at 5th year follow-ups	Bone disease does not seem to be associated with the peri-implantitis or failure of DIs

OP, osteoporosis; OPN, osteopenia; OR, odds ratio; ND, no data available; BMD, bone mineral density; MBL, marginal bone loss; DI, dental implant; SR, survival rate.

Table 10. Studies that indicate dental implant outcomes in patients with bone diseases.

year [52], and one other has reported a mean of 0.65 mm at fifth year [53]. Additionally, bone status does not seem to be a predisposition for DI failures.

2.10. Rheumatologic disorders

Rheumatologic disorders encompass a large number of diseases and syndromes such as rheumatoid arthritis, osteoarthritis, and osteoporosis, which are the most common rheumatologic diseases (RDs) [2]. Different RDs could affect DI success in different ways [28]. For instance, rheumatoid arthritis (RA) has not stated a predominant player for late implant loss in one study [21]. However, together with the connective tissue disease, RA increases bone resorption when compared to the connective tissue disease alone [55].

Today, there are only a few number of clinical studies with limited amount of participants that evaluate the success of DIs in patients with RD. Although RD was shown as risk factor for peri-implant MBL in a recent prospective study [16], no relationship was found with the implant failure risk or peri-implant pathology in another study [2]. Therefore it can be concluded that any relation of RD in DI success is unclear, and there is a certain need for further studies with sufficient number of participants (**Table 11**).

2.11. Bisphosphonate therapy

Bisphosphonates (BFs) suppress the osteoclast function and therefore are used for the treatment of disorders causing abnormal bone resorption such as OP, malignancies (multiple myeloma, bone metastases of breast, or prostate cancer), or nonmalignant bone diseases (the most prevalent of osteoporosis and Paget disease) [30, 37].

According to the recent meta-analyses, the consumption of oral BF in patients with OP could only be assumed to be a relative contraindication for DI. Further, there is no evidence that any BFs have a negative impact upon implant survival. In this context, patients should be informed about the related risks and DI could be placed under optimum oral care conditions. On the contrary, in patients who are under BF treatment intravenously together with RT doses of above 50 Gy, DI placement was reported to be a contraindication [30, 56].

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Alsaadi et al., 2008, Retrospective [21]	2 years	6 patients with RD	28	100%	–	RA does not seem predominant player for late implant loss
Krennmair et al., 2016, Prospective [16]	3 years	6 patients with RD (44 total)	ND	–	1.61 mm in RD	RD is risk factors for bone loss (OR: 50.1)
Neves et al., 2016, Retrospective [2]	7.3 years (mean)	36 patients with RD	–	80.6% (patient based)	25% (patient based)	RDs are associated neither with higher risk of implant failure nor peri-implant pathology (>4 mm pocket depth with BoP or MBL). However, it is associated with a higher number of implant failures

RD, rheumatologic disease; RA, rheumatoid arthritis; BoP, bleeding on probing; MBL, marginal bone loss; DI, dental implant; SR, survival rate; ND, no data available; OR, odds ratio.

Table 11. Studies that indicate dental implant outcomes in patients with rheumatologic disorders.

In conclusion, BFs do not seem to have an adverse effect on DI survival under optimum oral care conditions, and OBFs are not associated with occurrence of osteonecrosis of jaws (ONJ) (**Table 12**).

2.12. Head and neck cancer

Squamous cell carcinoma, adenocarcinoma, and ameloblastoma are the most common malignancies that are encountered in the head and neck regions. These patients with malignancies frequently go under challenging adjuvant therapeutic procedures such as radiotherapy (RT) or chemotherapy (CT) in addition to the tumor surgery. Due to the aggressive nature of the cancer and challenging cancer therapies, it is difficult to manage the DI surgery and prosthetic procedures.

Furthermore, studies that evaluate the DI success in cancer patients are limited because most of the studies had a control group of patients who are under another cancer treatment (instead of a healthy control group) or have no control subjects to compare the success of dental implants. Therefore, the results are sufficient to achieve a conclusion regarding DI success (**Tables 13** and **14**). According to these clinical studies, CT does not seem to be associated with the higher DI failure when compared with the surgical treatment only. RT seems to be impairing the osseointegration process. Regardless of the cancer-treatment procedure, smoking and alcohol consumption in patients diagnosed with head and neck cancer yield higher implant failures. Additionally, there are no studies about implant therapy in patients with malignant diseases that are treated with BFs [64], and no study determined peri-implant conditions of DI in such patient population.

For improving the DI success in cancer patients, implant surgery is recommended to be performed at least 21 days prior to the initiation or following after 9 months of radiotherapy under a strict surgical asepsis and antimicrobial prophylaxis. Premature loading of the implants should be avoided [28, 31].

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Jeffcoat, 2006, Longitudinal single-blind controlled [57]	3 years	50 (the half is under OBF, the other half is not used BF)	210	100% for OBF, and 99.2% for control group	–	OBF usage is not associated with occurrence of ONJ compared to placebo
Martin et al., 2010, Cohort [58]	>1 year	589 aged women	ND	26 implants loss in 16 patients	–	Implant failure occurred as early as 4 weeks and as late as 11 years after placement
Famili et al., 2011, Retrospective [59]	1 year	211 women	347	98.7%	–	OBF therapy is not significantly affects implant success
Al-Sabbagh et al., 2015, Retrospective [60]	6 years	39	51	86.4%	–	It is suggested that there is a possible association between implant failure and not using of BF in elder patients (OR: 9.22)
Mozzati et al., 2015, Clinical chart review [61]	10 years	235 middle-aged women under OBPs for OP	1267	98.7% (implant based) 93.2% (patient based)	–	The risk for developing BRONJ associated to DI surgery remains low for patients receiving oral BPs. The use of procedures that could enhance healing such as platelet concentrates is recommended
Siebert et al., 2015, Comparative prospective [54]	1 year	24 women (half under iv. BF, others without OP)	120	100%	ND (MBL is similar)	Immediate implant osseointegration can be successful in a patient with OP using once-yearly infusion of 5 mg iv. zoledronic acid
Suvarna et al., 2016, Retrospective [62]	3 years	112 (58 patients on OBF therapy)	140	92%	–	No significant risk of implant failure is seen in patients on OBP therapy compared with healthy patients
Tallarico et al., 2016, Prospective [63]	3 years	32	98	98%	1.35 ± 0.21	No prosthesis failed during the entire follow-up, and no major complications were recorded. OBF therapy is not significantly affecting DI success in case of accurate treatment selection, minimally invasive surgical approach and constant follow-up
Ata-Ali et al., 2016, Systematic review and meta-analysis [56]	1–7 years	1288 patients (386 cases and 902 controls)	4562 (1090 DI in cases,	Ranged between 66.7 and 100% in BF users, 95.5	–	There is not enough evidence that BFs have a negative impact upon implant SR Further, prospective studies

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
			3472 in controls)	and 100% in nonusers		involving larger sample sizes and longer durations of follow-up are required to confirm these results
Mean/total of values/subjects	1–10 years	1238	2233 (in 7 out of 8 available studies)	SR is about 97% in patients who are under BFs therapy	1.35 mm at 3rd year follow-up (in one study available)	BFs do not seem to have an adverse effect on DI survival under an optimum oral care conditions, and OBFs are not associated with occurrence of ONJ

BF, bisphosphonate; OBF, oral bisphosphonate; OP, osteoporosis; BRONJ, BP-related osteonecrosis of the jaws; ONJ, osteonecrosis of the jaws; MBL, marginal bone loss; DI, dental implant; SR, survival rate; ND, no data available.

Table 12. Studies that indicate dental implant outcomes in patients who underwent bisphosphonate treatment.

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Kovacs, 2001, Retrospective [65]	10 years (3 years of mean)	30 (received postsurgical adjuvant CT) and 17 (received only oncological surgery)	106 in CT group, 54 in surgery group	98.1% on implant basis	–	CT is not detrimental to the survival and success of DIs in the mandible
Cao and Weischer, 2003 [66] (abstract available)	?	27 total number of nonirradiated and irradiated patients	131 total	65% on patient basis	–	Implants and prostheses in irradiated patients have significantly lower survival rates than in nonirradiated patients
Korfage et al., 2011, Prospective [67]	5 years	50 (18 patients were treated with surgery only, 32 patients with RT in addition to the surgery)	195 (72 in surgery-, and 123 in surgery + RT)	98.6% for non-RT treated, 89.4% for RT-treated group	–	Implant loss is higher in patients with head and neck cancer who received RT posttumor surgery
Gander et al., 2014, Retrospective [26]	20 months	33 (29 patients with SCC, 24 underwent mandibular reconstruction)	136 total	92.5% (at 1st year), 87.5% (after 20th month)	–	Only smoking ($p = 0.016$) and alcohol abuse ($p = 0.001$) are associated with higher implant failure rates

SCC, squamous cell carcinoma; CT, chemotherapy; RT, radiotherapy; DI, dental implant; SR, survival rate; ND, no data available.

Table 13. Studies that indicate dental implant outcomes in head and neck oncology patients.

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Moy et al., 2005, Retrospective cohort [6]	2–20 years	22 patients received RT	ND	68.18% in irradiated patients	–	There is a correlation between head and neck radiation and increased failure rate (RR = 2.73)
Alsaadi et al., 2008, Retrospective [21]	2 years	2 patients received RT	15 in irradiated patients	80%	–	RT is affected significantly the late implant loss (OR: 3.32)
Carr, 2012, Retrospective case series [69]	2 years	ND (412 total)	ND (1512 total)	ND	ND	Late implant failure is influenced by the local factor of "implant location" and the systemic factor of "radiotherapy"
Mancha, 2012, Retrospective [70]	5 years	30 RT-group, 20 control (non-RT treated oral cancer group)	225 in RT group, 130 in control group	92.6% for irradiated (48.3% for ORN-developed patients)	–	Irradiated patients have significantly higher implant loss than nonirradiated patients (p = 0.063)
Korfage et al., 2014, Retrospective [71]	14 years	164 patients with oral cancer (also 91 of them are smoker, 65 are nonsmoker)	318 in RT-group, 206 in nonirradiated group	91.5% for irradiated, 99.5% for nonirradiated	–	Implant loss is higher in irradiated patients ($p < 0.001$) but no significant difference is shown for bone loss assessed on panoramic radiographs Smoking is also not found associated with the occurrence of ORN
Rana et al., 2016, Retrospective [72]	5 years	46 patients with oral cancer	162	67% (52 implant had lost)		RT dose of <50 Gy units also showed significantly increased amount of implant survival rate
Nooh, 2013, Systematic Review [68]	1–14 years	944 patients with oral cancer	3775	88.9% (for 3357 implants)	–	In preimplantation RT, SR of DI is significantly higher for the mandible (93.3%) than for the maxilla (78.9%) or for grafted bone (87.5%) While RT dose above 55 Gy significantly decreased implant survival
Mean/total of values/subjects	1–20 years	284 patients with oral cancer (in 5 out of 6 available studies), 54 irradiated patients (in 3/6)	720 implants in irradiated patients (in 4 out of 6 available studies)	Approx. 83.07% SR in irradiated patients		RT, especially a dose above 50 Gy, negatively affects DI success

ORN, osteoradionecrosis; RT, radiotherapy; DI, dental implant; OR, odds ratio; RR, risk ratio; SR, survival rate; ND, no data available.

Table 14. Studies that indicate dental implant outcomes in patients who underwent radiation therapy.

2.12.1. Radiotherapy and hyperbaric oxygen therapy

RT reduces the cellular and vascular processes of healing, therefore it is assumed to impair the osseointegration and increase the risk of DI-related complications [31]. RT doses higher than 50 Gy are known to hinder osseointegration of DIs [30]. On the other hand, DI placement becomes contraindicated in patients who have received additional therapy of BFs intravenously or hormonal therapy, corticosteroids or immunosuppressive medication [30]. According to the data retrieved from the recent studies, it can be concluded that implant loss is clearly higher in irradiated patients (**Table 14**). The failures are more prominent in mandible or in grafted bone [68].

In the past, adjuvant hyperbaric oxygen therapy (HBO) treatment was shown to lead lower DI failure rates in cancer patients who underwent RT than those nonirradiated and irradiated patients [73]. Whereas, according to the recent clinical studies and reviews (**Table 15**), it seems that HBO has no positive effect on implant survival in irradiated patients. Therefore, this issue remains controversial.

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Schoen et al., 2007, RCT [74]	1 year	26 (the half is HBO treated, others is control)	ND	85.2% in HBO group, 93.9% in non-HBO group	MBLs: 0.6 ± 0.6 mm in HBO-, 0.7 ± 0.7 mm in non-HBO group	Adjuvant hyperbaric oxygen therapy does not influence implant survival or peri-implant MBL in radiated mandibular jaw bone. There is no statistically significant difference for postoperative complications and patient satisfaction
Esposito and Worthington, 2013, Systematic review [75]	–	–	–	–	–	Despite the limited amount of clinical research available, it appears that HBO therapy in irradiated patients requiring dental implants may not offer any appreciable clinical benefits. There is a definite need for more RCTs to ascertain the effectiveness of HBO in irradiated patients requiring dental implants
Chambrone et al., 2013, Systematic review [76]	–	–	1689 in irradiated jaws	The mean SR of 15 studies ranged from 46.3 to 98.0%	–	The risk of implant failure increases significantly in irradiated patients (RR: 2.74) and in maxillary sites (RR: 5.96). HBO therapy does not reduce the risk of implant failure

HBO, hyperbaric oxygen; RR, risk ratio; RCT, randomized controlled trial; MBL, marginal bone loss.

Table 15. The effect of hyperbaric oxygen (HBO) on reducing the risk of DI failure in irradiated patients.

2.13. Immunosuppressive conditions

Immunosuppressive disabilities encompass several disorders and conditions including RDs, autoimmune skin diseases (scleroderma, pemphigus, burning mouth syndrome etc.), organ transplantation, and immunosuppressive drug usage [2, 77, 78].

Since a good immune response is necessary for wound healing, immunocompromised conditions have been commonly assumed as a contraindication for DI placement [31]. In animal studies, it is showed that immunosuppressive drugs reduce osteoblast's proliferation and impair implant osseointegration [79, 80]. Furthermore, immunocompromised condition may present additional risks for blood borne infections [28]. Therefore, installation of DIs in patients under long-term immunosuppressive treatment should be elucidated with additional measures [81].

2.13.1. Organ transplantation

Bone healing is negatively affected by immunosuppressive medications. There are reports of case series and clinical studies that show successful treatments of DIs in patients who underwent organ transplants (**Table 16**). Reviewers stated that DIs could be a valid treatment providing that the appropriate surgical procedures and hygienic conditions are ensured [28, 78]. Modification of the immunosuppressive medication could lead a significantly lower toxicity [78].

As a conclusion, it is apparent that DI is not contraindicated for the patients who had organ transplants. However, it is suggested that the patients' medical condition should be investigated with the relevant physician before DI surgery, and the surgery should also be conducted under prophylactic medication in order to reduce the risk of blood-borne infections [28, 31].

2.13.2. HIV-positive patients

Acquired immune deficiency syndrome (AIDS) is a condition that is caused by the infection of the human immunodeficiency virus (HIV). HIV-infected individuals may have compromised oral health because of having HIV-associated gingivitis and periodontitis etc. [85] that yield an additional impairment of the general health.

Recently, HIV-infection is regarded as a chronic disease rather than a terminal disease owing to the therapeutic regimen of highly active antiretroviral therapy (HAART) that includes combinations of diverse antiretroviral medications. This regimen, however, is associated with many adverse effects including bone disorders, osteopenia, osteonecrosis, and osteoporosis [86, 87]. Hence, there is a need for identifying the predictability of dental implant therapy in patients with HIV-infection.

According to the clinical studies available (**Table 17**), clinical outcomes regarding the peri-implant pathology are conflicting. There may be a tendency for peri-implant infections due to the immunocompromised condition. However, HIV infection does not seem to increase the failure in the short or long term. So DI could be regarded as an eligible treatment for improving quality of life in the HIV-positive patients.

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Gu and Yu, 2011, Case series [82]	3 years	13	45	100%	MBL is 1.30 mm	DI treatment can be offered to liver transplant patients who are stable under long-term immunosuppression. Stable liver function and general condition should be affirmed though overall examination and consultation
Gu et al., 2011, Case report [83] (only abstract available)	5 years	1	11	–	–	A stable osseointegration with moderate vertical bone loss is achieved
Montebugnoli et al., 2012, Prospective [84]	3 months	20 (10 have organ transplant, the other 10 are in control group)	32 (20 in transplanted, 12 in control group)	–	MBL is 0.21 mm for transplanted, 0.32 mm is for control group	The bone response around submerged DI in immunocompromised organ transplant patients does not differ from that observed in control patients
Montebugnoli et al., 2015, Prospective [81]	1 year	13 organ transplanted (11 hearts, two livers, and 13 control subjects)	29 in transplanted, 28 in healthy control subjects	–	For transplanted and control subjects, MBLs are 0.17 and 0.20 mm, PDs are 0.06 and 0.11 mm	It seems that bone and periodontal response and microbiological status around submerged DI in immunocompromised organ-transplanted patients do not differ 1 year after loading from those observed in healthy control patients
Mean/total of values/subjects	1–5 years	37 patients had organ-transplant	105 implants	100%	0.19 mm for 1st year 1.30 mm at 3rd year	SR outcome is scarce. MBL seems acceptable More studies needed

MBL, marginal bone loss; DI, dental implant; SR, survival rate; PD, pocket depth.

Table 16. Studies that indicate dental implant outcomes in patients who received organ transplant.

2.14. Psychiatric disorders

Patients with neurologic disorders or other disabilities such as cerebral palsy, mental retardation, epilepsy, Down syndrome, Rett's syndrome, Asperger syndrome, Prader-Willi syndrome, fragile X chromosome, dystrophia myotonica, autism, and schizophrenia cause many problems during implant treatment and prosthetic maintenance [93]. Epilepsy impairs the oral condition of patients due to nausea-induced vomiting, mechanical trauma caused by seizures, and antiepileptic drugs-associated oral complications such as gingival overgrowth, xerostomia, and yeast infections [94, 95]. Likewise, most widely used antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs), affect not only the nervous system but also peripheral tissues

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Stevenson et al., 2007, Prospective [88]	6 months	20 HIV+, and 9 HIV− edentulous adults	40 in HIV+, 18 in HIV− subjects	100% for both groups	–	No difference in short-term clinical outcome is found between the HIV+ and the HIV− subjects
Oliveira et al., 2011, Pilot study [89]	1 year	40 (11 PI-based HAART, 14 NNRTI-based HAART without PI, 15 control group of who had HIV−)	60 (20 in each groups)	100% for all groups	0.49 mm in PI-HAART group, 0.47 mm in NNRTI-HAART and 0.55 mm in control	The placement of DI in HIV+ patients is a reasonable treatment, regardless of CD4+ cell count, viral load levels, and type of antiretroviral therapy. Longer follow-ups are necessary to ascertain the success
Neves et al., 2016, Retrospective [2]	7.3 years of mean	5 HIV+	ND	60% (patient based)	60% (patient-based peri-implant pathology rate)	AIDS is not risk factor for neither higher implant failure nor peri-implant pathology (>4 mm pocket depth with BoP or MBL). However, these rates are high when compared mean failure rates of population
Gherlone et al., 2016, Prospective [90, 91]	1 year	66 HIV+	190	92.1% on implant basis (a, b)	MBL is 1.19 mm, peri-implantitis prevalence is 5.2% on implant basis (a, b)	Despite higher incidence of peri-implant infections in the first 6 months (a), DI is a suitable treatment with a slightly worse results (a, b) regardless of CD4+ cell count (b). HIV+ heavy smokers (>10 cig/day) demonstrated increased risk of early failure, peri-implantitis, pus, and pain (b)
Gay-Escoda et al., 2016, Retrospective case series [92]	6.5 years of mean	9 HIV+	57	98.3%	Success rate: 68.4%. Patient- and implant-based rates of peri-implant mucositis: 22.2%–10.5%, peri-implantitis: 44.4%–45.6%	Though there is a high prevalence of peri-implant diseases, DI in HIV+ patients seem to provide satisfactory clinical results
Mean/total of values/subjects	Up to 7.3 years	125 HIV+ patients	347 (in 4 out of 5 studies)	Approx. 90% SR	0.83 mm MBL in 1st year. 50% of peri-implant pathology rate for mean follow-up of 7 years	SR is acceptable. Mean MBL outcomes are scarce and conflicting. Peri-implant pathology incidences seem higher as compared to the healthy population

HAART, highly active anti-retroviral therapy; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; MBL, marginal bone loss; BoP, bleeding on probing; SR, survival rate; resp, respectively.

Table 17. Studies that indicate dental implant outcomes in HIV-infected patients.

Author, year, study design	Follow-up	No. of patients	No. of implants	SR of implant	Peri-implant pathology	Conclusion
Cune et al., 2009, Retrospective [95]	16 years	61 patients with epilepsy, additional motor and/or intellectual impairments	134	97.6%	72% of implants were considered having inadequate level of hygiene PD is 2 mm	Although adequate plaque control is not feasible in those patients, MBLs remained stable and implant loss is rare
Ekfeldt et al., 2013, Prospective [93]	10 years	22 patients with different neurologic disabilities	70	85.8%	Peri-mucositis: 14 implants in 10 patients (PD ≥ 4 mm). Peri-implantitis: 4 implants in 3 patients (bone loss ≥ 3 threads)	DI is a valid option in patients with ND, although maintenance often requires the management of more complications compared with healthy patients
Wu et al., 2014, Retrospective cohort [98]	3–67 months	490 total number of SSRI-users and nonusers	916 (94 in users, 822 in nonusers)	88.4% for users, 95.4% for nonusers	–	SSRI is associated with increased failure risk of osseointegrated implants, which might suggest a careful surgical treatment planning for SSRI users

ND, neurologic disabilities; SSRI, selective serotonin reuptake inhibitor; PD, probing depth; MBL, marginal bone loss; SR, survival rate.

Table 18. Studies that indicate dental implant outcomes in patients with psychiatric disorders.

including bones because of having serotonin receptors [96]. Therefore, SSRI blocks on bone cells have been reported to affect bone formation negatively [97].

Since bone metabolism and oral conditions have an influence on the osseointegration of DI, neuropsychiatric disabilities and the drugs used are considerable issues for DI treatment. Clinical research related to the effect of psychiatric disorders on DI success is limited. It seems that this kind of disorders do not cause higher failures or peri-implant pathology (**Table 18**). On the other hand, SSRIs might increase DI failure rate as presented in a cohort study with a large number of subjects. Further studies are required to ascertain the association between antidepressant drugs and DI failure.

3. Conclusion

Implant survival in the elderly population, osteoporosis (OP) and HIV infection seem to be similar with the healthy population. CVDs or diabetes may present a small risk. RT seems to have the worst effect on DI success with an average SR of 83%. Some of the other compromised conditions such as alcoholism, bleeding disorders, thyroid disorders, hepatitis, RDs, organ transplantation, and HBO therapy should be investigated with additional clinical data to reveal objective conclusions regarding DIs.

Results with regard to peri-implantitis or peri-implant conditions are insufficient and even conflicting for majority of the compromising systemic aspects. Future studies should be designed for indicating peri-implant tissue health and maintenance in compromised patients.

It must be taken into account that follow-up of the patients in a professional oral maintenance regimen after implant placement reduces the implant failure rate by 80% [12]. Thus, it can be stated that controlling the systemic diseases before the implant therapy and proper establishment of the medical conditions are more important than the presence of a compromise alone.

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References

[1] Austin S, Bailey D, Chandu A, Dastaran M, Judge R. Analysis of commonly reported medical conditions amongst patients receiving dental implant therapy in private practice. Australian Dental Journal. 2015;**60**(3):343-352. DOI: 10.1111/adj.12237

[2] Neves J, de Araújo Nobre M, Oliveira P, Martins Dos Santos J, Malo P. Risk Factors for Implant Failure and Peri-Implant Pathology in Systemic Compromised Patients. J Prosthodont. 2016 Jun 27. DOI: 10.1111/jopr.12508. [Epub ahead of print]

[3] Bartold PM, Ivanovski S, Darby I. Implants for the aged patient: Biological, clinical and sociological considerations. Periodontology 2000. 2016;**72**(1):120-134. DOI: 10.1111/prd.12133

[4] Srinivasan M, Meyer S, Mombelli A, Müller F. Dental implants in the elderly population: a systematic review and meta-analysis. Clin Oral Implants Res. 2017;**28**(8):920-930. DOI: 10.1111/clr.12898

[5] Hoeksema AR, Visser A, Raghoebar GM, Vissink A, Meijer HJ. Influence of age on clinical performance of mandibular two-implant overdentures: A 10-year prospective

comparative study. Clinical Implant Dentistry and Related Research. 2016;**18**(4):745-751. DOI: 10.1111/cid.12351

[6] Moy PK, Medina D, Shetty V, Aghaloo TL. Dental implant failure rates and associated risk factors. The International Journal of Oral & Maxillofacial Implants. 2005;**20**(4):569-577

[7] Manor Y, Oubaid S, Mardinger O, Chaushu G, Nissan J. Characteristics of early versus late implant failure: A retrospective study. Journal of Oral and Maxillofacial Surgery. 2009;**67**(12):2649-2652. DOI: 10.1016/j.joms.2009.07.050

[8] Lee HJ, Kim YK, Park JY, Kim SG, Kim MJ, Yun PY. Short-term clinical retrospective study of implants in geriatric patients older than 70 years. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 2010;**110**(4):442-446. DOI: 10.1016/j.tripleo.2010.02.019

[9] Busenlechner D, Fürhauser R, Haas R, Watzek G, Mailath G, Pommer B. Long-term implant success at the Academy for Oral Implantology: 8-year follow-up and risk factor analysis. Journal of Periodontal & Implant Science. 2014;**44**(3):102-108. DOI: 10.5051/jpis.2014.44.3.102

[10] Becker W, Hujoel P, Becker BE, Wohrle P. Dental implants in an aged population: Evaluation of periodontal health, bone loss, implant survival, and quality of life. Clinical Implant Dentistry and Related Research. June 2016;**18**(3):473-479. DOI: 10.1111/cid.12340

[11] Prasad S, Hambrook C, Reigle E, Sherman K, Bansal N, Hefti A. Implant Treatment in the Predoctoral Clinic: A Retrospective Database Study of 1091 Patients. J Prosthodont. 2016 Nov 22. DOI: 10.1111/jopr.12570

[12] Tran DT, Gay IC, Diaz-Rodriguez J, Parthasarathy K, Weltman R, Friedman L. Survival of dental implants placed in grafted and nongrafted bone: A retrospective study in a university setting. The International Journal of Oral & Maxillofacial Implants. 2016;**31**(2):310-317. DOI: 10.11607/jomi.4681

[13] Niedermaier R, Stelzle F, Riemann M, Bolz W, Schuh P, Wachtel H. Implant-supported immediately loaded fixed full-arch dentures: Evaluation of implant survival rates in a case cohort of up to 7 years. Clinical Implant Dentistry and Related Research. 2017;**19**(1):4-19. DOI: 10.1111/cid.12421

[14] Clementini M, Rossetti PH, Penarrocha D, Micarelli C, Bonachela WC, Canullo L. Systemic risk factors for peri-implant bone loss: A systematic review and meta-analysis. International Journal of Oral and Maxillofacial Surgery. 2014;**43**(3):323-334. DOI: 10.1016/j.ijom.2013.11.012

[15] Galindo-Moreno P, Fauri M, Avila-Ortiz G, Fernández-Barbero JE, Cabrera-León A, Sánchez-Fernández E. Influence of alcohol and tobacco habits on peri-implant marginal bone loss: A prospective study. Clinical Oral Implants Research. 2005;**16**(5):579-586. DOI: 10.1111/j.1600-0501.2005.01148.x

[16] Krennmair S, Weinländer M, Forstner T, Krennmair G, Stimmelmayr M. Factors affecting peri-implant bone resorption in four Implant supported mandibular full-arch restorations: A 3-year prospective study. Journal of Clinical Periodontology. 2016;**43**(1):92-101. DOI: 10.1111/jcpe.12469

[17] Ekfeldt A, Christiansson U, Eriksson T, Lindén U, Lundqvist S, Rundcrantz T, Johansson LA, Nilner K, Billström C. A retrospective analysis of factors associated with multiple implant failures in maxillae. Clinical Oral Implants Research. 2001;**12**(5):462-467

[18] Alsaadi G, Quirynen M, Komárek A, van Steenberghe D. Impact of local and systemic factors on the incidence of oral implant failures, up to abutment connection. Journal of Clinical Periodontology. 2007;**34**(7):610-617. DOI: 10.1111/j.1600-051X.2007.01077.x

[19] Holahan CM, Koka S, Kennel KA, Weaver AL, Assad DA, Regennitter FJ, Kademani D. Effect of osteoporotic status on the survival of titanium dental implants. The International Journal of Oral & Maxillofacial Implants. 2008;**23**(5):905-910

[20] Sverzut AT, Stabile GA, de Moraes M, Mazzonetto R, Moreira RW. The influence of tobacco on early dental implant failure. Journal of Oral and Maxillofacial Surgery. 2008; **66**(5):1004-1009. DOI: 10.1016/j.joms.2008.01.032

[21] Alsaadi G, Quirynen M, Komárek A, van Steenberghe D. Impact of local and systemic factors on the incidence of late oral implant loss. Clinical Oral Implants Research. 2008;**19**:670-676. DOI: 10.1111/j.1600-0501.2008.01534.x

[22] Alsaadi G, Quirynen M, Michiles K, Teughels W, Komárek A, van Steenberghe D. Impact of local and systemic factors on the incidence of failures up to abutment connection with modified surface oral implants. Journal of Clinical Periodontology. 2008;**35**(1):51-57. DOI: 10.1111/j.1600-051X.2007.01165.x

[23] Lee JY, Park HJ, Kim JE, Choi YG, Kim YS, Huh JB, Shin SW. A 5-year retrospective clinical study of the Dentium implants. The Journal of Advanced Prosthodontics. December 2011;**3**(4):229-235. DOI: 10.4047/jap.2011.3.4.229

[24] Cakarer S, Selvi F, Can T, Kirli I, Palancioglu A, Keskin B, Yaltirik M, Keskin C. Investigation of the risk factors associated with the survival rate of dental implants. Journal of Implant Dentistry. 2014;**23**(3):328-333. DOI: 10.1097/ID.0000000000000079

[25] Pedro RE, De Carli JP, Linden MS, Lima IF, Paranhos LR, Costa MD, Bós ÂJ. Influence of age on factors associated with peri-implant bone loss after prosthetic rehabilitation over osseointegrated implants. The Journal of Contemporary Dental Practice. 2017;**18** (1):3-10

[26] Gander T, Studer S, Studer G, Grätz KW, Bredell M. Medium-term outcome of Astra Tech implants in head and neck oncology patients. International Journal of Oral and Maxillofacial Surgery. 2014;**43**(11):1381-1385. DOI: 10.1016/j.ijom.2014.05.005

[27] Scully C, Hobkirk J, Dios PD. Dental endosseous implants in the medically compromised patient. Journal of Oral Rehabilitation. 2007;**34**(8):590-599. DOI: 10.1111/j.1365-2842.2007.01755.x

[28] Diz P, Scully C, Sanz M. Dental implants in the medically compromised patient. Journal of Dentistry. 2013;**41**(3):195-206. DOI: 10.1016/j.jdent.2012.12.008

[29] Elsubeihi ES, Zarb GA. Implant prosthodontics in medically challenged patients: The University of Toronto experience. Journal of the Canadian Dental Association. 2002;**68**(2):103-108

[30] Gómez-de Diego R, Mang-de la Rosa Mdel R, Romero-Pérez MJ, Cutando-Soriano A, López-Valverde-Centeno A. Indications and contraindications of dental implants in medically compromised patients: Update. Medicina Oral, Patología Oral y Cirugía Bucal Journal. 2014;**19**(5):e483-e489

[31] Donos N, Calciolari E. Dental implants in patients affected by systemic diseases. British Dental Journal. 2014;**217**(8):425-430. DOI: 10.1038/sj.bdj.2014.911

[32] Farbod F, Kanaan H, Farbod J. Infective endocarditis and antibiotic prophylaxis prior to dental/oral procedures: Latest revision to the guidelines by the American Heart Association published April 2007. International Journal of Oral and Maxillofacial Surgery. 2009;**38**(6):626-631. DOI: 10.1016/j.ijom.2009.03.717

[33] Esposito M, Worthington HV, Loli V, Coulthard P, Grusovin MG. Interventions for replacing missing teeth: Antibiotics at dental implant placement to prevent complications. Cochrane Database of Systematic Reviews. 2010;(7):CD004152. DOI: 10.1002/14651858.CD004152.pub3. https://www.ncbi.nlm.nih.gov/pubmed/20614437

[34] Findler M, Chackartchi T, Regev E. Dental implants in patients at high risk for infective endocarditis: A preliminary study. International Journal of Oral and Maxillofacial Surgery. 2014;**43**(10):1282-1285. DOI: 10.1016/j.ijom.2014.04.015

[35] Hwang D, Wang HL. Medical contraindications to implant therapy: Part I: Absolute contraindications. Implant Dentistry. 2006;**15**(4):353-360. DOI: 10.1097/01.id.0000247855.75691.03

[36] Hwang D, Wang HL. Medical contraindications to implant therapy: Part II: Relative contraindications. Implant Dentistry. 2007;**16**(1):13-23. DOI: 10.1097/ID.0b013e31803276c8

[37] Bornstein MM, Cionca N, Mombelli A. Systemic conditions and treatments as risks for implant therapy. The International Journal of Oral & Maxillofacial Implants. 2009;**24** (Suppl):12-27

[38] Nobre Mde A, Maló P, Gonçalves Y, Sabas A, Salvado F. Outcome of dental implants in diabetic patients with and without cardiovascular disease: A 5-year post-loading retrospective study. European Journal of Oral Implantology. 2016;**9**(1):87-95

[39] Michaeli E, Weinberg I, Nahlieli O. Dental implants in the diabetic patient: Systemic and rehabilitative considerations. Quintessence International. 2009;**40**(8):639-645

[40] Oates TW, Huynh-Ba G, Vargas A, Alexander P, Feine J. A critical review of diabetes, glycemic control, and dental implant therapy. Clinical Oral Implants Research. 2013;**24** (2):117-127. DOI: 10.1111/j.1600-0501.2011.02374.x

[41] Shi Q, Xu J, Huo N, Cai C, Liu H. Does a higher glycemic level lead to a higher rate of dental implant failure?: A meta-analysis. Journal of the American Dental Association. 2016;**147**(11):875-881. DOI: 10.1016/j.adaj.2016.06.011

[42] Napeñas JJ, Hong CH, Brennan MT, Furney SL, Fox PC, Lockhart PB. The frequency of bleeding complications after invasive dental treatment in patients receiving single and dual antiplatelet therapy. Journal of the American Dental Association. 2009;**140**(6):690-695

[43] Madrid C, Sanz M. What impact do systemically administrated bisphosphonates have on oral implant therapy? A systematic review. Clinical Oral Implants Research. 2009;**20** (Suppl 4):87-95. DOI: 10.1111/j.1600-0501.2009.01772.x

[44] Bacci C, Berengo M, Favero L, Zanon E. Safety of dental implant surgery in patients undergoing anticoagulation therapy: A prospective case-control study. Clinical Oral Implants Research. 2011;**22**(2):151-156. DOI: 10.1111/j.1600-0501.2010.01963.x

[45] Clemm R, Neukam FW, Rusche B, Bauersachs A, Musazada S, Schmitt CM. Management of anticoagulated patients in implant therapy: A clinical comparative study. Clin Oral Implants Res. 2016;**27**(10):1274-1282. DOI: 10.1111/clr.12732

[46] Marković A, Đinić A, Calvo Guirado JL, Tahmaseb A, Šćepanović M, Janjić B. Randomized clinical study of the peri-implant healing to hydrophilic and hydrophobic implant surfaces in patients receiving anticoagulants. Clin Oral Implants Res. 2016 Aug 18. DOI: 10.1111/clr.12948

[47] Feitosa Dda S, Bezerra Bde B, Ambrosano GM, Nociti FH, Casati MZ, Sallum EA, de Toledo S. Thyroid hormones may influence cortical bone healing around titanium implants: A histometric study in rats. Journal of Periodontology. 2008;**79**(5):881-887. DOI: 10.1902/jop.2008.070466

[48] Smirnova OA, Ivanov AV, Ivanova ON, Valuev-Éllison VT, Kochetkov SN. Cellular defense systems against oxidative and ER stresses: Mechanisms of regulation and influence of hepatitis C virus. Molecular Biology (Mosk). 2011;**45**(1):127-141

[49] Coates EA, Brennan D, Logan RM, Goss AN, Scopacasa B, Spencer AJ, Gorkic E. Hepatitis C infection and associated oral health problems. Australian Dental Journal. 2000;**45**: 108-114

[50] Marrone A, Lasserre J, Bercy P, Brecx MC. Prevalence and risk factors for peri-implant disease in Belgian adults. Clinical Oral Implants Research. 2013;**24**(8):934-940. DOI: 10.1111/j.1600-0501.2012.02476.x

[51] Dvorak G, Arnhart C, Heuberer S, Huber CD, Watzek G, Gruber R. Peri-implantitis and late implant failures in postmenopausal women: A cross-sectional study. Journal of Clinical Periodontology. 2011;**38**(10):950-955. DOI: 10.1111/j.1600-051X.2011.01772.x

[52] Temmerman A, Rasmusson L, Kübler A, Thor A, Quirynen M. An open, prospective, non-randomized, controlled, multicentre study to evaluate the clinical outcome of implant treatment in women over 60 years of age with osteoporosis/osteopenia: 1-year results. Clinical Oral Implants Research. 2017;**28**(1):95-102. DOI: 10.1111/clr.12766

[53] Chow L, Chow TW, Chai J, Mattheos N. Bone stability around implants in elderly patients with reduced bone mineral density - a prospective study on mandibular overdentures. Clin Oral Implants Res. 2017;**28**(8):966-973. DOI: 10.1111/clr.12907

[54] Siebert T, Jurkovic R, Statelova D, Strecha J. Immediate implant placement in a patient with osteoporosis undergoing bisphosphonate therapy: 1-year preliminary prospective study. Journal of Oral Implantology. 2015;**41**(1):360-365. DOI: 10.1563/AAID-JOI-D-13-00063

[55] Krennmair G, Seemann R, Piehslinger E. Dental implants in patients with rheumatoid arthritis: Clinical outcome and peri-implant findings. Journal of Clinical Periodontology. 2010;**37**(10):928-936. DOI: 10.1111/j.1600-051X.2010.01606.x

[56] Ata-Ali J, Ata-Ali F, Peñarrocha-Oltra D, Galindo-Moreno P. What is the impact of bisphosphonate therapy upon dental implant survival? A systematic review and meta-analysis. Clinical Oral Implants Research. 2016;**27**(2):e38-e46. DOI: 10.1111/clr.12526

[57] Jeffcoat MK. Safety of oral bisphosphonates: Controlled studies on alveolar bone. The International Journal of Oral & Maxillofacial Implants. 2006;**21**(3):349-353

[58] Martin DC, O'Ryan FS, Indresano AT, Bogdanos P, Wang B, Hui RL, Lo JC. Characteristics of implant failures in patients with a history of oral bisphosphonate therapy. Journal of Oral and Maxillofacial Surgery. 2010;**68**(3):508-514. DOI: 10.1016/j.joms.2009.09.055

[59] Famili P, Quigley S, Mosher T. Survival of dental implants among post-menopausal female dental school patients takingoral bisphosphonates: A retrospective study. Compendium of Continuing Education in Dentistry. 2011;**32**(6):E106-E109

[60] Al-Sabbagh M, Thomas MV, Bhavsar I, De Leeuw R. Effect of bisphosphonate and age on implant failure as determined by patient-reported outcomes. Journal of Oral Implantology. 2015;**41**(6):e287-e291. DOI: 10.1563/aaid-joi-D-14-00195

[61] Mozzati M, Arata V, Giacomello M, Del Fabbro M, Gallesio G, Mortellaro C, Bergamasco L. Failure risk estimates after dental implants placement associated with plasma rich in growth factor-Endoret in osteoporotic women under bisphosphonate therapy. Journal of Craniofacial Surgery. May 2015;**26**(3):749-755. DOI: 10.1097/SCS.0000000000001535

[62] Suvarna S, Dutt P, Misra A, Usmani N, Singh A, Suvarna C. Intricate assessment and evaluation of dental implants in patients on bisphosphonate therapy: A retrospective analysis. The Journal of Contemporary Dental Practice. May 1 2016;**17**(5):414-417

[63] Tallarico M, Canullo L, Xhanari E, Meloni SM. Dental implants treatment outcomes in patient under active therapy with alendronate: 3-year follow-up results of a multicenter prospective observational study. Clinical Oral Implants Research. August 2016;**27**(8):943-949. DOI: 10.1111/clr.12662

[64] Walter C, Al-Nawas B, Wolff T, Schiegnitz E, Grötz KA. Dental implants in patients treated with antiresorptive medication—A systematic literature review. International Journal of Implant Dentistry. 2016;**2**(1):9. DOI: 10.1186/s40729-016-0041-7

[65] Kovács AF. Influence of chemotherapy on endosteal implant survival and success in oral cancer patients. International Journal of Oral and Maxillofacial Surgery. 2001;**30**(2):144-147

[66] Cao Y, Weischer T. Comparison of maxillary implant-supported prosthesis in irradiated and non-irradiated patients. Journal of Huazhong University of Science and Technology. Medical Sciences. 2003;**23**(2):209-212

[67] Korfage A, Schoen PJ, Raghoebar GM, Bouma J, Burlage FR, Roodenburg JL, Vissink A, Reintsema H. Five-year follow-up of oral functioning and quality of life in patients with oral cancer with implant-retained mandibular overdentures. Head Neck. 2011;**33**(6):831-839. DOI: 10.1002/hed.21544

[68] Nooh N. Dental implant survival in irradiated oral cancer patients: A systematic review of the literature. The International Journal of Oral & Maxillofacial Implants. 2013;**28** (5):1233-1242. DOI: 10.11607/jomi.3045

[69] Carr AB. Implant location and radiotherapy are the only factors linked to 2-year implant failure. Journal of Evidence-Based Dental Practice. 2012;**12**(3 Suppl):217-219. DOI: 10.1016/S1532-3382(12)70042-8

[70] Mancha de la Plata M, Gías LN, Díez PM, Muñoz-Guerra M, González-García R, Lee GY, Castrejón-Castrejón S, Rodríguez-Campo FJ. Osseointegrated implant rehabilitation of irradiated oral cancer patients. Journal of Oral and Maxillofacial Surgery. 2012;**70** (5):1052-1063. DOI: 10.1016/j.joms.2011.03.032

[71] Korfage A, Raghoebar GM, Slater JJ, Roodenburg JL, Witjes MJ, Vissink A, Reintsema H. Overdentures on primary mandibular implants in patients with oral cancer: A follow-up study over 14 years. British Journal of Oral and Maxillofacial Surgery. 2014;**52**(9):798-805. DOI: 10.1016/j.bjoms.2014.05.013

[72] Rana MC, Solanki S, Pujari SC, Shaw E, Sharma S, Anand A, Singh HP. Assessment of the survival of dental implants in irradiated jaws following treatment of oral cancer: A retrospective study. Nigerian Journal of Surgery. 2016;**22**(2):81-85

[73] Granström G, Tjellström A, Brånemark PI. Osseointegrated implants in irradiated bone: A case-controlled study using adjunctive hyperbaric oxygen therapy. Journal of Oral and Maxillofacial Surgery. 1999;**57**(5):493-499

[74] Schoen PJ, Raghoebar GM, Bouma J, Reintsema H, Vissink A, Sterk W, Roodenburg JL. Rehabilitation of oral function in head and neck cancer patients after radiotherapy with implant-retained dentures: Effects of hyperbaric oxygen therapy. Oral Oncology. 2007;**43** (4):379-388

[75] Esposito M, Worthington HV. Interventions for replacing missing teeth: Hyperbaric oxygen therapy for irradiated patients who require dental implants. The Cochrane Database of Systematic Reviews. 2013;(9):CD003603. DOI: 10.1002/14651858.CD003603.pub3. https://www.ncbi.nlm.nih.gov/pubmed/24085641

[76] Chambrone L, Mandia Jr J, Shibli JA, Romito GA, Abrahao M. Dental implants installed in irradiated jaws: A systematic review. Journal of Dental Research. 2013;**92**(12 Suppl):119S-130S. DOI: 10.1177/0022034513504947

[77] Zigdon H, Gutmacher Z, Teich S, Levin L. Full-mouth rehabilitation using dental implants in a patient with scleroderma. Quintessence International. 2011;**42**(9):781-785

[78] Radzewski R, Osmola K. The use of dental implants in organ transplant patients undergoing immunosuppressive therapy: An overview of publications. Implant Dentistry. 2016;**25**(4):541-546. DOI: 10.1097/ID.0000000000000417

[79] Zheng X, Mo A, Wang Y, Guo Y, Wu Y, Yuan Q. Effect of FK-506 (tacrolimus) therapy on bone healing of titanium implants: A histometric and biomechanical study in mice. European Journal of Oral Sciences. 2017;**125**(1):28-33. DOI: 10.1111/eos.12320

[80] Annussek T, Kleinheinz J, Thomas S, Joos U, Wermker K. Short time administration of antirheumatic drugs—Methotrexate as a strong inhibitor of osteoblast's proliferation in vitro. Head & Face Medicine. 2012;**8**:26. DOI: 10.1186/1746-160X-8-26

[81] Montebugnoli L, Venturi M, Cervellati F, Servidio D, Vocale C, Pagan F, Landini MP, Magnani G, Sambri V. Peri-implant response and microflora in organ transplant patients 1 year after prosthetic loading: A prospective controlled study. Clinical Implant Dentistry and Related Research. 2015;**17**(5):972-982. DOI: 10.1111/cid.12207

[82] Gu L, Yu YC. Clinical outcome of dental implants placed in liver transplant recipients after 3 years: A case series. Transplantation Proceedings. 2011;**43**(7):2678-2682. DOI: 10.1016/j.transproceed.2011.06.037

[83] Gu L, Wang Q, Yu YC. Eleven dental implants placed in a liver transplantation patient: A case report and 5-year clinical evaluation. Chinese Medical Journal (England). 2011;**124**(3):472-475

[84] Montebugnoli L, Venturi M, Cervellati F. Bone response to submerged implants in organ transplant patients: A prospective controlled study. The International Journal of Oral & Maxillofacial Implants. 2012;**27**(6):1494-1500

[85] Ryder MI, Nittayananta W, Coogan M, Greenspan D, Greenspan JS. Periodontal disease in HIV/AIDS. Periodontology 2000. 2012;**60**(1):78-97. DOI: 10.1111/j.1600-0757.2012.00445.x

[86] Annapoorna N, Rao GV, Reddy NS, Rambabu P, Rao KR. An increased risk of osteoporosis during acquired immunodeficiency syndrome. International Journal of Medical Sciences. 2004;**1**(3):152-164

[87] Hofman P, Nelson AM. The pathology induced by highly active antiretroviral therapy against human immunodeficiency virus: An update. Current Medicinal Chemistry. 2006;**13**(26):3121-3132

[88] Stevenson GC, Riano PC, Moretti AJ, Nichols CM, Engelmeier RL, Flaitz CM. Short-term success of osseointegrated dental implants in HIV-positive individuals: A prospective study. The Journal of Contemporary Dental Practice. 2007;**8**(1):1-10

[89] Oliveira MA, Gallottini M, Pallos D, Maluf PS, Jablonka F, Ortega KL. The success of endosseous implants in human immunodeficiency virus-positive patients receiving antiretroviral therapy: A pilot study. Journal of the American Dental Association. 2011;**142**(9):1010-1016

[90] Gherlone EF, Capparé P, Tecco S, Polizzi E, Pantaleo G, Gastaldi G, Grusovin MG. Implant prosthetic rehabilitation in controlled HIV-positive patients: A prospective longitudinal study with 1-year follow-up. Clinical Implant Dentistry and Related Research. 2016;**18**(4):725-734. DOI: 10.1111/cid.12353

[91] Gherlone EF, Capparé P, Tecco S, Polizzi E, Pantaleo G, Gastaldi G, Grusovin MG. A prospective longitudinal study on implant prosthetic rehabilitation in controlled HIV-positive patients with 1-year follow-up: The role of CD4+ level, smoking habits, and oral hygiene. Clinical Implant Dentistry and Related Research. 2016;**18**(5):955-964. DOI: 10.1111/cid.12370

[92] Gay-Escoda C, Pérez-Álvarez D, Camps-Font O, Figueiredo R. Long-term outcomes of oral rehabilitation with dental implants in HIV-positive patients: A retrospective case series. Medicina Oral, Patología Oral y Cirugía Bucal. 2016;**21**(3):e385-e391

[93] Ekfeldt A, Zellmer M, Carlsson GE. Treatment with implant-supported fixed dental prostheses in patients with congenital and acquired neurologic disabilities: A prospective study. The International Journal of Prosthodontics. 2013;**26**(6):517-524. DOI: 10.11607/ijp.3511

[94] Stoopler ET, Sollecito TP, Greenberg MS. Seizure disorders: Update of medical and dental considerations. General Dentistry. 2003;**51**(4):361-366; quiz 367

[95] Cune MS, Strooker H, van der Reijden WA, de Putter C, Laine ML, Verhoeven JW. Dental implants in persons with severe epilepsy and multiple disabilities: A long-term retrospective study. The International Journal of Oral & Maxillofacial Implants. May-June 2009;**24**(3):534-540

[96] Tsapakis EM, Gamie Z, Tran GT, Adshead S, Lampard A, Mantalaris A, Tsiridis E. The adverse skeletal effects of selective serotonin reuptake inhibitors. European Psychiatry. 2012;**27**(3):156-169. DOI: 10.1016/j.eurpsy.2010.10.006

[97] Yadav VK, Ryu JH, Suda N, Tanaka KF, Gingrich JA, Schütz G, Glorieux FH, Chiang CY, Zajac JD, Insogna KL, Mann JJ, Hen R, Ducy P, Karsenty G. Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum. Cell. 2008;**135**(5):825-837. DOI: 10.1016/j.cell.2008.09.059

[98] Wu X, Al-Abedalla K, Rastikerdar E, Abi Nader S, Daniel NG, Nicolau B, Tamimi F. Selective serotonin reuptake inhibitors and the risk of osseointegrated implant failure: A cohort study. Journal of Dental Research. 2014;**93**(11):1054-1061. DOI: 10.1177/0022034514549378

Chapter 6

Multimodality Imaging to Detect Vulnerable Plaque in Coronary Arteries and Its Clinical Application

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Additional information is available at the end of the chapter

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Abstract

Postmortem studies have described the association between the thin-cap fibroatheroma (TCFA) and the occurrence of acute coronary syndrome (ACS). Both noninvasive and invasive techniques have been refined and used as a research tool to visualize the plaque at a high risk of disruption. There has been a considerable effort to develop the imaging modalities that offer detailed visualization of coronary pathology and accurately predict the adverse cardiac outcomes. This chapter provides an overview of the current and experimental coronary imaging methods to detect vulnerable plaque and discuss the potential implication of multimodality imaging in clinical practice.

Keywords: vulnerable plaque, imaging, IVUS, OCT, CCTA, CMR

1. Introduction

Cardiovascular diseases are the leading cause of death worldwide. It is predicted that by 2030, the number of deaths from coronary artery disease and stroke will increase from 17.3 million in 2008 to 23.3 million [1]. Current diagnostic strategies emphasize on preventing future coronary events by early identification of the vulnerable patient and modification of the risk by medication. The postmortem data have shown that the coronary events were associated with sudden luminal thrombosis due to plaque rupture. The thin-cap fibroatheroma is the most common constituent of a vulnerable plaque. Consequently, intensive studies in intracoronary imaging have been conducted to demonstrate the relationship between the imaging findings and the cardiovascular events. However, the results from such trials remain

controversial. In this chapter, we summarize the currently available coronary imaging techniques and the ongoing development of imaging technologies that detect vulnerable plaque. The clinical application of multimodalities imaging in detecting vulnerable plaque in clinic also discussed.

2. Definition and terminology of vulnerable plaque

The term "vulnerable plaque" has been established as a nomenclature to describe the instability of the plaque at a high risk of disruption, leading to thrombosis and rapid stenosis progression [2–4]. Retrospective autopsy studies reported that the most common histopathological finding associated with plaque rupture was thin-cap fibroatheroma (TCFA), which accounted for 55–60%, in 30–35% plaque erosion and in 2–7% calcified nodule [5]. However, it should be noted that not all TCFAs will rupture, nor will all ruptures lead to a cardiac event [3], but disruption and healing is the mechanism of plaque growth [6] and high-grade stenosis [7]. Consequently, the term "vulnerable patient" has been introduced to indicate the patient who has a high likelihood to develop cardiac events. It remains to be investigated whether we should identify and treat these kinds of vulnerable lesions or patients by coronary intervention before inducing clinical events.

3. Current imaging technique

3.1. Noninvasive imaging to detect vulnerable plaque

3.1.1. Coronary computed tomography angiography

Noninvasive imaging techniques could provide the unique opportunities to evaluate the entire coronary arteries and atherosclerotic plaque beyond luminal narrowing in single examination. Coronary computed tomography angiography (CCTA) has been intensively studied to establish its role for detecting vulnerable plaque and prognostic information of recurrent cardiovascular events.

CCTA has shown its capability to characterize plaque composition similar to intravascular ultrasound (IVUS) by the automated software to quantify the plaque. However, the limited spatial and contrast resolutions of CT preclude the detection of some histological features of vulnerable plaques such as fibrous cap thickness or plaque rupture [8]. Nevertheless, some distinct CCTA morphologies associate with high risk of acute cardiovascular events and should be considered as high-risk plaque: [1] large plaque volume; [2] low CT attenuation plaque (LAP); [3] napkin-ring sign (NRS); [4] positive remodeling (PR) and [5] spotty calcification. The total plaque volume measured by CCTA was independently associated with the coronary events [9, 10]. The patients who develop acute coronary syndrome (ACS) had total plaque volume and total noncalcified plaque volume at baseline higher than those who did not develop ACS (median 94 vs. 29 mm^3; $P < 0.001$ and 28 vs. 4 mm^3; $P < 0.001$, respectively)

[9]. Low CT attenuation plaques, defined by <30 HU, were frequently observed in patients with ACS [11] and ruptured fibrous cap [12]. Napkin-ring sign is defined as central low-attenuation plaque with a peripheral rim of higher CT attenuation. It has been suggested that napkin-ring sign is the result of differences in CT attenuation between the large necrotic core (a central low CT attenuation) and fibrous plaque tissue (ring-like higher attenuation) [13]. Presence of NRS is strongly associated with future ACS events, independent of other high-risk coronary CTA features (presence of obstructive plaque, positive remodeling, low-attenuation plaque) [14], and also associated with the presence of TCFA defined by optical coherence tomography (OCT) [15]. Postmortem data reported that positive remodeling is associated with a high macrophage count and large lipid core [16]. CCTA-derived remodeling index has a consistent with histopathological data, lesion with positive remodeling (remodeling index ≥1.1) on CCTA, are associated with a higher percent of the necrotic core and a higher prevalence of the TCFA assessed by virtual histology intravascular ultrasound (VH-IVUS) than those lesions without positive remodeling [17]. In a retrospective study of 1059 patients who underwent CCTA, patients with positive remodeling with low-attenuation plaques were associated with high risk of subsequent ACS as compared to those without such features. (HR: 22.8, 95% CI: 6.9 to 75.2, $p < 0.001$) [9]. Spotty calcification on CCTA is defined as a small, dense (>130 HU) plaque component surrounded by noncalcified plaque tissue and size <3 mm. Small spotty calcification (< 1 mm) was related to vulnerable plaque features defined by VH-IVUS [18]. From all of the above features, CCTA would be considered as a tool to detect vulnerable plaque in the future.

3.1.2. Cardiac magnetic resonance (CMR) imaging

Compared with CCTA, cardiac magnetic resonance (CMR) identifies coronary stenosis >50% comparable to CCTA [19] where it could provide a superior in defining soft tissue such as positive remodeling and increased coronary wall thickness [20]. High-intensity coronary signal on T1-weighted MRI is associated with vulnerable morphology [21, 22] and future cardiac events. It has been demonstrated that high-intensity signal is related to the formation of methemoglobin during subclinical plaque rupture or hemorrhage [23]. T2-weighted short inversion recovery sequences have shown their ability to detect coronary wall edema relating to culprit ACS lesions [24]. However, coronary assessment by CMR is hampered by an inherent susceptibility to motion artifact from prolonged acquisition time [25] that limits its application in clinical practice.

3.1.3. Combined positron emission tomography (PET)-CCTA

Despite the fact that CCTA and MRI demonstrate morphological characterization of plaque, they could not quantify the degree of plaque inflammation. The positron emission tomography (PET) has been combined with computed tomography to identify the anatomical and degree of inflammation. Although ^{18}F–fluorodeoxyglucose (FDG) is acknowledged as conventional tracer in this field, it is hampered by significant myocardium uptake [26] and arterial wall with inflammation. To avoid the myocardial metabolism artifact, ^{18}F–sodium fluoride (NaF) has been introduced to circumvent the myocardial uptake issue. ^{18}F–NaF could localize individual

coronary plaque with minimal background uptake. ^{18}F–NaF is a useful tool to detect molecular calcification which closely linked to plaque rupture. It also provides reliable identification and localization ruptured and high-risk coronary plaque in post-MI setting [27]. The ongoing trials (PREFFIR, NCT02278211 and NCT02110303) aim to investigate the prognostic value of ^{18}F–NaF coronary microcalcification to predict the progression and recurrent of events.

3.2. Invasive imaging to detect vulnerable plaque

3.2.1. IVUS and its derivatives

3.2.1.1. Grayscale IVUS

Grayscale IVUS (GS-IVUS) provides robust information of vessel dimension, lumen dimension, phenotype and distribution of the plaque. GS-IVUS has been incorporated in the guideline as a supporting tool to guide percutaneous coronary intervention in selected lesions [28]. It has been reported that increase plaque burden is associated with adverse cardiovascular outcomes [29]. The major drawback of GS-IVUS is the imprecision to detect lipid-rich plaque which is a marker of the plaque vulnerability [30]. Several GS-IVUS features have been reported that they linked to high risk for cardiovascular events: *Echo-attenuated* plaque was identified by the absence of the ultrasound signal behind plaque that was either hypoechoic or isoechoic to the reference adventitia without calcification [31]. This feature indicated the presence of a large NC or lipid pool, and the closer the attenuation was to the lumen, the more advanced of NC [32]. *Echolucent plaque* contained an intraplaque zone of absent or low echogenicity surrounded by tissue of greater echodensity. Echolucent zone indicated the presence of a relatively smaller NC or lipid pool compared with echo-attenuated plaque [32]. *Spotty calcification* contained small calcium deposits within arcs of <90°. IVUS spotty calcification is closely related to the presence of an NC, also indicating plaque instability [32].

Besides the ability to demonstrate plaque morphology, IVUS was fused with the coronary angiography to reconstruct the blood flow simulation model to examine the local hemodynamic forced on coronary plaque progression. The PREDICTION (Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology) Study, which is done in 374 patients with ACS, showed that the large plaque burden and low local endothelial shear stress (ESS) are independent predictor of plaque progression and lumen narrowing with positive predictive value of 41% [33].

3.2.1.2. Virtual histology intravascular ultrasound

Due to the limited ability of IVUS to determine the composition of plaque, the IVUS radiofrequency analysis (virtual histology, VH) has been introduced to characterize the plaque components. The main difference between GS-IVUS and VH-IVUS is that the GS-IVUS imaging is formed by the envelope (amplitude) of the radiofrequency signal, whereas VH-IVUS analysis uses several additional spectral parameters to identify four tissue types [34, 35]: fibrous (dark green), fibrofatty (yellow-green), necrotic core (red) and dense calcium (white). VH-IVUS-derived TCFA is defined by necrotic core-rich (>10% of the cross-sectional area) plaque being

in contact with the lumen and with a percent plaque volume of 40% seen on at least three consecutive images [36]. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial [37] reported the efficacy of VH-IVUS in predicting lesions that will progress and cause cardiovascular events in 697 patients with ACS. The investigators reported that plaque burden of 70% or greater, minimal lumen area of 4.0 mm^2 or less, and TCFA phenotype were associated with recurrent events after a median of 3.4 years of follow-up with a positive predictive value of 18.2%. The similar trend was reported in VIVA (VH-IVUS in Vulnerable Atherosclerosis) trial, and nonculprit TCFA phenotype was associated with nonrestenotic MACE, on both individual plaque and whole-patient analysis [38].

3.2.1.3. Intravascular ultrasound near-infrared spectroscopy

Near-infrared spectroscopy is an analytical technique that is used in science and industry to determine the chemical composition of substances [39]. A sample of interest is illuminated with near-infrared (NIR) light (800–2500 nm in wavelength) which is absorbed by C–H, O–H and N–H bonds. Each given molecule has a unique pattern of absorption known as its spectroscopic fingerprint. Therefore, NIRS could provide sample recognition and tissue classification [40]. NIRS has been applied to the catheter-based device to identify and quantify lipid cores which is the major composition of the TCFA, the most common type of vulnerable plaque [5]. In addition, NIRS can image through calcium, whereas conventional IVUS, VH-IVUS and OCT are not capable. The current intravascular ultrasound near-infrared spectroscopy (IVUS-NIRS) catheter, TVC Imaging System™ (InfraRedx Inc. Burlington, MA, USA), is CE (Conformité Européenne) marked and has an FDA clearance for lipid core-containing coronary plaques (LCP) detection. The information from the catheter will be processed via mathematical algorithm that predicts the probability of vulnerable plaque and are displayed on a chemogram, with lipid pools colored yellow in a background of red [39]. The "block chemogram" provides visual interpretation of the algorithm probability from zero to one for likelihood of LCP in the corresponding 2-mm chemogram segment (yellow $P > 0.98$, tan $0.84 \leq P \leq 0.98$, orange $0.57 \leq P < 0.84$ and red $P < 0.57$) [3]. The lipid core burden index (LCBI) represents the lipid burden in a vessel segment. LCBI is the fraction of valid pixels within the scanned region that exceed an LCP probability of 0.6 per million (%, multiplied by 1000) [40]. The $\text{maxLCBI}_{4\,\text{mm}}$ indicates sites of high lipid accumulation and is defined as the LCBI of the most lipid-rich 4-mm area within the segment of interest [39]. It should be noted that NIRS could provide only information about lipid core plaque, but it is not able to evaluate the depth and the volume of lipid core.

The autopsy-based study has shown that catheter-based NIRS system accurately identified LCP and IVUS-NIRS system significantly improved the sensitivity for detecting a histological fibroatheroma, especially in calcified lesions and lesions with a smaller plaque burden [41]. The data from diabetic/hypercholesterolemic animal model showed that IVUS-NIRS imaging detected and predicted future development of high-risk coronary lesions such as increased plaque and necrotic core areas, thinned fibrous cap, increased concentration of activated inflammatory cells and apoptotic cells within the fibrous cap [42, 43]. Recently, Oemrawsingh et al. has reported that coronary LCBI in patients with stable angina pectoris (SAP) or acute

coronary syndrome (ACS) is associated with 1-year adverse cardiovascular events throughout the entire coronary tree and not necessarily at the imaged segment or a lesion-specific risk [44]. Madder et al. reported that detection of LRP at nonstented sites was also associated with an increased risk of future major adverse cardiovascular events [45]. The ongoing PROSPECT II (NCT02171065), the Lipid-Rich Plaque (NCT02033694) [46] and ORACLE-NIRS (NCT02265146) will support the concept of vulnerable patient identification and may improve a better care in such patients.

3.2.1.4. Intravascular photoacoustic imaging

Intravascular photoacoustic imaging (IVPA) is an analytic technique, which is highly specific for lipid type. The principle of photoacoustics is based on the optical contrast which is provided by the differences in the absorption spectra of plaque components to image plaque composition [47], like NIRS. However, it has depth resolution, which makes IVPA possible to know the exact spatial location of the lipids within the plaque relative to the lumen border [47]. Lipid in the plaque mainly consists of cholesterol and cholesterol esters, whereas pericardial fat is stored as mixture of fatty lipid. IVPA could differentiate between lipid in the plaques and periadventitial fat. It is postulated that this modality would offer detailed assessment of plaque vulnerability and evaluation of the pharmacologic plaque modulation in future clinical studies. However, the hurdle of IVPA is that the image quality drastically deteriorates in the presence of the luminal blood that may require blood clearance during image acquisition [47]. The clinical application of IVPA remains to be demonstrated in clinical studies.

3.2.2. Optical coherence tomography and its derivatives

3.2.2.1. Optical coherence tomography

OCT uses low-coherence, near-infrared light (1.3 μm wavelength) emitted through a fiber optic wire with rotating lens [48]. The image is created based on reflection time and the intensity of the backscattered light [49]. The resolution of OCT image (10–20 μm axial and 20–40 μm lateral) allows precise visualization of the plaque morphology [48, 50]. It also enables the measurement of fibrous cap thickness [51, 52]. Another unique ability of OCT is identification of macrophages, which are relatively large (20–50 μm) [53], neovascularization [54–56] and microcalcifications [48].

Due to its limited tissue penetration (1–3 mm), it remains impossible to precisely assess the deeper layers behind light-attenuating plaques and thus accurate plaque volume. The imaging artifacts also lead to the misclassification of the stable plaque type to high-risk plaque type. For instance, tangential artifact can mimic superficial accumulation of macrophages or necrotic core [48, 57]. It has been demonstrated that not all bright spots are caused by macrophages and only 23% of bright spots represent macrophages. Other sources of bright spots can be generated by a combination of plaque components that create sharp changes in the index of refraction [58].

Besides the direct assessment of the plaque morphology, OCT also allows vascular profiling of coronary arteries that enables microenvironment study within the coronary arteries [59]. The advancement of computed fluid dynamic (CFD) in combination with precise OCT images

extends our current understanding of endothelial shear stress (ESS). OCT-based assessment of local ESS in nonculprit arterial regions of 21 patients presenting with acute coronary syndrome has shown that segments with low ESS (< 1 Pa) had higher prevalence of lipid-rich plaques (37.5 vs. 20.0%; $P = 0.019$) and thin-cap fibroatheroma (12.5 vs. 2.0%; $P = 0.037$) compared with segments with higher ESS (≥ 1 Pa) [60]. Additionally, areas with low ESS as compared to those with high ESS showed larger lipid accumulation, thinner fibrous cap, and greater macrophage density, which would contribute to plaque vulnerability [60].

3.2.2.2. Optical coherence tomography and near-infrared spectroscopy

Although OCT could provide excellent image resolution, its limitation is the light penetration depth and the capability to detect the plaque composition. The optical coherence tomography and near-infrared spectroscopy (OCT-NIRS) system utilizes a wavelength-swept light source for both OCT and NIRS. The catheter collects the backscattered OCT light together with the chemical substances from the plaque residing within the arterial wall [61]. Therefore, it will eliminate the uncertainty of plaque-type interpretation and will facilitate identification of the high-risk plaque location.

3.2.2.3. Optical coherence tomography and near-infrared autofluorescence (OCT-NIRAF)

Several intracoronary imaging methods have been developed to visualize plaque. However, those techniques could not provide the status of inflammation. Therefore, the molecular imaging of atherosclerosis has been studied to address the inflammatory activity, macrophage composition, presence of fibrin, cellular apoptosis and neoangiogenesis [62]. One of the molecular imaging-based approaches is near-infrared fluorescence (NIRF) [63]. The NIRF can detect the deposition of the indocyanine green (an FDA-approved NIRF-emitting compound) in lipid-rich and atherosclerotic plaques [64].

Due to the requirement of exogenous agent in NIRF technique, the "near-infrared autofluorescence (NIRAF)" has been developed to detect fluorescence from naturally occurring molecules. It has been reported that the combination of OCT and red-excited NIRAF (633 nm) with emission detected between 700 and 900 nm can be used to detect necrotic core and TCFA in cadaver coronary arteries [65]. Recently, Ughi et al. report the first-in-man study of optical coherence tomography and near-infrared autofluorescence (OCT-NIRAF) in 12 patients undergoing percutaneous coronary intervention. They showed that OCT-NIRAF was as safe as conventional OCT in terms of the capability to provide automatic and facilitated image interpretation [66].

3.2.2.4. OCT light property analysis

Despite the excellent resolution of OCT, the image interpretation of plaque morphology based on qualitative criteria can be ambiguous and time-consuming. To overcome those limitations, the automatic classification of atherosclerotic plaque and quantitative assessment of tissue characteristics with OCT light property analysis are investigated. Light property has three components: light intensity, light attenuation and backscatter. The light intensity indicates the amount of light signal detected at a certain location in the vessel wall based on reflection and

backscatter. The light attenuation, estimated as the depth-resolved attenuation coefficient, indicates how fast the light signal decays. It is the rate of exponential decreasing intensity related to the light propagation depth. The backscatter, estimated as the depth-resolved back-scattering coefficient, is related to the efficiency of light scattering in the tissue [67].

In ex vivo validation experiments, highly attenuating regions (attenuation coefficient $\mu_t \geq 8\ mm^{-1}$) have been associated with necrotic core or macrophages. Conversely, low attenuating regions $\mu_t < 6\ mm^{-1}$ were associated with healthy vessel, intimal thickening or calcified plaque [68, 69]. Thus, by using light attenuation analysis, it could detect the lipid-rich plaque component.

Liu and colleagues extended the light property analysis with light intensity and backscatter in addition to the light attenuation analysis [67]. They evaluated the light property values in each tissue type (fibrous, lipid, calcium, calcium with lipid, macrophages and necrotic core) in histology-matched OCT images and found that all tissue types have their own spectrum of light property, suggesting the possibility of automatic tissue characterization with OCT light property analysis in the near future.

4. Clinical application of multimodality imaging in detecting vulnerable plaque

4.1. Assessment of the effect of pharmacotherapy on plaque modulation

OCT has been used to evaluate the plaque stability by statin therapy, and an increase in fibrous cap thickness in coronary plaques was observed after the treatment [70, 71]. Recently, IVUS has been used to evaluate the effect of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors on the progression of coronary atherosclerosis in statin-treated patients. PCSK9 inhibition with evolocumab was associated with a reduction in percent atheroma volume for evolocumab (−0.95%) but not placebo (+0.05%) and a greater percentage of patients demonstrating plaque regression (64.3 vs. 47.3%) [72].

4.2. Assessment of the effect of local therapy on vulnerable plaque

Previously, bioresorbable scaffold (BRS) has been investigated for the capability of sealing superficial plaque [73–75]. The neointima on top of the BRS struts altered the plaque phenotype by covering the calcific spots and TCFA, thus transforming the TCFA to thick-cap fibroatheromas that associate with the plaque stability without compromising the luminal dimensions [73]. It has been speculated that BRS may prevent the cardiac adverse event by invasive sealing of the high risk to rupture plaques. The ongoing PROSPECT ABSORB (NCT02171065) trial will examine the treatment of vulnerable plaques with the ABSORB bioresorbable vascular scaffold (BVS) plus guideline-directed medical therapy (GDMT) in comparison with GDMT alone [76]. All randomized patients will undergo 2-year follow-up angiography with three-vessel repeat NIRS-IVUS imaging, thus enabling evaluation of plaque regression/progression in intervening vessels and nonintervening vessels [77]. The

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SECRITT-II study will investigate the ability of BVS to expedite the process of de novo fibrous cap formation in comparison with high-dose statin therapy [77].

5. Future perspective

Aside from the technical issues and validity of each imaging modality in detecting vulnerable plaque, and predicting the future events, a real question is whether identification of vulnerable plaque would have any impact on our practice [78–80]. Although it has been demonstrated that VH-IVUS TCFA is able to predict recurrence of events, the positive predictive value was 18% [37] with the risk of catheter-related complication of 0.6–1.6% [33, 37]. Thus, the improvement of imaging technologies is required to provide complete and detailed evaluation of plaque morphology, physiology, and biology to predict the future events [81]. New hybrid catheters have shown their capabilities in demonstrating the plaque vulnerability; however, the clinical benefit needs confirmation by larger studies. Noninvasive technique, especially CCTA combined with PET, may support the detection of vulnerable plaque and tailoring the treatment of those patients.

6. Conclusion

Either noninvasive or invasive imaging techniques have their unique properties in detecting the vulnerable plaque; however, none of the individual imaging techniques is able to provide complete plaque assessment. There has been a considerable effort to develop the imaging modalities that offer detailed visualization of coronary pathology and accurately predict the adverse cardiac outcomes. Combination of imaging techniques in single examination would provide mechanistic insight into the development and pathophysiology of the vulnerability of the plaque. To translate imaging information into clinical application, it requires randomized trials investigating whether interventions according to the imaging findings can improve clinical outcomes, along with an intensifying improvement of imaging technologies.

List of abbreviations

CCTA	Coronary Computed Tomography Angiography.
CE	Conformité Européenne.
CI	Confident Interval
CMR	Cardiac Magnetic Resonance Imaging.

FDA	Food and Drug Administration (US).
HR	Hazard Ratio.
MACE	Major Adverse Cardiac Events.
MI	Myocardial Infarction.
NC	Necrotic Core.
LCB	Lipid Core Burden Index.
LCP	Lipid Core-containing coronary Plaques.
LRP	Lipid-Rich Plaques.
SECRITT	vShield Evaluated at Cardiac Hospital in Rotterdam for Investigation and Treatment of TCFA.

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References

[1] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS medicine. 2006;**3**(11):e442

[2] Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death. Arteriosclerosis, Thrombosis, and Vascular Biology. 2000;**20**(5):1262

[3] Waxman S, Ishibashi F, Caplan JD. Rationale and use of near-infrared spectroscopy for detection of lipid-rich and vulnerable plaques. Journal of Nuclear Cardiology. 2007;**14**(5): 719-728

[4] Schaar JA, Muller JE, Falk E, Virmani R, Fuster V, Serruys PW, et al. Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. European heart Journal. 2004;**25**(12): 1077-1082

[5] Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the Vulnerable Plaque. Journal of the American College of Cardiology. 2006;**47**(8, Supplement):C13-C8

[6] Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, et al. Healed plaque ruptures and sudden coronary death: Evidence that subclinical rupture has a role in plaque progression. Circulation. 2001;**103**(7):934-940

[7] Mann J, Davies MJ. Mechanisms of progression in native coronary artery disease: Role of healed plaque disruption. Heart (British Cardiac Society). 1999;**82**(3):265-268

[8] Maurovich-Horvat P, Ferencik M, Voros S, Merkely B, Hoffmann U. Comprehensive plaque assessment by coronary CT angiography. Nature reviews Cardiology. 2014;**11**(7): 390-402

[9] Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. Journal of the American College of Cardiology. 2009;**54**(1): 49-57

[10] Kristensen TS, Kofoed KF, Kuhl JT, Nielsen WB, Nielsen MB, Kelbaek H. Prognostic implications of nonobstructive coronary plaques in patients with non-ST-segment elevation myocardial infarction: A multidetector computed tomography study. Journal of the American College of Cardiology. 2011;**58**(5):502-509

[11] Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. Journal of the American College of Cardiology. 2007;**50**(4):319-326

[12] Ozaki Y, Okumura M, Ismail TF, Motoyama S, Naruse H, Hattori K, et al. Coronary CT angiographic characteristics of culprit lesions in acute coronary syndromes not related to plaque rupture as defined by optical coherence tomography and angioscopy. European Heart Journal. 2011;**32**(22):2814-2823

[13] Seifarth H, Schlett CL, Nakano M, Otsuka F, Karolyi M, Liew G, et al. Histopathological correlates of the napkin-ring sign plaque in coronary CT angiography. Atherosclerosis. 2012;**224**(1):90-96

[14] Otsuka K, Fukuda S, Tanaka A, Nakanishi K, Taguchi H, Yoshikawa J, et al. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. JACC Cardiovascular imaging. 2013;**6**(4):448-457

[15] Kashiwagi M, Tanaka A, Kitabata H, Tsujioka H, Kataiwa H, Komukai K, et al. Feasibility of noninvasive assessment of thin-cap fibroatheroma by multidetector computed tomography. JACC Cardiovascular imaging. 2009;**2**(12):1412-1419

[16] Varnava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. Circulation. 2002;**105**(8):939-943

[17] Kroner ES, van Velzen JE, Boogers MJ, Siebelink HM, Schalij MJ, Kroft LJ, et al. Positive remodeling on coronary computed tomography as a marker for plaque vulnerability on virtual histology intravascular ultrasound. The American Journal of Cardiology. 2011;**107**(12):1725-1729

[18] van Velzen JE, de Graaf FR, de Graaf MA, Schuijf JD, Kroft LJ, de Roos A, et al. Comprehensive assessment of spotty calcifications on computed tomography angiography: Comparison to plaque characteristics on intravascular ultrasound with radiofrequency backscatter analysis. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 2011;**18**(5):893-903

[19] Hamdan A, Asbach P, Wellnhofer E, Klein C, Gebker R, Kelle S, et al. A prospective study for comparison of MR and CT imaging for detection of coronary artery stenosis. JACC Cardiovascular imaging. 2011;**4**(1):50-61

[20] Miao C, Chen S, Macedo R, Lai S, Liu K, Li D, et al. Positive remodeling of the coronary arteries detected by magnetic resonance imaging in an asymptomatic population: MESA (multi-ethnic study of atherosclerosis). Journal of the American College of Cardiology. 2009;**53**(18):1708-1715

[21] Matsumoto K, Ehara S, Hasegawa T, Sakaguchi M, Otsuka K, Yoshikawa J, et al. Localization of coronary high-intensity signals on T1-weighted MR imaging: Relation to plaque morphology and clinical severity of angina pectoris. JACC Cardiovascular imaging. 2015;**8**(10):1143-1152

[22] Ehara S, Matsumoto K, Shimada K. The clinical value of high-intensity signals on the coronary atherosclerotic plaques: Noncontrast T1-weighted magnetic resonance imaging. International Journal of Molecular Sciences. 2016;**17**(7):1187

[23] Moody AR, Murphy RE, Morgan PS, Martel AL, Delay GS, Allder S, et al. Characterization of complicated carotid plaque with magnetic resonance direct thrombus imaging in patients with cerebral ischemia. Circulation. 2003;**107**(24):3047

[24] Kim WY, Christiansen EH, Thrysoe SA, Al-Mashhadi RH, Botker HE, Bottcher M, et al. First in vivo demonstration of coronary edema in culprit lesion of patient with acute coronary syndrome by cardiovascular magnetic resonance. Circulation Cardiovascular imaging. 2011;**4**(3):344-346

[25] Scott AD, Keegan J, Firmin DN. Motion in cardiovascular MR imaging. Radiology. 2009; **250**(2):331-351

[26] Dweck MR, Chow MW, Joshi NV, Williams MC, Jones C, Fletcher AM, et al. Coronary arterial 18F-sodium fluoride uptake: A novel marker of plaque biology. Journal of the American College of Cardiology. 2012;**59**(17):1539-1548

[27] Joshi NV, Vesey AT, Williams MC, Shah ASV, Calvert PA, Craighead FHM, et al. ^{18}F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: A prospective clinical trial. The Lancet. 2014;**383**(9918):705-713

[28] Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: The task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European Heart Journal. 2014;**35**(37):2541-2619

[29] Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. Journal of the American College of Cardiology. 2010;**55**(21):2399-2407

[30] Low AF, Kawase Y, Chan YH, Tearney GJ, Bouma BE, Jang IK. In vivo characterisation of coronary plaques with conventional grey-scale intravascular ultrasound: Correlation with optical coherence tomography. EuroIntervention : Journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2009;**4**(5):626-632

[31] Pu J, Mintz GS, Brilakis ES, Banerjee S, Abdel-Karim AR, Maini B, et al. In vivo characterization of coronary plaques: Novel findings from comparing greyscale and virtual histology intravascular ultrasound and near-infrared spectroscopy. European Heart Journal. 2012;**33**(3):372-383

[32] Pu J, Mintz GS, Biro S, Lee JB, Sum ST, Madden SP, et al. Insights into echo-attenuated plaques, echolucent plaques, and plaques with spotty calcification: Novel findings from comparisons among intravascular ultrasound, near-infrared spectroscopy, and pathological histology in 2,294 human coronary artery segments. Journal of the American College of Cardiology. 2014;**63**(21):2220-2233

[33] Stone PH, Saito S, Takahashi S, Makita Y, Nakamura S, Kawasaki T, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: The prediction study. Circulation. 2012;**126**(2):172-181

[34] Garcia-Garcia HM, Gonzalo N, Regar E, Serruys PW. Virtual histology and optical coherence tomography: From research to a broad clinical application. Heart (British Cardiac Society). 2009;**95**(16):1362-1374

[35] Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. Circulation. 2002;**106**(17):2200-2206

[36] Rodriguez-Granillo GA, Garcia-Garcia HM, Mc Fadden EP, Valgimigli M, Aoki J, de Feyter P, et al. In vivo intravascular ultrasound-derived thin-cap fibroatheroma detection using ultrasound radiofrequency data analysis. Journal of the American College of Cardiology 2005;**46**(11):2038-2042

[37] Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. New England Journal of Medicine. 2011;**364**(3):226-235

[38] Calvert PA, Obaid DR, O'Sullivan M, Shapiro LM, McNab D, Densem CG, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: The VIVA (VH-IVUS in vulnerable atherosclerosis) study. JACC Cardiovascular imaging. 2011;**4**(8):894-901

[39] Waxman S, Dixon SR, L'Allier P, Moses JW, Petersen JL, Cutlip D, et al. In vivo validation of a catheter-based near-infrared spectroscopy system for detection of lipid Core coronary plaques: Initial results of the SPECTACL study. JACC: Cardiovascular Imaging. 2009;**2**(7):858-868

[40] Kilic ID, Caiazzo G, Fabris E, Serdoz R, Abou-Sherif S, Madden S, et al. Near-infrared spectroscopy-intravascular ultrasound: Scientific basis and clinical applications. European heart journal cardiovascular Imaging. 2015;**16**(12):1299-1306

[41] Kang S-J, Mintz GS, Pu J, Sum ST, Madden SP, Burke AP, et al. Combined IVUS and NIRS detection of Fibroatheromas: Histopathological validation in human coronary arteries. JACC: Cardiovascular Imaging. 2015;**8**(2):184-194

[42] Patel D, Hamamdzic D, Llano R, Patel D, Cheng L, Fenning RS, et al. Subsequent development of fibroatheromas with inflamed fibrous caps can be predicted by intracoronary near infrared spectroscopy. Arteriosclerosis, Thrombosis, and Vascular Biology. 2013;**33**(2):347

[43] Saybolt MD, Lilly SM, Patel D, Hamamdzic D, Llano R, Fenning RS, et al. The vulnerable artery: Early and rapid deposition of lipid in coronary arteries is associated with subsequent development of thin-cap fibroatheromas. EuroIntervention. 2016;**11**(14):e1612-e1618

[44] Oemrawsingh RM, Cheng JM, Garcia-Garcia HM, van Geuns RJ, de Boer SP, Simsek C, et al. Near-infrared spectroscopy predicts cardiovascular outcome in patients with coronary artery disease. Journal of the American College of Cardiology. 2014;**64**(23):2510-2518

[45] Madder RD, Husaini M, Davis AT, VanOosterhout S, Khan M, Wohns D, et al. Large lipid-rich coronary plaques detected by near-infrared spectroscopy at non-stented sites in the target artery identify patients likely to experience future major adverse cardiovascular events. European heart journal cardiovascular Imaging. 2016;**17**(4):393-399

[46] Waksman R, Torguson R, Spad M-A, Garcia-Garcia H, Ware J. Wang R, et al. The Lipid-Rich Plaque Study of Vulnerable Plaques and Vulnerable Patients: Study Design and Rationale. American Heart Journal; 2017 [Epub ahead of print 16 Feb 2017]

[47] Jansen K, van Soest G, van der Steen AFW. Intravascular Photoacoustic imaging: A new tool for vulnerable plaque identification. Ultrasound in Medicine & Biology. 2014; **40**(6):1037-1048

[48] Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: A report from the international working Group for Intravascular Optical Coherence Tomography Standardization and Validation. Journal of the American College of Cardiology. 2012;**59**(12):1058-1072

[49] Suh WM, Seto AH, Margey RJP, Cruz-Gonzalez I, Jang I-K. Intravascular detection of the vulnerable plaque. Circulation: Cardiovascular Imaging. 2011;**4**(2):169

[50] Jang IK, Bouma BE, Kang DH, Park SJ, Park SW, Seung KB, et al. Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: Comparison with intravascular ultrasound. Journal of the American College of Cardiology. 2002;**39**(4): 604-609

[51] Kume T, Akasaka T, Kawamoto T, Okura H, Watanabe N, Toyota E, et al. Measurement of the thickness of the fibrous cap by optical coherence tomography. American Heart Journal. 2006;**152**(4):755.e1-e4

[52] Tenekecioglu E, Albuquerque FN, Sotomi Y, Zeng Y, Suwannasom P, Tateishi H, et al. Intracoronary optical coherence tomography: Clinical and research applications and intravascular imaging software overview. Catheterization and Cardiovascular Interventions. 2017;**89**(4):679-689

[53] Tearney GJ, Yabushita H, Houser SL, Aretz HT, Jang IK, Schlendorf KH, et al. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. Circulation. 2003;**107**(1):113-119

[54] Kitabata H, Tanaka A, Kubo T, Takarada S, Kashiwagi M, Tsujioka H, et al. Relation of microchannel structure identified by optical coherence tomography to plaque vulnerability in patients with coronary artery disease. The American journal of cardiology. 2010; **105**(12):1673-1678

[55] Tian J, Hou J, Xing L, Kim SJ, Yonetsu T, Kato K, et al. Significance of intraplaque neovascularisation for vulnerability: Optical coherence tomography study. Heart (British Cardiac Society). 2012;**98**(20):1504-1509

[56] Kato K, Yonetsu T, Kim SJ, Xing L, Lee H, McNulty I, et al. Nonculprit plaques in patients with acute coronary syndromes have more vulnerable features compared with those with non-acute coronary syndromes: A 3-vessel optical coherence tomography study. Circulation Cardiovascular imaging. 2012;**5**(4):433-440

[57] van Soest G, Regar E, Goderie TPM, Gonzalo N, Koljenović S, van Leenders GJLH, et al. Pitfalls in plaque characterization by OCT: Image artifacts in native coronary arteries. JACC: Cardiovascular Imaging. 2011;**4**(7):810-813

[58] Phipps JE, Vela D, Hoyt T, Halaney DL, Mancuso JJ, Buja LM, et al. Macrophages and intravascular OCT bright spots: A quantitative study. JACC: Cardiovascular Imaging. 2015;**8**(1):63-72

[59] Papafaklis MI, Bourantas CV, Yonetsu T, Vergallo R, Kotsia A, Nakatani S, et al. Anatomically correct three-dimensional coronary artery reconstruction using frequency domain optical coherence tomographic and angiographic data: Head-to-head comparison with intravascular ultrasound for endothelial shear stress assessment in humans. EuroIntervention. 2015;**11**(4):407-415

[60] Vergallo R, Papafaklis MI, Yonetsu T, Bourantas CV, Andreou I, Wang Z, et al. Endothelial shear stress and coronary plaque characteristics in humans: Combined frequency-domain optical coherence tomography and computational fluid dynamics study. Circulation: Cardiovascular Imaging. 2014;**7**(6):905

[61] Fard AM, Vacas-Jacques P, Hamidi E, Wang H, Carruth RW, Gardecki JA, et al. Optical coherence tomography--near infrared spectroscopy system and catheter for intravascular imaging. Optics Express. 2013;**21**(25):30849-30858

[62] Psaltis PJ, Nicholls SJ. Imaging: focusing light on the vulnerable plaque. Nature reviews Cardiology. 2016;**13**(5):253-255

[63] Jaffer FA, Kim D-E, Quinti L, Tung C-H, Aikawa E, Pande AN, et al. Optical visualization of Cathepsin K activity in atherosclerosis with a novel. Protease-Activatable Fluorescence Sensor. Circulation. 2007;**115**(17):2292

[64] Vinegoni C, Botnaru I, Aikawa E, Calfon MA, Iwamoto Y, Folco EJ, et al. Indocyanine green enables near-infrared fluorescence imaging of lipid-rich, inflamed atherosclerotic plaques. Science Translational Medicine. 2011;**3**(84):84ra45-84ra45

[65] Wang H, Gardecki JA, Ughi GJ, Jacques PV, Hamidi E, Tearney GJ. Ex vivo catheter-based imaging of coronary atherosclerosis using multimodality OCT and NIRAF excited at 633 nm. Biomedical Optics Express. 2015;**6**(4):1363-1375

[66] Ughi GJ, Wang H, Gerbaud E, Gardecki JA, Fard AM, Hamidi E, et al. Clinical characterization of coronary atherosclerosis with dual-modality OCT and near-infrared autofluorescence imaging. JACC Cardiovascular Imaging. 2016;**9**(11):1304-1314

[67] Liu S, Sotomi Y, Eggermont J, Nakazawa G, Torii S, Ijichi T, et al. Tissue characterization with depth-resolved attenuation coefficient and backscatter term in intravascular optical coherence tomography images. Journal of Biomedical Optics. 2017;**22**(9):1-16

[68] van Soest G, Goderie T, Regar E, Koljenovic S, van Leenders GL, Gonzalo N, et al. Atherosclerotic tissue characterization in vivo by optical coherence tomography attenuation imaging. Journal of Biomedical Optics. 2010;**15**(1):011105

[69] Ughi GJ, Adriaenssens T, Sinnaeve P, Desmet W, D'Hooge J. Automated tissue characterization of in vivo atherosclerotic plaques by intravascular optical coherence tomography images. Biomedical Optics Express. 2013;**4**(7):1014-1030

[70] Takarada S, Imanishi T, Kubo T, Tanimoto T, Kitabata H, Nakamura N, et al. Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: Assessment by optical coherence tomography study. Atherosclerosis. 2009;**202**(2): 491-497

[71] Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, et al. Effect of atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque as assessed by optical coherence tomography: The EASY-FIT study. Journal of the American College of Cardiology. 2014;**64**(21):2207-2217

[72] Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, et al. Effect of Evolocumab on progression of coronary disease in statin-treated patients: The GLAGOV randomized clinical trial. Journal of the American Medical Association. 2016;**316**(22): 2373-2384

[73] Bourantas CV, Serruys PW, Nakatani S, Zhang YJ, Farooq V, Diletti R, et al. Bioresorbable vascular scaffold treatment induces the formation of neointimal cap that seals the underlying plaque without compromising the luminal dimensions: A concept based on serial optical coherence tomography data. EuroIntervention. 2015;**11**(7):746-756

[74] Tenekecioglu E, Bourantas CV, Onuma Y, Serruys PW. Sealing of calcified plaques after bioresorbable scaffold implantations: A five-year follow up. The International Journal of Cardiovascular Imaging. 2017;**33**(4):451-452

[75] Brugaletta S, Radu MD, Garcia-Garcia HM, Heo JH, Farooq V, Girasis C, et al. Circumferential evaluation of the neointima by optical coherence tomography after ABSORB bioresorbable vascular scaffold implantation: Can the scaffold cap the plaque? Atherosclerosis. 2012;**221**(1):106-112

[76] Uppsala University. PROSPECT II & PROSPECT ABSORB - an Integrated Natural History Study and Randomized Trial. [cited 04-03-2017]. Available from: https://clinicaltrials.gov/ct2/show/NCT02171065

[77] Ahmadi A, Stone GW, Leipsic J, Shaw LJ, Villines TC, Kern MJ, et al. Prognostic determinants of coronary atherosclerosis in stable ischemic heart disease: Anatomy, physiology, or morphology? Circulation Research. 2016;**119**(2):317-329

[78] Tuzcu EM, Weissman NJ. Imaging coronary artery histology: A virtual pursuit? Circulation Cardiovascular Imaging. 2010;**3**(4):348-350

[79] Arbab-Zadeh A, Fuster V. The myth of the "vulnerable plaque": Transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. Journal of the American College of Cardiology. 2015;**65**(8):846-855

[80] Libby P, Pasterkamp G. Requiem for the 'vulnerable plaque'. European Heart Journal. 2015;**36**(43):2984-2987

[81] Patel K, Tarkin J, Serruys PW, Tenekecioglu E, Foin N, Zhang YJ, et al. Invasive or noninvasive imaging for detecting high-risk coronary lesions? Expert Review of Cardiovascular Therapy. 2017;**15**(3):165-179

Chapter 7

"Calendarium Vitae" for Hospice Patients and their Caregivers: A Pilot Study

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Additional information is available at the end of the chapter

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Abstract

Although palliative care is designed to provide holistic comfort care and support, several patients still experience loss of purpose in life, and suffer from distress, sadness, anxiety, or decreased quality of life (QoL). To address these unmet needs, novel interventions, focused on psychosocial sources of distress, in hospice patients are needed. One such intervention is dignity therapy (DT), defined as a brief, individualized psychotherapy, applied for the purpose of relieving psychological distress at the end of life. "Calendarium Vitae" (CV) as a form of DT represents a feasible, safe, and effective, patient-friendly approach, targeting end-of-life psychological issues. In particular, DT can alleviate suffering and distress, help preserve psychophysical integrity, and support caregivers, during the bereavement period. This pilot study is designed to collect preliminary data, prior to conducting a larger randomized controlled trial (RCT) that will investigate the correlations of DT intervention with QoL, and possible reduction of distress and suffering, in the Eastern and Central European hospice patients (and their caregivers). Since DT is unknown in this part of Europe, the proposed pilot study, followed by RCT, will be the first step on the way to explore the DT intervention in research, among the vulnerable hospice patient population.

Keywords: hospice, terminal disease, palliative care, distress, suffering, coping strategies

1. Introduction

1.1. Scientific aim of the project

Background: Despite enormous progress that has been made in reducing the morbidity and mortality from a variety of neoplastic diseases, a large number of cancer patients progress to

advanced stages of malignancy. Such patients are usually referred for palliative care services, and if their prognosis is estimated to be less than 6 months, they are often admitted to the hospice setting [1]. In case of an incurable metastatic cancer, in addition to multiple disease-related physical symptoms, many of such patients painfully experience loss of purpose in life and severe distress [2]. Although palliative care is designed to provide holistic comfort care, spiritual and psychosocial support until the end of life (and also during bereavement, for family members), several hospice patients still suffer from psychological distress and decreased quality of life (QoL).

To fulfill these unmet needs, novel interventions, able to directly address psychosocial sources of distress, among the hospice patients are needed [3–5]. One such intervention is dignity therapy (DT), defined as a brief, individualized psychotherapy, applied for the purpose of relieving psychological distress at the end of life [6]. Based on scientific evidence from published research in this field, derived from international studies, DT has been shown to be a feasible and effective novel strategy that targets psychophysical suffering in terminally ill patients [7]. In particular, DT attempts to help such patients reflect upon issues that are most meaningful to them, and document them in form of the "final document" [8]. However, DT is unknown in Eastern and Central Europe, and thus should be explored among hospice patients in these countries.

1.2. The study hypothesis

The study hypothesis is that the proposed pilot study will gather necessary information to create a foundation for a further randomized controlled trial (RCT) that will explore the correlations (or impact) of dignity therapy (DT) intervention with quality of life (QoL), and possible reduction of distress and suffering, among the hospice patients in Eastern and Central Europe.

It is expected that the patients in the DT intervention group (study group, SG) might have improved QoL, compared to the control group (CG), receiving a standard palliative care only. In addition, the caregivers of patients in the DT intervention group (SG) may also have improved QoL and psychophysical health condition during bereavement, compared to the control group (CG).

2. Psychophysical and social importance of the study theme

2.1. State of the art relevant to knowledge on dignity therapy (DT) intervention in hospice setting

In many palliative care programs, a significant progress in pain management and symptomatic control has been accomplished among patients with terminal stages of metastatic cancer. However, despite these advances, dignity-related issues, including loss of personal autonomy and sense of purpose in life, or feeling a burden to family represent common causes of spiritual suffering, psychological distress (e.g., anxiety and depression), and decreased

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quality of life (QoL) among hospice patients. To respond to this challenge, innovative strategies are necessary. One such exemplary intervention is called dignity therapy (DT) [9]. DT is a psychotherapeutic intervention that was developed by Prof. Chochinov and colleagues, in 2012, in Canada. The main goal of DT is to decrease emotional and spiritual suffering, enhance quality of life, and increase a sense of meaning and purpose of life among terminally ill patients near death. In particular, DT attempts to help such patients reflect upon things that are most meaningful to them, and collect these memories in form of the "final document" [9].

Dignity therapy question protocol (DTQP) is a set of standard questions that a therapist asks during an interview (conveniently conducted at the bedside) with the patient [10]. Evidence from recent research studies (conducted in Canada, Australia, and the USA) has revealed significant reduction of sense of suffering, depressed mood, and improvement in sense of dignity among terminally ill patients [11]. In summary, DT was found to be satisfactory to the patients, helpful to their relatives during grief period, and acceptable to the hospice personnel (e.g., better relations with patients and increased job satisfaction were reported) [12, 13].

2.2. Justification of the study theme

The proposed novel pilot study is going to explore the correlations between the perceived distress (anxiety, sadness, and depression) and emotional suffering (related to terminal stages of cancer), and DT intervention (in form of the Calendarium Vitae, CV) in hospice patients.

An analysis of the data from this pilot study is going to answer the following research questions:

1. Is the DT intervention (used in the design of this study) feasible for the local hospice system?
2. In which way the study should be adapted to the local hospice setting?
3. Can this study estimate some effects in the area of psychological distress, and in quality of life (QoL) that are expected to happen in relation with the DT intervention?
4. Can this study assess the effects on psychophysical health of the caregivers (e.g., family members) of the hospice patients that are expected to happen with the DT intervention?

2.3. Justification of the innovative character of the study

Although many hospice patients suffer from psychological distress (anxiety and depression), they are usually not aware of potential benefits of the DT intervention. According to the scientific literature, implementation of DT, as one of the components of comprehensive palliative care, represents a manageable therapeutic approach to hospice population that might, to some extent, improve coping with end of life psychosocial distress, and alleviate mental and spiritual suffering. Therefore, DT—as an innovative, simple, safe, patient-friendly, and

cost-effective option to fulfill unmet needs among growing population of hospice patients—deserves an analysis in research. Moreover, it can be expected that in the future, depending on the preliminary study results, a possible implementation of DT, as a supportive care option, added to standard palliative care, could bring some beneficial effects for many suffering patients at the end-of-life stage in Eastern and Central European countries.

2.4. The importance of the study results for the development of scientific discipline and civilizational progress

The results of the proposed project (as evidenced in a recent, substantial body of scientific literature in this field) will have a significant impact on the development of several scientific disciplines, such as psycho-oncology, psychology, medicine, nursing, rehabilitation, pedagogy, humanistic, or social sciences, as well as general civilizational progress, civilizational progress oriented on universal human values.

In addition, research infrastructure, created in this study, will provide a unique opportunity for education and training of students and postgraduates in psycho-oncology and related disciplines. Moreover, the project will create a support network and educational center for caregivers ("care for the caregivers"), hospice personnel and volunteers, as well as students or postgraduates, working on their MS degrees in the above-mentioned medical, psychological, social, pedagogical, or other disciplines related to the health care. On the basis of the above facts, exploring DT intervention as a potential component of multidisciplinary palliative care is justified in the hospice setting and merits support. In conclusion, research studies (both pilot and RCT) investigating various aspects of DT (in form of the CV intervention) should have a chance of being conducted in hospice patients in Eastern and Central Europe.

3. The main concept and aims of the pilot study

3.1. Dignity therapy: a concept of the study

A concept of the study is dignity therapy (DT), which has international scientific recognition (as safe and effective supportive therapy), but is unknown in Eastern and Central Europe and should be explored in research (e.g., first in a pilot study and then in RCT) among hospice patients in Eastern and Central European countries.

The pilot study will collect preliminary data, prior to conducting a larger randomized controlled trial (RCT) that will investigate the correlations (impact) of dignity therapy (DT) intervention with quality of life (QoL), and possible reduction of distress and suffering in the Eastern and Central European hospice patients. Also, for caregivers of the study patients, the effects of DT intervention, in relation to their psychophysical health condition, during bereavement will be explored. Simultaneously, the caregivers will be asked to provide their opinions about the DT intervention.

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For the purpose of this study, a form of DT intervention, which is also called "Calendarium Vitae" (CV), involves both patients and (whenever possible) caregivers (participating as a team: patient and caregiver). The patients will be asked questions about their most important achievements, roles, and other important aspects of their life. In addition, CV intervention encourages patients to saying things to their loved ones that have remained unsaid. At the same time, CV invites the caregivers to contribute to the creation of the DT final document (CV album) that will be a "treasure" for the family and friends during bereavement.

3.2. The primary aims of this pilot study

The primary aims of this pilot study are as follows:

- Test feasibility of the dignity therapy (DT) before conducting a larger randomized clinical trial (RCT) among hospice patients in Eastern and Central European countries.
- Adapt the DT intervention to local health care circumstances (Eastern and Central European hospice patients).
- Learn the caregiver perspectives with regard to the benefits and possible concerns of DT intervention, when provided as a therapeutic procedure, added to palliative care.

3.3. The particular goals of RCT

The particular goals of RCT are as follows:

- To examine whether the addition of dignity therapy (DT) in form of the Calendarium Vitae (CV) to standard palliative care (PC) could reduce psychological distress (anxiety and depression) and augment quality of life among the hospice patients (Pts) in Eastern and Central European countries.
- To test whether the addition of the CV intervention (to standard PC for the patients) could influence their caregiver's psychophysical health.
- To conduct a follow-up assessment of the caregiver psychophysical health (post 6–12 months).

These findings will be compared to the results of the control group receiving standard PC.

3.4. A possible adaptation of the pilot study into Eastern and Central European hospice setting: initial plan of the study

It is estimated that in this study, a total of about 100 patients diagnosed with an advanced neoplastic disease and poor prognosis (life expectancy < 6 months), who receive palliative care in the hospice, will be randomly assigned to either DT (CV) or PC in a 1:1 ratio. Patients will be prescreened and included to the study, if they report increased psychological distress (anxiety or depression, based on the Hospital Anxiety and Depression Scale (HADS)).

The therapy will be guided by therapists (working in teams with postgraduate students). CV consists of three tape-recorded + one final sessions. The main goal of the CV intervention is to invite patients to reflect on their most important accomplishments, roles in their lives, or other things that they would most want to be remembered. Upon completion of the intervention, the recorded sessions will be transcribed and edited to provide a clear narrative CV document (album) that can be given to a person selected by the patient (e.g., family member, friend), or donated to hospice (as an option). The proposed CV intervention, in addition to the original DT model, introduces a patient-caregiver "team" approach in which both the patient and the caregiver (usually a close family member) actively participate in creation of the final DT document (CV album) (e.g., the patient is mostly involved with the 1st, "conceptual" part, and the caregiver is helping with the 2nd "executive" part, by "gathering evidence" (such as photos, for the CV album).

4. Study methodology

4.1. Methodology and implementation of the pilot study

Study design RCT: Interventional, experimental, prospective, randomized, controlled, parallel, with a follow-up (6–12 months).

Study group (SG): Hospice patients (with caregivers, women, and men, aged >18, with preserved cognitive skills, diagnosed with advanced cancer, with life expectancy <6 months), receiving palliative care at the stationary or home hospice setting, plus DT. Control group (CG) (similar in size to the SG), hospice patients (as in SG), receiving standard palliative care at the stationary or home hospice setting.

4.1.1. Study intervention

Calendarium Vitae (CV), as a form of DT, involves patients and caregivers (as teams) asking the patients questions about their most important achievements, roles, and other important aspects of life. Simultaneously, CV invites the caregivers to contributing to the creation of the DT final document (CV album).

4.1.2. Eligibility criteria

Inclusion criteria for patients (Pts):

- Signed informed consent form
- Diagnosis of advanced cancer, with life expectancy < 6 months
- Receiving palliative care at the hospice (stationary or home)
- ≥18 years of age
- Preserved cognitive skills

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Exclusion criteria for patients (Pts):

- Cognitive impairment (e.g., dementia, delirium)
- Deterioration of illness precluding further participation in the study

Inclusion criteria for caregivers:

- Signed informed consent form
- Taking care of a close relative admitted to hospice (stationary or home), with life expectancy < 6 months
- ≥18 years of age
- A desire to alleviate suffering and distress of the terminally ill relative, beyond standard care

Exclusion criteria for caregivers:

- Physical or mental illness precluding participation in the study

4.1.3. Study outcome measures (OM) and tools

Outcome measures for hospice patients (Pts):

1. Psychological distress: measured by the Hospital Anxiety and Depression Scale (HADS)
2. Health related quality of life: (HRQol)

(Time frame: Pre-postintervention (when the final study document = CV album is received by the patient, and again 2 weeks later)

Outcome measures for caregivers:

1. Psychophysical condition: measured by General Health Questionnaire (GHQ 12) and Patient Health Questionnaire (PHQ 9)
2. Brief survey presenting caregivers' opinions about the benefits and possible concerns relevant to the dignity therapy (in form of the CV), added to standard PC

(Time frame: 1, pre-postintervention, and again 2 weeks later; 2, with the last evaluation)

The main study procedures:

Orientation meeting for the study therapists, investigators, coordinators, hospice staff, and caregivers. CV intervention includes four sessions:

1. introduction (60');
2. intake session (60');
3. editing session (60');
4. final session (60')

(each session could be extended to 2 hours, depending on the patient's condition)

All sessions will be conducted by a team, including a therapist (e.g., a psychologist, or a physician) and a student (a graduate student preparing MS thesis, or a specially trained hospice volunteer (optional))

All therapy sessions will be tape-recorded, transcribed, edited by the team and returned to the patient and the caregiver.

Construction and editing of the CV album requires a brief training session for the team members (to assure quality of care and to avoid bias)

Total duration of pilot study: 2 weeks (intervention) + 3 months follow-up.

Total duration of RCT: 2 weeks (intervention) + 6, 12 months follow-up.

Statistical analysis: descriptive statistics.

Equipment: laptops, dictaphones, paper, pens, pencils, graphic, and printing services.

4.2. Detailed description of the study operationalization: logistics of the study

4.2.1. Setting

This study will be conducted in Eastern and Central European hospice setting. Therapists (such as psychologists or physicians in collaboration with MS students, forming teams) who are interested and eligible to participate in the study and who are professionally involved with palliative care (PC) hospice settings will be invited to participate. It is estimated that the number of therapist-investigators should be approximately 2–4.

4.2.2. Investigators

Before initiation of the program, each team will receive an individual training with regard to the study design, procedures, and methodology, as described in the study protocol. In addition, every therapist-investigator will be trained in DT, in order to conduct the DT intervention.

4.2.3. Participants

Adult patients with terminal stage of cancer (<6 months prognosis) who are referred by their attending physicians (oncologists or family physicians) for palliative care (PC) hospice service and who express their interest in participation in the study will be invited as candidates, shortly after admission to hospice within the study recruitment period. The participants will be recruited from adult oncology patients, discharged from the University Hospitals or Oncology Centers.

4.2.4. Recruitment

Information about the study, together with an invitation to participate in it, will be conveyed to potential candidates, during routine hospice visits via flyers, posters, and also through

advertisements in local newspapers, and via the Internet. Interested patients (and their caregivers) will receive detailed information regarding the DT course and will be screened (with the HADS). First-inclusion and exclusion criteria will be checked in a standardized interview, and then the patients (and the caregivers) will have a brief introduction conducted by the study investigator or coordinator.

It is estimated that the number of participants screened for the study should be approximately 100, in order to enroll into the study about 10–20 patients with terminal cancer, for the study group (SG), and about 10–20 patients, for the control group (CG). Eligible candidates will sign an ICF (after explanations about the study principles and voluntary participation in it) and will be enrolled into the study, which will be commenced in the year 2017.

4.2.5. Study groups

In 2017, about 100 adult patients, who suffer from terminal cancer (diagnosed at least 3 months prior to entering of the pilot study) will be randomized to a study group or control group.

The study group (SG) (N = 10–20) will be composed of women and men with terminal cancer, with <6 months prognosis, aged >18 years, treated with a standard palliative care will receive DT intervention.

The control group (CG) (similar in size, age, diagnosis, and prognosis to the SG) will be composed of hospice patients and will receive a standard palliative care (PC) only.

Duration of the study DT intervention equals to 2 weeks, and includes: 2-week DT process, with 4 bi-weekly sessions (the study intervention = Calendarium Vitae, CV).

The patients in the SG will be obligated to:

- participation in the DT sessions; and
- filling out research questionnaires.

The patients in the CG will be receiving PC only, and filling out research questionnaires.

The pilot study participants in both groups will continue their regular, standard PC.

4.2.6. Management of randomized controlled trial (RCT) examining DT intervention among hospice patients.

After completing of the pilot study, a subsequent step of recruitment of the volunteers-participants for the RCT (DT in hospice patients) will be conducted according to the same design, by therapists-investigators in the year 2017, and continued for the consecutive steps of the project.

As in the pilot study, during the above-mentioned recruitment periods, the therapists-investigators will invite to take part in this trial, a larger number of patients with terminal cancer admitted to hospice care facility. Adult men and women (>18 years of age) with

terminal cancer and <6 months prognosis, who are interested in participation in the trial will be given information about the study, upon admission to hospice, within the trial recruitment phase.

In the process of recruiting the hospice patients-volunteers to RCT (including distribution of the trial information and pre-screening via the standardized interview and HADS), the same methodology as in the pilot study will be used.

It is estimated that the number of participants screened for the RCT should be approximately 500, in order to enroll into the trial about 50–100 patients with terminal cancer for the study group (SG) and 50–100 patients with terminal cancer for the control group (CG).

Eligible candidates, who meet the Inclusion/exclusion criteria, will sign an ICF (after explanations about the trial principles, and voluntary participation in it), and will be enrolled into the trial, which will start in the year 2018. The trial will use the same procedures (including randomization), eligibility criteria, psychometric measurements, and outcome measures, as the pilot study. In 2019, a follow-up of this trial will be conducted using the same outcome measures as the ones used in the pilot study.

4.2.7. Inclusion/exclusion criteria: (pilot study and trial (RCT))

Eligibility criteria: Inclusion/exclusion for participants (as previously listed)

Based on:

- screening interview,
- meeting of the inclusion criteria (all the responses are Yes),
- meeting of the exclusion criteria (all the responses are No), and
- signing a voluntary informed consent form (ICF),

patients who meet qualification criteria will be enrolled into the pilot study/RCT.

The data derived from the study participants will be summarized and then utilized in statistical analyses. Pilot study parameters, which will be analyzed, according to the questionnaire, prepared for the purpose of this study, will contain the following variables:

1. The participant's identification number (for confidentiality purposes)
2. Date of birth (age)
3. Gender
4. Education (higher, medium, or elementary level)
5. Place of residence (country, town)
6. Type of the cancer
7. Duration of the oncological therapy—how many years?

8. State of health prior to a diagnosis of cancer
9. Presence of serious/chronic diseases—what kind?

With regard to caregivers of the study patients, the analogical questionnaire (with modification of items 6–9) will be used as follows:

1. The caregiver's identification number (for confidentiality purposes)
2. Date of birth (age)
3. Gender
4. Education (higher, medium, or elementary level)
5. Place of residence (country, town)
6. Type of the cancer of the relative admitted to hospice care
7. Duration of to taking care of the relative with terminal cancer—how many years?
8. State of health prior to taking care of a relative with terminal cancer, admitted to hospice
9. Presence of preexisting serious/chronic diseases—what kind?

The electronic database will be created using software program, and analyses of variables will be performed, utilizing the statistical program. Decisions regarding exclusion of the records from the statistical analyses will be made in the case of:

1. lack of the complete answers in the questionnaire form;
2. illegible or ambiguous record in the questionnaire, precluding proper evaluation of variables in statistical analyses;
3. lack of written signature of the study/trial participant (informed consent form); and
4. documented information of the therapist-investigator regarding further participation in the study.

Psychometric measurements will be taken on the day of initial survey completion, and then post-DT intervention, and again, one 2 weeks after it. The study teams will collect the data using the study clinical report forms (CRF), based on the patients' questionnaires and psychometric measurements obtained during the study visits.

DT intervention (described in detail in another section) will be offered in one hospice center and will consists of a 1–2 hour sessions, 2 times per week (for 2 weeks), during which, the participants will complete the DT final document = CV album (including "life reflection interview" that will be transcribed and revised, before final edition of the CV album). The primary focus of the DT is to have a positive reflection on life, leading to decreased psychophysical distress and suffering that should translate into better QoL. Similarly, for the caregivers, the

main focus of the DT is to be able to better cope with stress and suffering, related to terminal disease of the relative.

4.2.8. Study timeline

Schedule of the research visits.

V# 1—Orientation/introduction (0 week),

V# 2—Intake/interview (1 week),

V# 3—Revision/edition (2 weeks),

V# 4—Final (3 weeks).

Abbreviations used in the schedule: V—visit.

From a practical point of view, the pilot study and RCT will analyze the measured psychological parameters, which characterize daily distress and health-related quality of life (QoL). Similarly, for the caregivers, the parameters that characterize psychophysical health will be analyzed. These measurements are easily available and can be promptly and safely conducted in the hospice setting. In addition, the caregivers will complete a survey related to the DT intervention benefits or possible concerns.

4.2.9. Statistical analysis

SG and CG will be compared using chi-square analysis for discrete data and independent *t*-tests for continuous data on demographics and baseline variables. For each outcome measure (except the caregivers' survey), the results of the DT intervention will be compared by analyses of covariance (ANCOVA) taking the postintervention measurement as dependent values. Respective baseline value of the outcome (V1) will served as a covariate. Within the statistical model, the group variable will serve as between-subject factor, and the postintervention measures as dependent factors. Statistical significance is set at the 0.05 level. The intention-to-treat principle will be used in this study. The CV transcript will be analyzed for content. All the statistical analyses will be conducted using the statistical program.

4.2.10. Reference therapy

Usual palliative care in patients with terminal cancer includes medically indicated nonpharmacological therapy, combined with pharmacological comfort care (e.g., pain control) and holistic care, focusing on management of psychophysical and spiritual needs and personal care (e.g., skin care). Despite that many hospice patients suffer on a daily basis from loss of personal autonomy, dignity, as well as mental distress, depression, and anxiety, in addition to physical discomfort.

Safety, potential risk of the study: No risk/adverse effects to participants have been documented with regard to the DT intervention.

Study discontinuation: The participants may withdraw from the study due to any reason, without any consequences, and they will continue palliative care.

Limitations of the study: The interpretation of the results might be limited due to a small sample size.

Conflict of interests: There is no conflict of interests.

5. Conclusion

In summary, dignity therapy (DT) (based on research evidence from international studies, published in scientific literature) represents a feasible, safe, and effective, patient-friendly approach, targeting end-of-life psychological problems. DT has a unique potential to help patients with terminal stages of cancer. In particular, DT can fulfill some unmet psychological and spiritual needs, help preserve psychophysical integrity, and distress, as well as support caregivers, during the bereavement period [3, 6, 11, 13]. Since DT is unknown in Eastern and Central Europe, the proposed pilot study, followed by RCT, will be the first step on the way to explore the DT intervention in research among hospice patients in this area.

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References

[1] Chochinov HM. Health care, health caring, and the culture of medicine. Current Oncology. 2014 Oct;**21**(5):e668-9

[2] Chochinov HM. The secret is out: Patients are people with feelings that matter. Palliative Supportive Care. 2013;**11**:287-288

[3] Corn BW, Chochinov HM, Vachon M. Integrating spiritual care into the practice of oncology. Current Opinion in Supportive and Palliative Care. 2012;**6**:226-227

[4] Sinclair S, Norris JM, McConnell SJ, Chochinov HM, Hack TF, Hagen NA, et al. Compassion: A scoping review of the healthcare literature. BMC Palliative Care. January 19, 2016;**15**:6. DOI: 10.1186/s12904-016-0080-0

[5] Sinclair S, McClement S, Raffin-Bouchal S, Hack TF, Hagen NA, McConnell S, Chochinov HM. Compassion in Health Care: An empirical model. Journal of Pain and Symptom Management. 2016;**51**:193-203

[6] Chochinov HM. Dignity in care: Time to take action. Journal of Pain and Symptom Management. November 2013;**46**(5):756-759. DOI: 10.1016/j.jpainsymman.2013.08.004. Epub 2013 Oct 5

[7] Houmann LJ, Rydahl-Hansen S, Chochinov HM, Kristjanson LJ, Groenvold M. Testing the feasibility of the dignity therapy interview: Adaptation for the Danish culture. BMC Palliative Care. September 22, 2010;**9**:21. DOI: 10.1186/1472-684X-9-21

[8] Chochinov HM, McClement S, Hack T, Thompson G, Dufault B, Harlos M. Eliciting personhood within clinical practice: Effects on patients, families, and health care providers. Journal of Pain and Symptom Management. 2015;**49**:974-80.e2

[9] Houmann LJ, Chochinov HM, Kristjanson LJ, Petersen MA, Groenvold M. A prospective evaluation of dignity therapy in advanced cancer patients admitted to palliative care. Palliative Medicine. 2014;**28**:448-58

[10] Chochinov HM, McClement SE, Hack TF, McKeen NA, Rach AM, Gagnon P, et al. The patient dignity inventory: Applications in the oncology setting. Journal of Palliative Medicine. 2012;**15**:998-1005

[11] Montross L, Winters KD, Irwin SA. Dignity therapy implementation in a community-based hospice setting. Journal of Palliative Medicine. 2011;**14**:729-734

[12] Chochinov HM, McClement SE, Hack TF, McKeen NA, Rach AM, Gagnon P, et al. Health care provider communication: An empirical model of therapeutic effectiveness. Cancer. 2013;**119**:1706-1713

[13] Montross LP, Meier EA, De Cervantes-Monteith K, Vashistha V, Irwin SA. Hospice staff perspectives on dignity therapy. Journal of Palliative Medicine. 2013;**16**:1118-1120

Clinical Trials

Chapter 8

Ethical Aspects of Vulnerable Group of Patients in Clinical Trials

Ekaterina Ivanova, Ilko Getov and Hristina Lebanova

Additional information is available at the end of the chapter

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Abstract

The current publication aims to review and analyse the ethical aspects and regulations to protect the category of vulnerable patients, as defined in the European legislation. These patients need special protection and require more detailed approach throughout the clinical trials' life cycle.

Keywords: clinical trials, vulnerable patients, ethical aspects, informed consent

1. Introduction

According to the National Institutes of Health USA, the number of clinical trials shows a stable trend for growth. Nearly 28% of all clinical trials worldwide are conducted in Europe [1]. It is therefore important that clinical trials are regulated legally and monitored with needed level of detail. They must also comply with the ethical standards that promote respect for human beings and protect their health and well-being.

Often, researchers included patients who are vulnerable and need special protection. The chapter aims to provide an overview of the ethical issues in clinical trials with vulnerable patients.

Based on European legislation, specifically Regulation (EU) No. 536/2014 of the European Parliament and Council and ICH GCP E6 (R1), several categories of so-called vulnerable groups of patients might be defined:

1. Pregnant or breastfeeding women
2. Minors

3. Students and employees
4. People suffering from multiple chronic conditions or terminally ill
5. Ethnic minorities
6. Older people
7. Military
8. People affected by mental health disorders

Each of the listed groups has its specific need, which has to be taken into consideration. While standard requirements towards clinical trials life cycle are outlined in European legislation, some ethical issues related to the vulnerable groups of patients need to be also part of ethical codes of conduct or local legislation. These include additional requirements related to the objectives of the study, risk-benefit assessment, strict adherence to the study protocol and additional steps in the course of obtaining informed consent.

It is important to constantly improve access to treatments available for vulnerable groups. Therefore, medical products of significant clinical value should be appropriately studied for their effects in these specific populations. Vulnerable groups of patients require more detailed approach and in cases when the legislation does not provide needed level of detail or is outdated, ethical issues outlined in the chapter could be taken into consideration by members of ethics committees and investigational staff.

2. Clinical trials on women of reproductive age, pregnant or breastfeeding

Until the early 1990s of the twentieth century, the inclusion of women of reproductive age in clinical trials Phases I and II is very limited. One of the reasons behind this is FDA's 1977 guideline, which recommended excluding women with childbearing potential from participating in early phases of drug trials. The recommended exclusion was broadly applied to any 'premenopausal female capable of becoming pregnant', but explicitly did not apply to women with life-threatening diseases [2]. The results of such a major limitation were:

- the rights of sick women were limited, as they cannot get timely treatment with more effective drugs;
- the efficacy of many medical products on the women was unknown, although they were prescribed both men and women.

Thus, in 1993, under pressure from the public and the scientific community, FDA issued 'Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs', according to which women should be allowed to determine for themselves the appropriateness of participating in early clinical trials [2].

In 1998, experts from the World Health Organisation (WHO) and United Nations (UN) issue a report 'Women and Health Mainstreaming the Gender Perspective into the Health Sector' [3]. The report concludes women need to be included in clinical trials, but their participation must be accompanied by informed consent.

Thus, the inclusion of women of **reproductive age** in clinical trials remains a pivotal issue. Ethical committees must ensure proportional participation of both sexes in order to obtain reliable trial data; however, the inclusion of women in the study should only take place when drug safety data is available and measures to protect women's and future offspring's health are undertaken. Women should receive information about the risks on their reproductive system and contraception methods during the study. They should immediately inform the medical team in the event of planned or already occurred pregnancy.

Studies on **pregnant women** should only be conducted in cases when the required data cannot be obtained from another patient's categories and when the purpose of the study corresponds to the mother's and foetus's health needs with minimal risk. It is mandatory that the informed consent is obtained, and information about possible consequences for the health of the women, foetus or future child is promptly communicated.

Studies related to monitoring **pregnancy, childbirth and the postpartum period** are usually conducted to evaluate the standards and pathologies during pregnancy, childbirth, postpartum and breastfeeding periods. Some of them are targeting diseases arising during pregnancy (hypertension, diabetes, etc.). In cases when a standard therapy does not work, it is necessary to conduct experimental treatment. In cases when the benefit is minimal and the risk for a woman or foetus is indefinite or high, the testing should be stopped. However, provided that the test drug is vital for a pregnant woman, her consent may be sufficient to implement the experimental therapy—even if the risk to the foetus is unknown or exceeds the minimum.

There are no specific guidelines for the inclusion of **breastfeeding women**. Nonetheless, the ethical committee should pay close attention to the safety of the health of breastfed children (mother's own child or the one who gets the breast milk). Medical team should regularly take samples from the breast milk and monitor the composition and protein component in colostrum or milk.

As defined by European legislation, along with standard requirements, additional conditions should be in place for a clinical trial on pregnant or breastfeeding women. Some of them are as follows:

- The clinical trial is required to indicate a direct benefit for trial subject (pregnant or breastfeeding woman, or her embryo or child). The benefit should outweigh the risks involved.
- If the research involves a breastfeeding woman, additional actions need to be taken to ensure no negative impact on child's health.

In cases where there is no direct benefit for the trial subjects (pregnant or breastfeeding woman, or her embryo or child), a clinical trial can only be allowed:

- if it cannot be conducted on other patient groups;
- if it contributes greatly to obtaining results which could be beneficial to pregnant or breast-feeding women, or other children or embryos;
- if it holds minimal risk to the subjects [4].

3. Clinical trials on minors

In paediatrics, it is often that methods and therapies are applied based on studies conducted on adults. But the results in children are not always the same. Therefore, the treatment for children needs to constantly improve and enhance based on clinical trials conducted on children population. However, the best interests of the child should be a primary consideration.

According to the Convention on the Rights of the Child adopted by the UN General Assembly in 20 November 1989, the children have the same rights as adults. Thus, clinical trials on children should meet the same requirements needed for such trials on adults. However, due to children's vulnerability, they require special care and additional protection of their interests. It is essential to obtain informed consent, assess the risks to the child and minimise the fear and pain during the study.

There are two main concepts on the child's participation in a clinical trial:

- Informed consent
- Assent

For the first time, the term assent is mentioned in the Declaration of Helsinki, which states that when a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative [5].

Prior including a child into a clinical trial, his assent needs to be obtained. If such is missing, this fact, along with reasonable explanations of the same, needs to be noted in the Informed Consent of child's parents or legally authorised representative. Child's assent alone is not sufficient; it should always be accompanied with the informed consent of the parents. If a child reaches age of legal competency during the trial, his informed consent should be obtained and enclosed to the study documentation.

However, the degree of child's involvement in the decision depends on its age and maturity. Ethical committee can determine the age of the child when it can give consent to participate. This decision should comply with the local laws. Only the child's age, however, is not determinative of whether it is capable of giving consent to participate. The level of development, intellectual ability and experience may also be decisive. In all cases, trial information provided to a child needs to be adapted to its age and mental maturity.

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The ethical expertise usually assesses and determines the risks and the benefits of clinical trials. The main principle is that the best interests of the child shall be a primary consideration. In practise, risk assessment on children depends on many factors. For example, taking a small quantity of blood from a child suffering from haemophilia creates risk, significantly exceeding the minimum. Children suffering from a chronic disease usually perceive easier various medical treatments. So they are at less risk compared to children who have no similar experience in illness.

During clinical trials on children, it is important to reduce and mitigate painful manipulations, by applying effective methods of pain reduction—usage of corresponding equipment and personnel trained or experienced in working with children.

Clinical studies on minors would also include some additional requirements:

- No incentives or financial benefits are allowed. The only exception that can be considered is a compensation for expenses directly related to the clinical trial.
- The medical condition being treated occurs only in minors population.
- The clinical trial aims to validate data already collected on adult population to confirm it can be applied in minors.
- The clinical trial relates directly to a medical condition of a child.

4. Clinical trials on students and employees

When attracting healthy volunteers, it is imperative that they take the decision to participate in a clinical trial on their own and without pressure. They should receive all needed information related to the trial and declare their voluntary informed consent. Volunteers are usually compensated for their time, discomfort and possible risks. Thus, ethical commission is to make sure that these cash compensations are not unreasonably high and that attracted patients are not from category that is easily persuaded and influenced (*people with low incomes or without education*).

Healthy volunteers are usually patients in Phase I clinical trials. The task of this phase is to evaluate drug's safety, determine a safe dosage range, pharmacokinetics and side effects.

The researcher should consider possible action in the event that a patient volunteer gets sick or hurt during the tests. These actions must be thoroughly listed in the informed consent form:

- Whether the patient will receive medical treatment and at whose expenses in case he gets sick or hurt during the course of the study
- Primary point of contact in case of injury
- Opportunity to withdraw from the clinical trial at any time without having to provide any justification

The participation of **students and employees** in clinical trials is widely discussed. There are two ethical issues: whether the decision to participate was completely voluntary and privacy concerns.

On the one hand, students' and employees' participation in clinical trials conducted on campus puts under question the free nature of this decision. The student/employee may decide to participate in the study with the idea that his/her participation will be beneficial for the learning process or work conditions (better grades, good recommendations, etc.). Conversely, there is concern that non-participation in the study may have a negative impact on relations with the teaching staff or employer.

On the other hand, the ban on students' and employees' participation in clinical trials limits their right of choice. Therefore, the Good Clinical Practice highlights the requirement to investigator to recruit patients-volunteers exclusively through advertisement of a general nature and not through individual approach to minimise any coercion or pressure in decision-making.

Another ethical concern is data privacy issue. The researched should guarantee protection and confidentiality of personal data of the participants. This may not be so easy to achieve if study involves students or employees of medical institution which conducts the trials. In this case, there is a conflict of interest as participants in the study are students or employees, and the investigational staff is the employer.

5. Clinical trials in emergency situation and on people suffering from incurable diseases

In general, clinical trials with patients who require emergency treatment or intensive therapy differ from studies with patients in stable condition. These differences are mostly related to the problem of obtaining informed consent—the patient has blurred consciousness, unresponsive or unconscious, lack of time and opportunity to discover his legal representatives.

Ethical standards and legislation allow informed consent to be missing in cases where the patient's life is in danger, and alternative ways of treating are missing. In all cases, however, the informed consent shall be sought after the performed emergency intervention to continue the participation of the subject in the clinical trial.

If the patient or his/her legal representative does not give consent, he/she has the right to object to the use of data collected from the clinical study.

The situation is different in clinical trials and treatment of deadly diseases. They suggest another category of patients—terminally ill. Such trials are of a great importance, as often there are no alternative types of patients that might be involved due to this is not justified from the ethical stand point.

It should be borne in mind that it is possible terminally ill patients wrongly to suggest that participation in testing is a necessary condition to receive medical care and that it is better to

receive any medical care than nothing. Some terminally ill patients consider their participation in the trial as an opportunity to be helpful to others. It is therefore important that they are properly informed and do not participate in the trial based on false assumptions.

Nowadays the topical question is around participation of terminally ill patients in Phase I clinical trials from, as medicines in this phase can be dangerous (e.g. a new kind of chemotherapy). Despite the researcher's willingness to be helpful and give positive results of the tests, the patient may not improve or even get worse. For this reason, it is very important for the patient to be thoroughly informed the potential risks and benefits of the research, without giving unnecessary hope. Study participants must be informed whether their participation or non-participation in the study is a prerequisite for treatment in a hospital, and whether the stay in hospital is at patient's cost.

The AIDS epidemic boosts new kind of demand—access to investigational drugs. Many terminally ill patients are willing to take investigational drugs in a clinical trial because there is no other way to get them—they are either not available or too expensive.

In the United States, there are several examples of treatment use of investigational drugs. In 1976, the 'Group C' treatment was established by agreement between FDA and the National Cancer Institute. The purpose of the programme is to distribute investigational drugs to oncologists to treat cancer under studies outside the controlled clinical trial. Another expanded access concept is so-called Parallel Track policy announced by FDA in April 1992, which permits wider access to new drugs for AIDS/HIV-related diseases [6].

In Europe, 'Compassionate use' programmes allow a medicinal product, without marketing authorisation, to be given to patients with a life-threatening disease when no alternative authorised treatments exist. The European Regulation 726/2004/EC provides directions to 'compassionate use' programmes in the European Union. It states that patients must have a chronic or life-threatening disease, and the medicinal product must be undergoing assessment in a clinical trial or be in the marketing authorisation stage. However, details around authorisation procedures are still missing and ultimately the programmes are governed by individual member states [7].

6. Clinical trials on ethnic minorities

Ethical standards suggest unbiased approach to selecting patients—inclusion or exclusion criteria should not be based on gender, race or ethnicity. Most diseases are applicable to all populations, so the researcher must include the most diverse types of patients. This way the results obtained in the course of the study may be useful for all people who are at risk for a disease being treated. The researcher should provide clear justifications on inclusion or exclusion of specific populations.

Yet there are diseases that often occur in certain ethnic groups. For example, sickle cell disorders are more common among people whose ancestors have lived in tropical and subtropical regions. In such studies, the inclusion of patients from specific ethnic minority is a must.

Exclusion or under-representation of ethnic groups would be unfair approach, as thus they are deprived of the equal benefits of treatment during the study.

An example of abuse and racial discrimination is The Tuskegee Study of Untreated Syphilis in the Negro Male (1932–1972). The purpose of this study was to observe the natural progression of untreated syphilis in rural African-American men in Alabama, US.

Usually, clinical trials with homogeneous populations are cheaper. The more diverse the group of test patients is, the more variables occur throughout clinical study live cycle. Ultimately, all this leads to additional costs. Therefore, in cases where patients represent a homogeneous group, the study results should be applicable for the same group and not for the population in general.

When attracting ethnic minorities, investigator and ethics committee should ensure that:

- patients representing ethnic minorities are not exposed to additional risk;
- in cases when representatives of minorities are poor or illiterate, their rights are protected and there is no coercion or undue incentives for their participation in the clinical trial;
- documentation is in a language understandable to the minority patients.

Different racial and ethnic groups experience disease and respond to treatments differently. Therefore, it is important that various populations participate in clinical trials to ensure that the treatments and interventions are going to be relevant to those populations.

7. Clinical trials on older people

Population ageing is a long-term trend which began several decades ago in Europe [8]. The older population (aged 65 years and over) is constantly increasing. As seen on **Figure 1**, European population is projected to continue to age. And therefore, the importance of additional research on diseases typical for older people is becoming increasingly important.

In general, there is no certain age, after which the patient involvement is not recommended. Yet some researchers avoid recruitment of older patients because of certain difficulties they entail. Older people tend not to respect the regime of medications, have difficulties to the specific requirements of the study, especially when they are in conflict with their daily life (diet, daily regime, etc.).

Older people often have problems seeing and hearing, which means more time and effort to explain the purpose and conditions of the study. They tend more often to interrupt their participation in the trial, suggesting larger initial screening of patients.

Despite the above-mentioned complications, participation of older people in clinical trials is absolutely necessary and very important given the overall ageing of the population.

But can the elderly make a conscious choice? It has been known that the elderly people usually perceive new information worse than younger ones. Older people have a bad memory,

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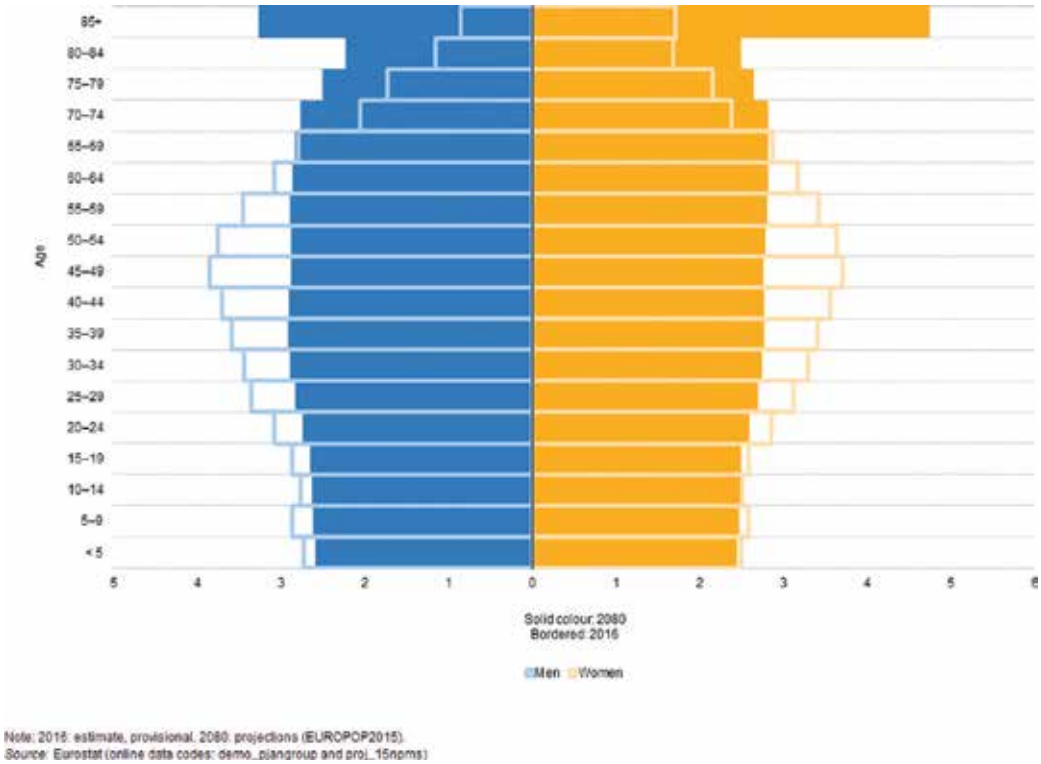

Figure 1. Population pyramids, EU-28, 2015: provisional; estimate. 2080: projections (EUROPOP2013) (% of the total population). Source: Eurostat (online data codes: demo_pjangroup and proj_13npms).

and show lower performance in some cognitive functions—hearing, vision, and reaction time. Thus, older people need more time to absorb and understand a similar volume of mental work than people in younger age.

Thus, in order to ensure that old patients understand and remember information and requirements regarding the study, the researcher is advised to split the procedure of obtaining informed consent in two parts. The purpose of the second part is to verify and confirm whether the old patient understands and remembers the information obtained in the first meeting. Patients who cannot remember important facts about the study should not participate in the trial.

8. Clinical trials on military

In the past, military participation in clinical trials has been quite common for many reasons—controlled diet, easy access to patient homogeneity of the population, etc. But the number of clinical trials conducted in the past in accordance with the norms and principles of Good Clinical Practice is comparatively small.

Examples of some of these studies include radiation exposure, mustard gas experiments and lysergic acid diethylamide (LSD) testing in non-volunteer human subjects [9], not to mention human experimentations before and during the World War II.

The ethical problem with clinical trials on military population is obvious—the military are in a position of subordination and dependency. There are methodological challenges associated with these clinical trials:

- Age range limitation does not allow to determine a strategy for prevention and treatment of the general population.
- Limited duration of the study group. Often, this is associated with the period of military service or contract, as well as frequent redeployments in other locations or divisions.
- Density of settlement contributes to high levels of disease in acute respiratory tract infections.
- Specific conditions of life style and daily regimen during military service may be a factor that could affect the test results.

Thus, clinical studies on military should be initiated and conducted with the consent of the ethical committee only in cases where the data cannot be collected from the civilian population or purpose of the test is the prevention or treatment of conditions and/or diseases peculiar to military population.

An example is the study of the probiotic foods with Lactobacillus bulgaricus. Effect of the probiotic foods with Lactobacillus bulgaricus was investigated on 56 sailors from the Bulgarian Submarine fleet and 60 pilots from the Air Force of Bulgaria, who were put to extensive mental and physical pressure. There are lots of clinical studies of the use of probiotic food containing Lactobacillus bulgaricus as a nutritional support and a part of the medical treatment in 60 cases of severe intoxication accompanied by poly-organic insufficiency. As a result, these probiotic foods were included in the regular diet of the pilots from the Air Force of Bulgaria, sailors from the Submarine fleet of Bulgaria and of commandos [10].

9. Clinical trials on people affected by mental health disorder

Clinical trials involving patients with psychosocial or cognitive disorders, as well as those suffering from drug or alcohol addiction bring up an ethical question—if these patients are able to make their own rational decisions.

People with intellectual or psychosocial disorders are deprived of their legal capacity and put under some form of guardianship. There are two main guardianship models: full and partial. People under partial guardianship keep their main civil rights but certain capacities are transferred to a legal representative, such as financial affairs. Those under full guardianship, on the other hand, lose almost all of their civil rights.

There are European countries where guardians besides other life spheres are also empowered to take decisions on behalf of the individual in regards to health care. Guardian's consent may

result in hospitalisation or medical interventions. This is considered as voluntary, even though the consent from the individual concerned is not present. The interventions might even be against the individual's expressed will, however in a legal sense will still be considered as voluntary. In other European countries, guardians or other legal representatives cannot make health care decisions. However, non-consensual interventions in the psychiatric field are still possible in most countries if a doctor finds them necessary and a court confirms the same.

European legislation outlines additional protection requirements towards inclusion of incapacitated patients into clinical trials:

- The informed consent of the legal representative has been obtained; consent must represent the subject's presumed will and may be revoked at any time, without detriment to the subject.
- Information received during the informed consent process should be adequate in view of the patient's capacity to understand it.
- No incentives or financial inducements are given except compensation.
- There are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all.
- The clinical trial is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical trials on persons able to give informed consent, or by other research methods.
- The incapacitated patient should take part in the informed consent procedure as far as possible [4, 11].

In the past years, the so-called paradigm shift in disability policy is widely discussed. This is a shift from the deprival of legal capacity to the right to support for exercising legal capacity.

Such example is a person diagnosed with Down's syndrome applying for a certain service. If he/she is provided information in easy-to-read format and adequate time and support, he/she may be able to understand pros and cons of the service and choose whether or not to use it. In this situation, no disability arises. However, if information is provided in standard language and no additional effort taken to explain it in a manner adequate to person's condition, disability becomes a fact. The paradigm shift calls for legal, attitudinal and environmental changes [12].

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References

[1] ClinicalTrials.gov a service of the U.S. National Institutes of Health. Map of All Studies on ClinicalTrials.gov [Internet]. October 2015. Available from: https://clinicaltrials.gov/ct2/search/map [Accessed: 23 January 2017]

[2] US Food and Drug Administration. Gender Studies in Product Development: Historical Overview [Internet]. 20 May 2016. Available from: https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134466.htm [Accessed: 23 January 2017]

[3] Expert Group Meeting. Women and Health Mainstreaming the Gender Perspective into the Health Sector. In: United Nations Division for the Advancement of Women Department of Economic and Social Affairs, editors. 28 September - 2 October 1998; Tunis, Tunisia. New York, USA: United Nations Division for the Advancement of Women Department of Economic and Social Affairs; 1998

[4] European Parliament and the Council of the European Union. Regulation 536/2014/EC of the European Parliament and of the Council of 16 April 2004. Official Journal of the European Union [Internet]. 2014. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

[5] World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects [Internet]. June 1964 [Updated: October 2013]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ [Accessed: 23 January 2017]

[6] U.S. Food and Drug Administration. Treatment Use of Investigational Drugs – Information Sheet [Internet]. 19 January 2016. Available from: https://www.fda.gov/RegulatoryInformation/Guidances/ucm126495.htm [Accessed: 24 February 2017]

[7] Kate Whitfield. Compassionate use of interventions: results of a European Clinical Research Infrastructures Network (ECRIN) survey of ten European countries. Whitfield et al. Trials 2010. DOI: https://doi.org/10.1186/1745-6215-11-104

[8] Eurostat Statistics Explained. Population Structure and Ageing [Internet]. June 2016 [Updated: June 2017]. Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Population_structure_and_ageing [Accessed: 24 February 2016]

[9] McManus J. Informed consent and ethical issues in military. Academic Emergency Medicine. 2005;**12**(11):1121

[10] Daflorn Ltd. Laktera [Internet]. 2012. Available from: http://www.laktera.com/probiotics-modern-history.html [Accessed: 24 February 2017]

[11] European Parliament and the Council of the European Union. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 [Internet]. 4 April 2001 . Available from: http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf [Accessed: 15 February 2016]

[12] Commissioner for Human Rights. Who Gets to Decide? Right to Legal Capacity for Persons with Intellectual and Psychosocial Disabilities [Internet]. April 2012. Available from: https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=09000016806da5c0

Chapter 9

Nature of Vulnerability in Biomedical and Psychosocial Research

Pablo Alejandro Millones Gómez

Additional information is available at the end of the chapter

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Abstract

This chapter explores the ethics of research as one of the requirements in daily work, considering the protection of the dignity of subjects and the publication of information. It identifies which are the most vulnerable populations as well as the conflicting ones and the ambiguity in the decision making, which in many occasions recurrently appear in the review of the literature on human research. Also, it described strategies to overcome the ethical difficulties encountered in the call and follow-up, with a cultural sensitivity.

Keywords: vulnerability condition, biomedical, psychosocial research

1. Introduction

Often, ethics committees or thesis jury members are in the uncertainty whether to approve or not some work involving the study in humans under so-called vulnerable conditions. And to what extent this could limit or surpass the rights of study subjects. It is necessary to know in detail what the characteristics of these populations are as well as the strategies to overcome these limitations considering the ethical and moral aspects that allow them. The objective of this chapter is to show basic concepts of studies in vulnerable populations, as well as their most relevant characteristics.

2. Vulnerability condition

It begins by defining vulnerability to disability or disability—temporary or permanent, individual or group—to make a valid assessment of the risk-benefit relationship in the context of

an investigation. It is essentially a condition that compromises the exercise of autonomy. The vulnerability condition is dual, which speaks of the reciprocity of actions between the investigator and the participant. Research becomes vulnerable to the extent that one of its actors exhibits limitations for the full protection of personal integrity.

Vulnerable people have limited capacities to consent; this can be given by the absence of power of choice and decision, as in prisoners; legal capacity to consent, for example, in minors; or ability to understand, as it occurs in people with mental illness. A researcher is also vulnerable when choosing a special population. Ethical shortcomings in the recruitment process or in the same experiment can seriously compromise the generalization of the results to other populations, thus fulfilling the biostatistics conditions. In addition, the criminal and civil consequences that involve the fissures in the ethical structure of a research.

The researcher who includes a special group has to recognize that this fact implies a greater sharpness and refinement in the devices that he uses to obtain his results, and even in the long-term follow-up of those who have been his participants. The Bioethics Committee, for its part, has to monitor and advise with particular rigor the protection of the interests of the people linked to the investigative process.

The Helsinki Declaration of the World Medical Association of October 2000 adds, "Medical research on human beings should be carried out only by scientifically qualified persons and under the supervision of a clinically competent physician. The responsibility of human beings must always rest with a person with medical training, and never with the participants in the research, even if they have given their consent." This warning regarding medical research serves to emphasize the need for the appropriate professional qualification of researchers as a means of reducing the vulnerability inherent in the personnel conducting the study.

Often reflection on vulnerability is concentrated on the participants and the analysis of the conditions of the researchers is neglected. In recent years, proposals have been presented to ensure the ethical transparency of research projects. One of the central points in this order of ideas is the declaration of conflicts of interest. A researcher becomes a vulnerable individual when he or she does not fully state the economic, political, or other interests that may substantially compromise his or her ability to make decisions in the course of research. This is a mode of vulnerability that is just beginning to be explored "researchers must be aware and obliged to declare, not only to the Research Ethics Board, but also to the research subjects, any conflict of interest that they may have and any financial gain they expect to obtain per patient as a result of the recruitment." To this point, it is advisable to make a point the researcher, and of course his work group, can also acquire the condition of vulnerability essentially due to deficiencies in training professional and scientific and also for the partial declaration of conflicts of interest.

Bioethics Committees should be alert to the cautious reviews of protocols that focus exclusively on potential organic damage and do not address the likelihood of moral damage. Written registration in the consent of measures such as limits of confidentiality or the means of communication for the call and follow-up denote the interest to prevent the increase in vulnerability derived from participation in the study.

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3. Level of dependency

For special and vulnerable populations, their relationship with the biomedical and psychosocial research apparatus determines another criterion for evaluating the conditions for the granting of valid informed consent.

Ethical tension is heightened when research is merged with medical care. "Intimidation, in any way that is done, invalidates informed consent. Potential subjects, who are both patients, often depend on the physician/researcher's medical care, which therefore has some credibility before their eyes, and whose influence on them can be considerable, particularly if the protocol of study has a therapeutic component. They may fear, for example, that refusal to participate would damage the therapeutic relationship or mean the omission of health services. The physician/investigator must assure them that their decision to participate will not affect the therapeutic relationship or other benefits to which they are entitled. In this situation, the ethics review committee should consider whether informed consent should be sought by a neutral third party" [1].

The type of link between the researcher and the participant can increase the vulnerability in a bidirectional way. The researcher may feel more comfortable with people who have already been approached clinically and with whom recruitment is usually easier given prior recognition. However, there are several risks such as intimidation, undue influence and even the introduction of statistical bias due to limitations in sampling, which in turn ethically compromise the study by obtaining restricted results in its generalization.

On the patient/participant front, the situation is also equally complex. People can remain in an investigation, against their personal desire, only to avoid a loss or deterioration in the therapeutic attention they are receiving "even a fully capable person may have difficulty objecting to following a project due to their dependence on the relationship medical, and the vulnerability inherent in such dependence" [2].

Additionally, it should be noted how deficiencies in assertiveness can lead to vulnerability in participants. This becomes more prominent in some Latin American populations where the figure of medical personnel is inserted in a paternalistic model of care that confers an almost absolute power in the therapeutic relationship.

Extending the concept of dependence out of the therapeutic context are similar ethical difficulties in doubles as employer/employee or teacher/student. Dependency is connected to subordination. Faced with economic difficulties or problems in academic performance, linking to a research project, even if it seems voluntary and free, may be the effect of an attempt to please the superior and obtain employment or academic opportunities. A teacher can use his charisma and academic prestige to link his students just as a doctor influences his patients.

The level of dependence marks a criterion of special populations and raises a reflection that must always be present in the formulation and revision of research protocols.

4. Capacity/competence

Capacity and competence criteria have traditionally been reviewed in the field of informed consent. The Nuremberg Code identifies voluntary consent as necessary and essential for the conduct of investigations with persons. Considering the capacity and competence in the discussion of special populations is relevant because precisely their evaluation allows the researcher and the Bioethics Committee to establish whether they have the minimum conditions for obtaining valid informed consent and what kind of additional protective devices should be implemented.

Capacity refers to "the necessary physiological, mental and emotional integrity required to make decisions, and therefore to be considered legally competent" [2]. Capacity is a medical term that results from the evaluation that the investigator or a specialized physician performs, among others, the spheres of mental functioning and the organic state in general.

Capacity may be compromised by fluctuations in a chronic disease or by the intensity of an acute event such as encephalocranial trauma. Similarly, states of limited capacity may be medically induced as during general anesthesia or the use of sedative medication in agitated patients. The ability also refers to the proper integration of external stimuli with the internal mental reality and the behaviors that are executed accordingly. To understand, even more, the concept of capacity is required to integrate variables, which, although they make the analysis more complex, enrich the criteria that base a conclusion, in this order are psychophysiological maturity and sociocultural influences.

For its part, the Competition, a legal term, is "a construction that indicates that a person has the necessary capacity to deal with legally defined acts such as signing contracts, witnessing, being prosecuted or accepting medical interventions." The link between capacity and competence guides the basic conditions that a researcher must have when working with people belonging to special populations and with vulnerability.

5. Risk-benefit ratio

This relationship is another of the criteria that must be integrated when making the ethical approach of special populations. It was previously defined as vulnerability to disability or disability, temporary or permanent, individual or group, to make a valid assessment of the risk-benefit relationship in the context of an investigation. The logical sequence is then to describe that the distorted evaluation of the risk-benefit relationship generates vulnerability, which in turn results in the condition of subject or special population.

Perhaps the complex of talking about special populations in these times is not so much to identify groups that for decades have been classically recognized as vulnerable. The focus of the discussion should shift to subjects and populations we call "normal" and in which a significant degree of vulnerability is not perceived. The above is mentioned because it is just

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the distortion in the assessment of risks and benefits added to the explosion of a plethora of economic incentives that can make that transition in the gray scale from nonvulnerable to vulnerable.

A terrain where the slippery slope of bioethics becomes steeper is that of healthy volunteers. They often participate in research where they are exposed to new drugs or procedures without responding to the reality of a disease or condition that is their own. While recognizing their altruism in exposing their well-being, it is questionable when economic or other rewards motivate their link. The reflection points to the fact that the researcher and the Bioethics Committees recognize in these subjects their vulnerability, despite precisely being "normal."

The issue of vulnerability lies essentially in the area of autonomy and respect for people with diminished autonomy, while that of the risk-benefit relationship corresponds to distributive justice. When applying the principle of justice, it should also be understood that the objectives of the research and its likely outcomes account for a problem that affects the level of well-being and health conditions of vulnerable individuals included. In this way, the expectation of interventions and procedures, which directly benefit their health, would justify their participation.

If we use the principle of beneficence, the researcher and his work group must maximize benefits and reduce risks. However, research with special and vulnerable populations requires additional effort to identify and prevent risks before, during and after the intervention. Precisely the vulnerability increases when the study has concluded the individuals present some damage in their integrity and do not find who respond for damages.

In an attempt to circumvent the difficulties involved in obtaining valid informed consent in special populations, the concept of minimum risk has been introduced to justify interventions or research procedures that have no possibility of direct benefit to their health "Minimum risk means that the probability and magnitude of the predicted harm or discomfort in the research are no greater in themselves than those commonly encountered in daily life or during routine physical or psychological examinations or tests" [2].

At this point, it should be noted that even if the investigative intervention is of minimal risk, or slightly exceeds, this does not exempt from seeking the available channels obtaining consent or assent, if any, for the beginning of the same. Any sign of rejection or desire to leave should be respected without having to request rigorous or extensive explanations about it. In addition, the researcher should question about psychosocial risks such as breach of confidentiality, invasion of privacy, or stigmatization and not focus exclusively on physiological organic risk.

The informed consent process must therefore be particularly rigorous so that individuals or their legal representatives have the option of adequately assessing the benefits of linking them to research in the face of risks.

To summarize, special populations have to be evaluated in the convergence of the criteria of vulnerability condition, level of dependency, capacity/competence, and risk-benefit ratio. With these elements in mind, it is possible to continue the discussion on each particular population group.

5.1. Children

This group includes people who have not reached the age of majority are considered legally incompetent to consent. The extent of this human group and the complexity of its inclusion in research projects deserve a close analysis. The ethical nuclei that guide the evaluation of the protocols and the ethical decision making in this case are condensed in the following three points:

1. Research is aimed at addressing the health needs of children; consequently, it requires that it be performed with this population and not with adults.
2. The parents or legal representatives of the child must authorize their participation.
3. The minor agrees to participate by means of the form of assent and in case of refusal, his decision is respected.

On the other hand, four options have been distinguished for the linking of minors to research projects:

1. The "surrogate" solution allows for investigations with children as with other populations if the parents give consent. This solution can increase the chances of damage if included in high-risk projects. The tutorial and protective role of parents should be guided by the search for welfare for minors; parents do not have the moral authority to enroll their children in potentially harmful research projects.
2. The "non-consent-non-research" solution derived from the Nuremberg code proposal represents the hard line in these solutions. It considers that children are not competent to rationally consent and therefore cannot be recruited into an investigation, even if it provides some benefit to them.
3. The solution "no consent—only therapy" arises from the interpretation of the content of the Declaration of Helsinki. He argues that people with lack of capacity to give consent can only be included in projects that investigate therapeutic options for their disease or condition. However, this proviso does not exclude minors from experiencing discomfort from tests and hospitalizations linked to the therapeutic research. On the other hand, it limits the options of producing and renewing useful knowledge to improve the health conditions of children regardless of a therapeutic objective.
4. The "risk-benefit" solution is governed by United States federal regulations. Investigation with minors is permitted if there are reasonable expectations of direct benefit with a minimized and acceptable level of risk. This modality stresses the need for review by ethics committees, obtaining parental consent and consent. This solution tries to determine if the risks are proportional to the benefits for each participant, it also seeks to strike a balance between the social utility of finding new knowledge and protecting the interests of children undergoing experimentation.

Seeking to protect them has been excluded from research projects, more frequently in studies of new drugs. This has produced a paradoxical situation because the use of drugs in children

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ends up being guided by the results obtained in adults, which creates additional risks, unlike projects that are done directly with minors and ethical recommendations. This lack of data and studies with children has led to the formulation of the term "therapeutic orphans" to refer to the situation of inequity in the construction of new knowledge for the therapeutic needs of this population.

Other, more vulnerable subgroups such as fetuses, neonates, and preterm infants can be found in the group of minors. The literature describes cases such as the application of oxygen above the needs of the neonate, leading to blindness and damage to the infant. Crystalline, in therapeutic approaches that were performed without the controlled studies due, it was avoided to perform investigations precisely to not cause damage [3–7].

Researchers must also be alert to expressions of disapproval or refusal of participation by the child, even when parental consent is already available. If it is further considered that the child in question does not have the psychological maturity to accept participation with understanding or giving assent. We are then faced with the figure of deliberate objection. In any case, it should be considered that this does not apply to manifestations such as crying or exaltation to any stimulus. Due to the above, it is also convenient to observe or accompany, if appropriate, a parent while performing the procedures or interventions of the research.

A context in which the vulnerability of minors is multiplied is institutionalization. The formulation and review of research protocols with these children should be especially sensitive to their situation and prevent coercion or undue influence by linking them. They should always be reminded that it is possible to withdraw the research without meaning the discharge of the institution or the loss of special care or care that they require. Researchers must make efforts to explain, as clearly as possible, what the research consists of and how the child's participation will take place, in understandable terms for their age and their cognitive development.

5.2. Women

The condition of women is often pierced by multiple vulnerabilities. In Latin America and the Caribbean, women and their minor children often suffer from more severe situations of inequity and economic underdevelopment.

Traditionally research with women has taken place to address the health difficulties derived from their reproductive role. Results of research on new drugs, such as those performed with men, have often been generalized without studies being conducted to address the particular physiological and sociocultural conditions of women.

The inclusion of women as a "special" or "vulnerable" population has a record of discrimination, since it seems to presuppose a condition of normality in men and an abnormality in them. "Although women have essentially gained this status as special because they are not men, the fact that they menstruate, become pregnant or experience menopause is highlighted as a reason why researchers need to show special consideration if women who go to be included in the studies" [11]. The work of bioethics must consist precisely in assimilating positive discrimination against women and reorganizing it as a source for overcoming conditions of inequity.

In the 1990s, there was a movement in North America that denounced the scant research being done on the health needs of women. It was proposed, then, the implementation of an already existing policy of inclusion of women in research, which would overcome the low representation in the samples usually selected.

In 1991, the American Medical Association recommended that "the results of medical evaluations made only on men should not be generalized to women without the evidence that these results can be safely and effectively applied to both sexes." The recommendations have in some cases yielded positive results in the investigation of new drugs, including the study of gender differences, even if costs are increased.

The policy of protectionism or exclusion of women of childbearing age by the risk of becoming pregnant and thus causing harm to the fetus during experiments with new drugs, procedures, or interventions has paradoxically produced a knowledge gap that ends up violating the situation—health of the mother and the fetus. This situation of injustice is added to the restriction on the autonomy of women.

The inclusion of women as research subjects has also had to overcome arguments such as methodological limitations and increased project costs "For the research findings to be meaningful, sample sizes should not only be large enough but also representative of the group to which the findings will be generalized. However, a basic premise for the development of an experimental design is that it uses a sample that excludes subjects whose characteristics may interfere with a clear explanation of the differences between the experimental group and the control." In some cases, too large samples would be required to detect subtle differences between groups such as gender, age or racial differences. "Consequently, according to the perception that women are special (because of their variable hormonal constitution related to the menstrual cycle, menopause and the use of oral contraceptives or estrogen replacement therapy) they have been excluded from the studies because they control. These variables would require larger and more expensive master sizes." This methodological justification has been one of the most frequent excuses of the delay in the inclusion of women as research subjects.

The participation of pregnant women in research should be guided by the following recommendations: it should be established whether the research seeks to promote the health of the mother or the fetus and what type of risks it poses for the two. The fetus will be under the minimal risk necessary to meet the mother's health needs.

Information on the risks to the embryo and the fetus should be included in informed consent if the woman became pregnant during the course of the investigation. The bioethics committee must demand that the appropriate devices be available so that the participating women are informed in a timely manner about the techniques of contraception and the pregnancy report when the situation arises.

In research that seeks to obtain information about the diseases of pregnant women, the health needs of the mother tend to have preeminence with respect to those of the fetus except, perhaps, when the health benefit to the mother is minimal and the risk to the fetus is high. Finally,

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in women who are breastfeeding the committee should ensure that they are given adequate information about the risks they run and the nutritional alternatives they have.

5.3. Older adults

Older adults become more vulnerable when they experience cognitive impairment or are institutionalized, often resulting in difficulties in making decisions for themselves in the time required. For the researcher and for the Bioethics Committee, it may be difficult to introduce older adults as a vulnerable population because they can, on the one hand, attend to particular protection needs, but on the other, their self-respecting status may be affected.

Usually, the older adult does not necessarily have to be always considered a vulnerable person. In accordance with the principle of justice, older adults should also be included in biomedical research to share the potential benefits derived from them. On the other hand, the researcher must consider, for example in the case of experimental drugs, the particular physiological conditions that this population group keeps and not necessarily make inferences from the studies carried out in young adults.

The most described limitations for the inclusion of older adults in research are the presence of several chronic diseases for which they receive multiple medications, which represents methodological difficulties and additional statistics in controlled studies; high dropout rate; greater time of dedication to the realization of informed consent due to hearing and visual difficulties, among others; cognitive deficit isolated or associated with a dementia syndrome; and loss of autonomy that is reflected in relationships of dependence with caregivers or entry to asylum institutions.

The CIOMS guidelines of 2002 mention in this regard "Older adults are commonly considered vulnerable. As the age advances, people are more likely to acquire characteristics that define them as vulnerable. They may, for example, be hospitalized or develop various degrees of dementia. It is appropriate to regard them as vulnerable, and treat them as such, only when they have acquired those attributes." This helps to understand that it is often not the age that marks intrinsically the condition of vulnerability but the pathological or deficient characteristics associated with it.

At the beginning of the chapter, the level of dependency was mentioned as a criterion of vulnerability. To conceptually integrate these elements with aging, I will take the proposal of on the three forms of dependence generated by aging, namely (1) the deficiency or impairment that corresponds to a reversible alteration or at least can be corrected with adaptations in life as with delayed walking; (2) the disability or objective and irreversible impairment in some or several social functions as happens with presbyopia or hearing loss; and (3) the disability that corresponds to a total reorganization of life according to the disabilities or disabilities that are suffered.

"As it is evident that there can be impairments without disabilities and disabilities without disabilities, it is evident that the process of helplessness, incapacity, or incompetence—focused individually and societally—is not biological invariant but biographical development. Being a biography

and not biology, its social construction is a matter related to culture, language and beliefs. It may be argued, however, that there is a quantum of progressive deprivation that is personally and socially estimated and that it constitutes the addition of impairments, disabilities and handicaps and is expressed in different spheres. For example, there is a situational helplessness, which excludes people, according to their age, from certain contexts. There is a cognitive mismatch or incompetence, which allows us to relativize the attentional or anemic yields and even expect a coefficient of functional loss …." The central point will then be in the estimation of the quantum of helplessness proposed by this author, which should be part of the work of the researcher and the Bioethics Committee. The level of dependence generates a situation of vulnerability that will be considered in the evaluation of the capacity and competence to give a valid informed consent.

When informed consent is made, researchers should consider more than age, the conservation of autonomy, the level of education achieved, the state of health and the conditions under which it is performed. This is in order to determine the cognitive difficulties that may compromise the ability and competence to process the information provided. It is convenient to link in this process the caregivers or responsible persons with the well-being of the older adult, without this meaning the substitution of the decision-making capacity by the participant.

In the process of informed consent, it is essential to insist on the simple description of the basic conditions of the study and to verify that the information has actually been retained and can be evoked when required. In this sense, some authors recommend to include only those elderly who, after having received an initial information, are able to pass a test about their participation in the study. What is complex for researchers is to establish, what the minimum level of understanding they require in their participants so that consent is valid through the study. It is advisable to reiterate the basic conditions of your participation, emphasizing the risk-benefit relationship and your rights as a patient.

5.4. People with cognitive disabilities

There is an ethical tension between the interests of society and science to gain new knowledge about mental illness and cognitive disorders and the need to fully protect the interests of those who suffer from them. Some authors even point to this tension as the cause of the slowness in the application of modern neurosciences to psychiatric diseases.

To begin with, it is important to define the population group, special and vulnerable, which is included in this category. Cognitive impairment refers to "those persons who have a psychiatric disorder (psychosis, neurosis, personality disorder, or behavioral disorder), an organic deterioration (dementia), or a developmental disorder (mental retardation) that affects cognitive or emotional functions and which Lead to a significant decrease in judgment and reasoning. Other people can also be included as drug addicts or those who are under the influence of substances (drugs, alcohol), people with degenerative brain diseases, terminal patients, and people with severe physical disabilities" [5, 8].

The fundamental criterion that ethically justifies the linkage of people with cognitive disabilities to consent is that the research is oriented to obtain knowledge about diseases or conditions that directly affect them and could not be done with other types of people. The central axis of reflection for researchers and the Bioethics Committee is to determine the ability to

understand the information provided the ability to make a reasonable decision about their participation and the consequences of it. Competition may fluctuate as a function in the natural course of a mental illness, in response to treatment, as medication effect, or as damage to general physical health, among other factors. The competition criteria propped up in deliberation and rationality can in turn be influenced by mood, for example, people with psychotic depression can consent to high-risk research as a way to atone for their guilt.

Not every subject with cognitive defects is necessarily incompetent "… cognitively impaired subjects form a heterogeneous population of patients, and may have, to varying degrees, impaired their ability to give a valid informed consent." Cognitive impairment alone does not disqualify the person to give consent. As a general rule, all adults should be considered competent to give informed consent, regardless of their diagnosis or condition, unless there is evidence of severe mental incapacity to impair judgment and reasoning.

People with cognitive disabilities who are in institutions multiply their special and vulnerable population status. An institutional context may favor conditions for the researcher accessibility to participants, close supervision to control environmental variables and availability of resources for monitoring and emergency care. However, the recruitment of people in these media can compromise the voluntary nature of their participation in the study. Individuals who are totally dependent on an institution may feel pressured to participate in exchange for continuing inpatient care. The recommendation is not to include institutionalized individuals as far as possible.

Now, it is convenient to clarify that not all people by the fact of being institutionalized have simultaneously lost their capacity and competence to give consent. The measures taken in the investigation should be clearly indicated to avoid or reduce the likelihood of adverse reactions, as well as to specify how the privacy of the individuals will be protected and the confidentiality of their information. The effect of institutionalization on the ability to make a free choice (voluntary) should be considered. It is important to protect the privacy of all subjects and the confidentiality of information obtained in research that contains emotionally sensitive topics (sensitive information).

People who are legally the guardians or legal guardians of people with mental disabilities should also be vigilant so that the investigation does not run beyond the minimal risk and avoid causing harm or discomfort. Even in cases of individuals with legal guardians, it is advisable to ask the consent to the people with mental limitation. So, you must respect your feelings, expressed wishes, and the right to exercise deliberate objection.

Summarizes the ethical requirements of research in people with cognitive disabilities as follows: (1) risk is only minimal, (2) research is related to patient problems that cannot be investigated with competent persons, (3) disabled persons by themselves have not verbally or behaviorally objected to their participation, (4) family members agree upon being fully informed, and (5) the ethics committee has given its approval [9–16].

5.5. People in institutions or subordinates

It is a group that each gains more ground in the bioethical discussion of special populations. It includes, among others: prisoners, students, employees, soldiers, and people residing in institutions such as asylums, convents, etc.

The CIOMS guidelines of 2002 refer to this "The quality of consent of potential young subjects or subordinate members of a hierarchical group should be carefully considered, since their acceptance, whether justified or not, may be unduly influenced by the possibility of preferential treatment or for fear of disapproval or retaliation in case of refusal. These groups include medical and nursing students, subordinate staff from hospitals and laboratories, employees of pharmaceutical companies and members of the armed forces or police. Because these people work closely with researchers, they tend to require them mostly to participate as research subjects, and this can lead to an unequal distribution of research burdens and benefits."

In the following it will be mentioned the prisoners and students as representative of the collective of people in institutions or subordinates.

5.6. Prisoners

Prisoner is understood to mean a person involuntarily confined in a penal institution because he was sentenced according to the codes in force in each country; he is detained and pending judgment or sentence; he is interned by legal mandate for the treatment of drug dependence and alcoholism.

Until the 1970s, researchers used to include prisoners in their experiments because of the facilities in terms of accessibility, permanence, control of external variables, and cost reduction. However, on the obverse are various ethical tensions such as coercion, undue inducement, unbalanced risk-benefit relationship, multiple studies with the same subjects, limitation in the ability to make autonomous decisions, excessive or poor economic remuneration for their participation, and breaches of confidentiality in the prison environment, given the security conditions that are applied. As in other special groups, the researcher must ask himself if his study is designed to respond to a particular situation of this population that can only be clarified with his participation.

Institutions of incarceration are characterized by being "totalitarian" institutions, that is, they have defined the environment and social relations at the service of a central authority, often exert acts of submission or subordination to preserve such control. Under these conditions, it is very complex to establish the voluntariness of informed consent and respect for autonomy, in accordance with the postulates of the Nuremberg Code.

Ethically, difficulties arise in obtaining free consent when healthcare improvements, places of confinement or economic rewards are offered. Some authors defend the participation of the prisoners as one more work that they can carry with their body while they are rehabilitated; However, the current trend is to break this connection "… prisoners may be free enough to consent to prison work but not to consent to an investigation."

A central issue in analyzing the subject of prisoners is their subordinate nature, so their voluntary participation may be compromised by the relational and authority characteristics of their detention center. Situations of economic demands are often given to prisoners to provide basic conditions such as a mattress or food. The researcher can inadvertently be introduced into this dynamic and favor inequality conditions. The precarious conditions of many detention

centers in Latin America and the Caribbean pave the way for undue influence when financial rewards are offered for participation in experimentation.

The United States Department of Health and Human Services has delimited the participation of prisoners in investigations that as follows (1) inquire into the causes, effects, and processes of incarceration and criminal conduct, and which do not involve minimum risk; (2) study prisons as institutional structures or prisoners as interned; (3) explore conditions that affect them in a particular way; and (4) try therapies that are likely to benefit them directly as inmates [17, 18].

5.7. Students

In the case of students, it is important to distinguish if they are in a position to freely choose their participation in the study. Often their teachers are the same researchers. A rejection of participation could therefore be understood as a lack of cooperation with the very development of the knowledge it is receiving. The situation becomes more complex when the participation is part of the same evaluative process of the course that is advanced. If a student is faced with performing a written assignment or submitting a test, on the one hand, and participating in an investigation, on the other hand, he is likely to be inclined to link to the study thereby ensuring course approval and obtaining teacher complacency.

The researcher may be inclined to take students as participants in the research projects given their accessibility and frequent availability. However, caution should be exercised when working with homogeneous populations (such as university students) as the study findings are not necessarily generalizable to all students and the general population. Another aspect is the so-called Educational Benefit, whereby recruitment into research is understood as an opportunity for practical learning. This argument is particularly delicate because it conflicts with the student's willingness to face his desire for academic training.

In order to make the linkage of students to research projects more transparent and ethically sustainable, a number of recommendations have been formulated. One is to conduct calls for research openly to the entire group of students and not individually. When the request is made individually, there is a risk of undue influence, whether due to the type of relationship (academic or work) that the researcher has with the candidate. The information transmitted should not reduce risks or magnify benefits. Another recommendation is to unlink the research participation of the evaluation process of the subject; the student should be offered alternative activities comparable to the link to the study. The US regulations consider possible economic compensation for the participants as long as it is adjusted to the time spent, the discomfort experienced, and the risk assumed.

In the context of research with student subjects, the mechanisms that protect the collected information, especially sensitive information such as sexual activity, mental health, or drug use, should be considered.

The employees follow ethical guidelines similar to those of the students to guarantee precisely the absence of coercion or undue pressure and the confidential preservation of the data

collected. As in all research with special and vulnerable populations, it must be borne in mind that their design must obey the need to know and improve the particular conditions of the subjects under study.

5.8. People in critical medical conditions or in coma

Often the ability of polytraumatized people with severe life or coma risk is severely compromised. The commitment of the state of conscience or the urgency for the accomplishment of a medical intervention limits the granting of a valid informed consent.

The FDA allows exceptions to informed consent when the investigator and another nonresearch physician can certify in writing that these are life-threatening situations, the participant's consent can not be obtained because of their inability to communicate or give A legally valid consent, there is insufficient time to obtain the consent of a legal representative and there is no alternative or generally accepted or approved therapy offering an equal or greater likelihood of saving life. Documentation of these conditions must be sent to the ethics committee within 5 business days after the event.

On the other hand, there are opinions that defend the exclusion of traumatized subjects or coma in investigations with risk above the minimum if they do not have the proper informed consent or the authorization of a previously authorized legal representative. Otherwise, the person should receive conventional care for their urgent situation.

The Bioethics Committee should establish the risk-benefit ratio and whether the possible benefit is reasonable in relation to the risks involved. When the risk is greater than the minimum, the informed consent of the patient or his/her legal representative must be obtained. However, in the context of emergency care, it may happen that there is no accessibility or time to contact a relative or legal representative who can give the respective consent. In some investigations, it is foreseeable that urgent situations arise or the surgeries of critically ill people are scheduled, in which cases consent must be obtained in advance.

5.9. People with terminal illness

These are people who have a life-threatening disease or deteriorating condition for which there is no effective standard treatment. The terminally ill are a highly vulnerable population in which researchers and the Bioethics Committee should carefully analyze research protocols to avoid coercion and undue influence. Individuals can unconditionally accept treatments or interventions in an ultimate desire to improve or cure their terminal condition.

In developing countries, the situation becomes more complex since entering the research protocols represents for many people the only option to receive medication or some therapeutic modality that can alleviate the difficult situation experienced. People with terminal illness may consider that if they do not agree to participate in an investigation they may lose health care they are receiving or that their doctor would not be interested in other efforts to improve their health conditions. On the other hand, they may also consider receiving the treatment under investigation is better than receiving nothing. Some also understand that their involvement has an altruistic sense to improve the conditions of future patients.

The 2002 CIOMS guidelines state "People who have potentially crippling or fatal serious diseases are highly vulnerable." As in other cases, research must address the particular conditions and needs in health and quality of life of individuals with the specific disease or condition that the participants have. Their desire to withdraw at any time must be respected, but the necessary information must also be given to assess the risk-benefit ratio.

It is important to make the difference between risks justified by the likely therapeutic benefits of the research and the risks associated with procedures carried out purely for investigative purposes. The subjects must exercise their autonomy based on a sufficient explanation of the risks and benefits and the degree of uncertainty regarding the results; Consent must conform to real expectations so as not to create false expectations or to break down all hope. If it is considered advisable, the informed consent process must be carried out in the company of a family member or legal representative. Particular emphasis should be given to consent to the conditions of eligibility of individuals based on their diagnosis and prognosis, as well as to show the alternative treatments and define the advantages between receiving and not receiving treatment. The ethics committee should also ask why it is appropriate for the treating physician to act as a researcher [5].

5.10. Healthy volunteers

In healthy volunteers, the dual vulnerability between participant-researcher described at the beginning of the chapter is presented. The researcher knows partially the risk-benefit relationship; in fact, to overcome such situation is that research, while the healthy volunteer participates based on the information, usually partial, that they provide. This mutual ignorance of the risks and benefits added to economic, labor, or social pressures has made them increasingly considered as a special and vulnerable group, so much of the pharmacological knowledge of the twentieth century has been built with their participation.

For healthy volunteers, their participation does not result in a direct therapeutic benefit although there are levels of risk that up to that time have not had other human beings. The role of the researcher should therefore be to reduce as much as possible the level of risk, this to establish reciprocity with the altruistic motivation that leads them to bond.

Healthy volunteers should receive available information about the research and reasonably expected results that the investigator believes may be expected. Consent must be free from coercion and undue inducement to participate. The latter is considered mainly in the field of economic remunerations that must be consistent with the time spent, discomfort generated, and risk assumed. In studies with increased risk should be considered that a motivation of volunteers may be precisely the money offered; In this situation, which is frequent in Latin America, a type of vulnerability is derived from economic and educational status that compromises the ability to objectively assess the risks assumed when informed consent.

In this chapter, the special populations of biomedical and psychosocial research have been approached considering the convergence of the criteria of vulnerability, level of dependence, capacity/competence and risk-benefit ratio as a proposal of an approach that favors the inclusion and NOT the exclusion of these people and human groups in the production and transformation of knowledge.

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References

[1] CIOMS. Pautas Éticas Internacionales de las Ciencias Médicas (CIOMS) en colaboración con la Organización Mundial de la Salud-Ginebra 2002. Programa Regional de Bioética OPS/OMS. Santiago: LOM Ediciones; 2003

[2] Arboleda Florez J. La investigación en sujetos humanos: poblaciones vulnerables. En: Investigación en Sujetos Humanos: Experiencia Internacional. Pellegrini Filho A, y Macklin R, editors. OPS/OMS Serie Publicaciones. Programa Regional de Bioética. 1999

[3] Real Academia Española. Diccionario de la Lengua Española. Vigésima Segunda Edición. Tomo II. Madrid: Espasa Calpe; 2001

[4] Drane J. The many faces of competency. In: Mappes Th, Zembaty J, editors. Biomedical Ethics. 3rd ed. New York: McGraw-Hill; 1991

[5] Reich W, editor. Children: Health-Care and Research Issues. Encyclopedia of Bioethics. New York: Simon&Schuster MacMillan; 1995

[6] Levine RJ. Ethics and Regulation of Clinical Research. 2nd ed. New Haven: Yale University Press; 1986

[7] Perlman M. Ethics of research in neonatos. In: Koren G, editor. Textbook of Ethics in Pediatric Research. Malabar: Krieger Publishing Company; 1993

[8] Gracia D. Ética de los confines de la vida. Ética y vida. Estudios de bioética 3. Bogotá, El Búho; 1998

[9] Cabello F. Experimentación en humanos y derechos humanos. ¿Está permitida la experimentación biomédica con niños? Revista Medica De Chile. 1986;**114**:57-60

[10] Wilson A. Women: Research issues. In: Encyclopedia of Bioethics. Reich WTh/New York; Simon&Schuster MacMillan, 1995

[11] Sachs G. Aging and the aged: Health-Care and Research Issues. In: Encyclopedia of Bioethics. Reich WTh/New York: Simon&Schuster MacMillan; 1995

[12] Lolas F. Bioética y Vejez: el proceso de desvalimiento como constructo biográfico. OPS/OMS. Cuadernos del Programa Regional de Bioética. Número 2. Santiago. 1996

[13] Cuénod M, Passer J. Symposium on consent and confidentiality. Research on the mentally incompetent. Journal of Medical Ethics. 2003;**29**:19-21

[14] Elliott C. Mentally disabled and mentally ill persons: Research issues. In: Encyclopedia of Bioethics. Reich WTh/New York, Simon&Schuster MacMillan; 1995

[15] Lavados Montes M. Aspectos éticos relacionados con la participación de sujetos cognitivamente impedidos en proyectos de investigación biomédica. OPS/OMS. Cuadernos del Programa Regional de Bioética. Número 3. Santiago. 1996

[16] Wing J. Ethics and psychiatric research. In: Psychiatric Ethics. 2nd ed. Trowbridge: Oxford Medical Publications; 1994

[17] Branson R. Prisoners: Research issues. In: Encyclopedia of Bioethics. Reich WTh/New York: Simon&Schuster MacMillan; 1995

[18] Millar B. Students as research subjects. In: Encyclopedia of Bioethics. Reich WTh/New York: Simon&Schuster, MacMillan; 1995

Chapter 10

Access to Clinical Trials Closer to Home Using Tele-health

Sabe Sabesan and John Zalcberg

Additional information is available at the end of the chapter

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Abstract

The purpose of this chapter is to outline key considerations for increasing access to clinical trials for people with cancer living in rural and remote locations, and outline the contribution of tele-health models to facilitate study activity across rural and remote locations. Regional and rural group of the Clinical Oncology Society of Australia (COSA), the peak multidisciplinary cancer clinician body in Australia, has developed the Australasian Teletrial Model in collaboration with its stakeholders to improve rural access to clinical trials. Benefits of this model are not limited to regional, rural and remote systems. This model has the potential to connect larger centres even within the same city and improve the rate of recruitment of highly specialised clinical trials, including rare cancer trials. This model has been developed in consideration of the requirements for the proper conduct of clinical trials ensuring the protection of the rights and safety of trial participants and quality data for the demonstration of safe and efficacious cancer treatments. Ethical and safe conduct of clinical trials using this model requires that the following aspects are considered and addressed by implementation plans.

Keywords: clinical trials, tele-medicine, rural, tele-trials, tele-oncology

1. Introduction

Access to specialist cancer care services is a significant issue faced by residents of rural, remote, indigenous and some regional communities in countries with large rural and outer metropolitan populations [1]. For these communities, the lack of access to specialist services may be due to a lack of specialist oncologists locally, limited scope of practice of other rural health professionals and/or overall rural workforce shortages. Poor access to such specialised health care services could be one of the contributors to the disparity in survival and

disease-related outcomes that exist between metropolitan and non-metropolitan patients [2–5], although the authors acknowledge this issue as complex and may also relate to other factors such as behavioural or cultural factors.

It is recommended by leading authorities, such as the National Comprehensive Cancer Network (www.nccn.org) and Cancer Research UK [6], that support for the provision of clinical trials to people diagnosed with cancer is a core component of providing optimal cancer care through specialist cancer centres, hospitals and other treatment facilities. Indeed, in many cases such guidelines recommend participation in clinical trials as the best option for many cancer patients.

Clinical trials offered to people diagnosed with cancer may include new and experimental drug therapies or imaging technologies, minimally invasive diagnostic or surgical techniques, or supportive care interventions. However, as with access to specialist care, patients living outside of major metropolitan centres face many barriers in accessing clinical trials. Barriers to participation include the limited availability of trial sites closer to home and the increased cost and inconvenience of travel to major centres where the trials are taking place [7, 8].

While it may be reasonable to establish clinical trials units in large regional cancer treatment centres, the logistics of maintaining a suitably trained workforce and undertaking the ethical and regulatory responsibilities of clinical trials may be difficult in smaller rural and regional sites with limited resources and low patient numbers.

Tele-oncology models of care have been shown to satisfy many specialist health care needs of rural and regional patients in countries with large rural populations [1]. Using tele-oncology models, many cancer centres have been able to facilitate the administration of complex chemotherapy in rural and regional areas [9–11]. Around the world, such centres have implemented safe and successful tele-oncology models that are acceptable to patients, families and health professionals, saved money for health service provision and enhanced the capabilities of rural health systems in oncology services to provide cancer care [10, 12–17]. In addition, cancer services can be delivered to rural patients closer to home in a timely manner [18]. Tele-oncology models of care may outline a system-level intervention to address issues of equity and access to clinical trials. For example, adopting this model would enable rural and regional sites with limited resources to provide access to Phase III comparative effectiveness studies and potentially trials of new and novel therapies for the local population.

This document outlines a feasible and effective tele-health strategy to increase access to clinical trials closer to home, while at the same time ensuring the proper conduct of cancer clinical trials.

1.1. Overview of established clinic and treatment models of tele-oncology in Australia and globally

Similar to most of the specialist tele-health models around the world, the Townsville tele-oncology [15] model enables medical oncologists from Townsville, Australia to provide their services to rural sites, using traditional videoconferencing technology or web-based systems (**Figure 1**). At larger rural centres, rurally-based doctors, chemotherapy-competent nurses and allied health workers accompany patients during tele-consultations. At other rural sites, patients are accompanied by either a doctor or a nurse for post-treatment reviews, toxicity reviews or follow-up visit(s) tele-consultations [12].

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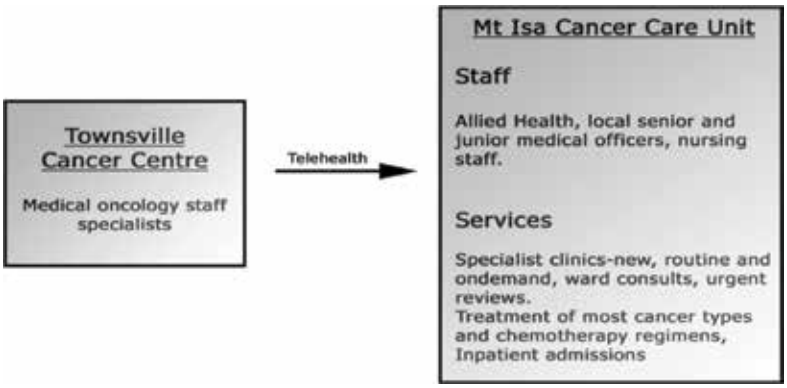

Figure 1. A model of a rural specialist unit with specialist support via tele-medicine model of care. Sabesan et al. EJCC, 2015.

When a patient is assessed as fit for chemotherapy or targeted therapy, medical oncologists write the care plan and send the prescriptions to rural sites where chemotherapy is given by chemotherapy-competent nurses. Where electronic systems are available, care plans are made and approved online. For oral chemotherapy, authority scripts are sent by medical oncologists to patients, rural hospitals or the local pharmacy after appropriate education by medical oncologists, nurses or pharmacists. Prior to the clinic, informed consent for participation in the tele-oncology clinic is obtained from the patients.

1.2. Remote chemotherapy supervision model

While the models mentioned above are largely medical tele-health models, models such as the Queensland Remote Chemotherapy Supervision (QReCS) model [19] enables rural generalist nurses to administer chemotherapy at rural sites with the support of the rural generalist doctors and pharmacists, under the supervision of medical oncologists and chemotherapy-competent nurses from larger centres using tele-medicine and tele-nursing respectively (**Figure 2**) [20].

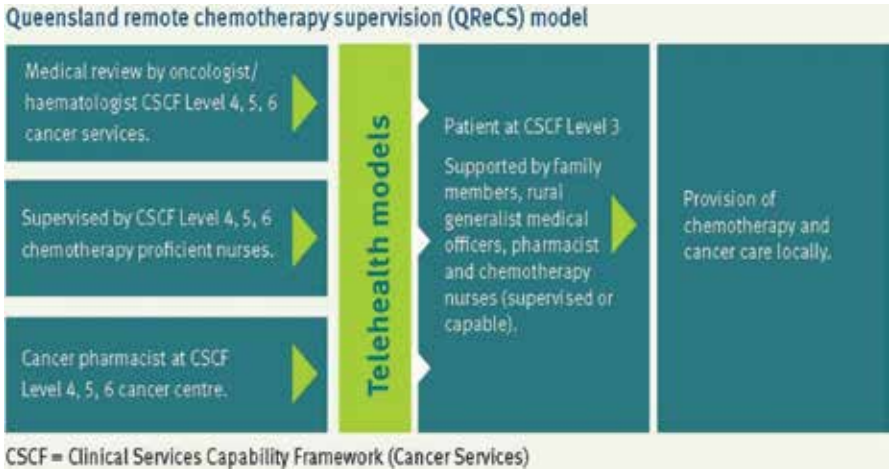

Figure 2. Remote chemotherapy supervision model.

2. Core principles of the tele-trial model

The core principles of the tele-trial model are as follows:

1. To increase accessibility to trials thereby reducing the need for people with cancer to travel to larger centres to attend study-related visits and undertake study-related procedures. Using tele-oncology models, there is an opportunity for patients from rural or regional sites to be recruited, consented, and treated, and to attend follow-up visits—a hub-and-spoke approach between a primary trial site and a satellite site. The roles and responsibilities for each site need to be clearly defined at the outset of each trial and appropriately contracted (**Figure 3**).
2. To develop collaboration and networking between regional/rural and metropolitan centres and between tertiary centres even within the same metropolitan setting with the aim of delivering greater engagement in research activity, improving adherence to evidence-based practice, improve the rate of recruitment of patients into clinical trials, reducing the disparity in cancer outcomes for geographically dispersed populations, building clinical trial capacity, and providing trial-related training.
3. To articulate the relationship between the primary site and satellite site as a trial cluster. The trial cluster co-ordinates the trial across multiple sites including a primary site and one or more satellite site(s), ideally through streamlined trial processes (**Figure 4**). A trial cluster may exist in the following settings: (a) larger metropolitan centres as primary sites with other metropolitan centres as satellites even within the same city; (b) larger metropolitan centres or large regional centres as primary sites with smaller regional or rural sites as satellites; or (c) larger regional centres as primary sites with metropolitan centres as satellites in an attempt to improve the capabilities and community profile of regional centres.

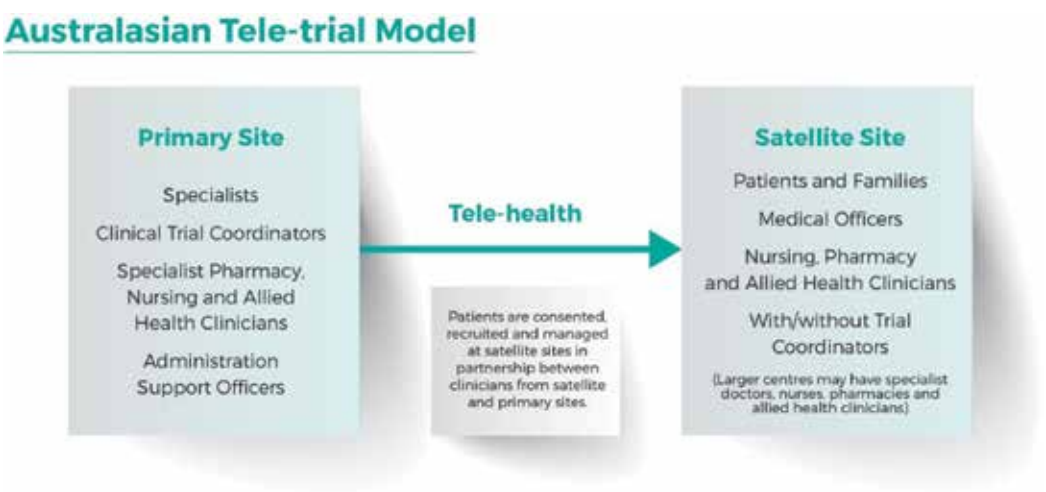

Figure 3. Australasian teletrial model. Adapted from Sabesan and Zalcberg [21].

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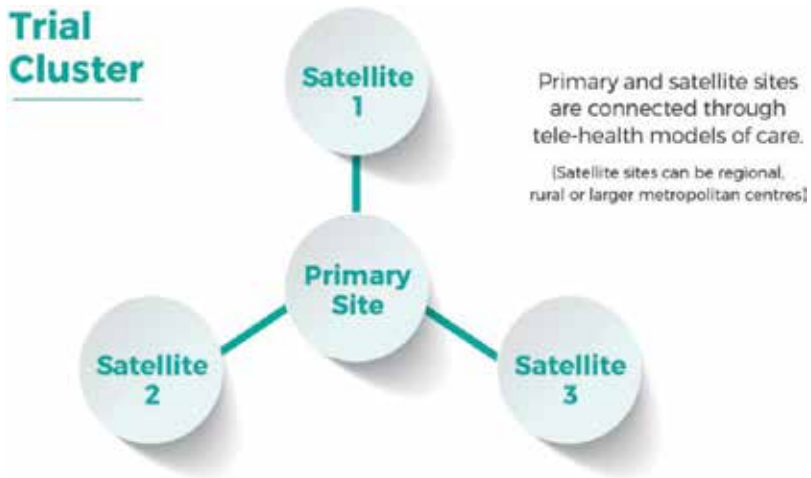

Figure 4. A tele-trial cluster.

2.1. Anticipated benefits

Similar to tele-health models for delivering routine cancer care, there are a range of benefits associated with conducting clinical trials using tele-health strategies. Modern informatics supporting technological advancements in communication enable a greater depth of reach to more Australians. Notably the tele-trial model has the potential to make clinical trials accessible to people with cancer from rural and remote centres closer to home. Increasing accessibility for increased participant recruitment may also improve collaboration and networking between rural and metropolitan centres, provide workforce development, facilitate engagement in research activity for improved adherence with guideline recommended care and reduce the disparity in cancer outcomes for geographically dispersed populations.

There is a second related benefit of the model for Australia's geographic reality, and comparatively small population for which tele-trials may provide a useful solution. This benefit relates to the complexity and innate molecular and phenotypic heterogeneity of cancer. That is, any one tumour type is actually made of multiple discrete subgroups. Hence, trials requiring the eligible population to have a similar tumour subtype in order to compare two different interventions are more and more difficult to conduct. Increasingly, these studies involve numerous centres around Australia or indeed internationally. The corollary of such an observation is that individual centres, even large tertiary referral centres will only see a very small number of patients whose tumour fits the eligibility criteria for these studies in any one year. As the cost of establishing and maintaining the infrastructure to open poorly recruiting studies is so high, such centres are becoming increasingly reluctant to open these studies in the first place. Consequently, these studies recruit even fewer patients overall than might reasonably be expected because the only trial site(s) recruiting to one of these studies is geographically distant from the potential participant.

Another advantage is workforce development. Exposure to, and involvement in research provides professional development opportunities through collaboration with leading clinical

researchers. This may have flow-on benefits for improved access to trials and improved quality of care. There are also advantages for Australia to develop a more flexible approach to the conduct of trials; given our relatively small population and geographic barriers to recruitment. Recruiting specific patient cohorts is an ever-present challenge. Without multisite collaboration, Australia is less attractive to international trial Sponsors, which limits the availability of experimental, life-saving treatments. Developing these clinical trial networks through models like this tele-trial concept, we can better promote our capacity to support a wider range of trials.

Tele-trials offer the unique opportunity to impact this inevitable cascade of circumstances that compound the difficulties of defining new treatments for so many cancers in the modern era of molecular characterisation of cancer across regional and rural Australia.

2.2. Anticipated costs and threats

While the benefits discussed above have positive flow on effects on patient care and the Australian Health system as a whole, system improvement using this model is unlikely to be achieved without added cost for the sponsors (including increased site visits, medication transport cost to satellites, etc.), hospitals and governments (increased workforce, technological and pharmacy infrastructure). Benefits of improved rural access to clinical trials and enhanced rate of recruitment can offset those extra costs. Reforms on remote monitoring, site accreditation, ethical, governance and contractual processes are required at a system level to reduce financial and human resource cost.

Geographic isolation due to distance may cause several problems including workforce stability, transporting and handling of medications and devices, access to source documents and communication between sites which can be mitigated by implementing the processes outlined in this document.

3. Requirements for implementation of the tele-trial model

Satellite sites (regional, rural or metropolitan) would vary in their capability to conduct trials based on resources and prior experience. Based on the capabilities of the satellite sites, primary sites may delegate to the satellite sites some or all aspect of trials, in agreement with the sponsors and satellites.

3.1. Selection of satellite sites and suitable trials

Site feasibility assessments may have to consider the capability of the whole cluster and potential satellite sites are indicated during the site feasibility process. This informs the trial Sponsor of the referral relationship between the primary site and satellite sites within the cluster. The cluster may include hospitals within the same region, network or local health district or hospitals in other regions, networks and local health districts. Once the primary site is chosen, the acceptance of the satellite sites by a trial Sponsor will depend on the prior experience of the satellite site in conducting clinical trials, the complexity of the trial, and the medical,

nursing, allied health, pathology and pharmacy research capabilities. Site capacity and trial complexity will determine the ability of the site to conduct trial-related activities at the satellite site and will be assessed by the Sponsor at the time of site selection. It is not anticipated the satellite site will undertake all trial-related activities. Satellite sites that have established trial capabilities are able to take part in complex protocols from the outset. At sites that have no or limited experience in delivering clinical trials, a staged approach may allow for gradual building of clinical trials capacity from simple to more complex trials.

3.1.1. Accreditation of satellites

For sites that have not taken part in clinical trials previously, as required under current practice, it is likely that the Sponsor may wish to perform a site visit. The Sponsor may also wish to delegate this responsibility to the primary site.

3.1.2. Supervision plan

Some registration bodies require that the primary site Principal Investigator (PI) take responsibility for overall supervision of the trial across a cluster. Tele-health offers a unique opportunity for direct supervision of patient management. A supervision plan agreed between the primary and satellite sites and the Sponsor needs to be developed and formalised at the outset of a trial. The supervision plan may include, but not be limited to, details on joint consultations using tele-health, collation and monitoring of documents, frequency of joint trial meetings across a cluster (with minutes of these meetings) and any site visits performed by the PI.

3.1.3. Site visits

While the travel by staff and patients is reduced as the result of this model, Sponsors may wish to undertake site visits for accreditation and monitoring purposes, unless remote monitoring is agreed by the Sponsor and source documents are available at the primary site.

3.2. Workforce: roles and responsibilities

The workforce requirements of current tele-health models could be extended to the tele-trial model. While larger rural and regional centres may have resident or visiting medical oncologists, oncology clinicians and trial nurses, satellite sites may have limited specialised services. Under the current tele-health models, urban specialists at a primary site provide their services using videoconferencing. Service delivery is supported and facilitated by doctors, nurses and allied health professionals at a satellite site. The nature of support to and by the rural health professionals would be determined by the complexity of the trial and the clinical capabilities at the site [22, 23]. The delegated responsibilities would need to be agreed by the Sponsor, clearly documented within the master site file and trial-related training records provided before this delegation could occur.

Defining roles and allocating specific responsibilities to staff within a cluster can ensure the safe and efficient conduct of clinical trials. The satellite team would need to take part in the Investigator Meeting & Study Initiation Visit so that they are fully aware of the requirements

for compliance with the Investigational Brochure (IB), study protocol and the importance of these required processes. Tele-health technologies offer the opportunity to conduct investigator meetings and study initiation visits across geographically dispersed clusters. This is particularly important for reporting and managing adverse events and serious adverse events, and ensuring that patient reported outcomes are completed in a timely manner without excessive missing data.

3.3. Good clinical practice

All clinical trials involving Clinical Trial of Investigational Medicinal Products (CTIMPs) must be conducted according to the principles of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and local laws for Good Clinical Practice (GCP). ICH and GCP requirements, local laws and regulations and the Sponsors' protocol and company requirements as outlined in the Australian legislative requirements applying to prescription medicines are contained in the Therapeutic Goods Act 1989 and the Therapeutic Goods Regulations 1990.

3.4. Roles and responsibilities of trial site staff

Prior experience of staff and capabilities of the satellite sites would determine the roles of the satellite trial staff. PI may delegate some or all of the trial-related processes to the satellite site staff, in agreement with the sponsor and satellite staff. It is important that roles and responsibilities are agreed and formalised at the outset.

3.4.1. Primary investigator at primary sites

Some registration bodies require that the PI is responsible for overall supervision of the trial, including satellite sites. Therefore, it is important to develop a supervision plan including cover for holidays and unexpected leave at the outset of a trial and incorporate this into the contract.

1. Participate in trial consultations with satellite site medical officers via tele-health if required.
2. Take part in the consenting and recruitment process remotely or on-site as required via tele-health.
3. Communication with satellite investigators regarding protocol revisions,
4. Provide oversight of SAE reporting, ensuring satellite sites provide source documents and reports as required.
5. Be available to consult on the management of Serious Adverse Events and adverse events (SAE/AEs) as required.
6. Maintain a delegation log for all research staff at both primary site and satellite sites.
7. Ensure all staff at both the Primary and Satellite Site are trained in the trial specific activities delegated to each.

8. Develop arrangements for radiology and pathology reviews and for engagement with other clinicians including genetic counsellors, other specialists and allied health professionals, as dictated by trial protocols, across a cluster.

3.4.2. Satellite site investigators

Satellite site medical officers will be the local contact for trial-related matters within a satellite unless the PI and the primary site agree to take this responsibility. Depending on the prior experience of satellite site investigators and satellite capabilities, the PI may delegate some or all of the trial-related responsibilities to the satellite site investigators:

1. Conduct joint trial visits with primary sites when required by the trial Sponsor.
2. Satellite sites would require monitoring visits to review source documents that are not entered into an electronic medical record (EMR) system or shared between the satellite site and primary site.
3. Undertake ICH-GCP accreditation and training on the study protocol.
4. Take part in the consenting process, perform and document physical assessments.
5. Manage, store and dispense CTIMP if required and accredited to do so.
6. Undertake activities related to study follow-up.
7. Timely communication and management of AEs and SAEs and study reporting in collaboration with primary sites.
8. Develop arrangements in collaboration with the PI for radiology and pathology reviews and for engagement with other clinicians including genetic counsellors, other specialists and allied health professionals, as dictated by trial protocols, within their site.
9. Develop plans for local contacts during periods of cover for holidays and unexpected leave.

3.4.3. Trial co-ordinators

Trial co-ordinators at primary sites act as a contact for coordinators at both the primary and satellite sites.

1. Coordinate the study and monitor progress across the cluster.
2. Collate and coordinate documentation from satellite sites including the preparation of CRFs.
3. Identify staff changes and initiate appropriate training.
4. Conduct trial meetings by including satellite sites.
5. Manage the regulatory processes and reporting requirements to the trial Sponsor, and human research ethics committees as required.

3.4.4. Pharmacy and pharmacy facilities

Trial Sponsors may elect to deliver CTIMP directly to the site, dispensing the CTIMP and maintain drug accountability documentation at the site. Sponsors may delegate this responsibility to the primary sites. This requires the primary and satellites sites to work together collaboratively. Both the primary and the satellite site(s) would need to ensure that adequate documentation is in place to allow full drug accountability and be suitably qualified to undertake the following:

1. The primary site pharmacist is responsible for overall service provision in collaboration with satellites, i.e. receipt of the IP, storage and handling, dispatch to satellite or trial participant, reconciliation and communicating the management of IP with the satellite site. The primary site pharmacist will be the first point of contact when trials involving CTIMPs are under consideration by the primary site.
2. Designated pharmacy staff providing a clinical trial service must be adequately qualified, trained and experienced to assume clinical research responsibilities and should be able to provide up-to-date GCP training records.
3. The pharmacy must hold training records and signature logs for those staff involved in a clinical trial in the pharmacy department. These will be held at the site and should include all staff involved at either the primary site or satellite sites. These records may also be held in a central location and should be readily available for inspection if required.
4. Appropriate facilities should be available before agreeing to support a clinical trial particularly one involving radiopharmaceuticals or Advanced Therapy Medicinal Products (ATMPs) such as gene therapy and cell therapy. The pharmacy lead site for clinical trials should liaise with, and seek advice from, satellite sites with experience in handling these types of products.
5. The institution (pharmacy department) is required to hold a GMP licence as per the TGA annotated guidelines annex 13.
6. Manufacturing must be performed to GMP and release performed by a Qualified Person—in certain circumstances labelling may be performed at a site but the facilities have to be certified and reach GMP standards etc.
7. If the satellite site does not have access to a local GMP qualified facility they would not be able to participate in trials with this requirement.
8. Pharmacies should have facilities that allow for CTIMPs to be stored separately from normal pharmacy stock in an area with access restricted to pharmacy staff. Licensed products used as CTIMPs do not have to be stored separately as long as there is a process in place to ensure traceability.
9. CTIMPs that are returned by patients or expired should be stored separately from unused CTIMPs. Quarantined medication should be clearly identified and segregated from working stock.

10. Regular temperature monitoring of CTIMP storage facilities should be undertaken and records maintained for both primary and satellite sites. All CTIMP storage areas should be fitted with calibrated temperature monitoring devices that record minimum and maximum temperatures, with a robust system to alert staff if the temperature falls outside of the specified range. The temperature monitoring devices should have a valid calibration certificate which is maintained for reference. The pharmacy should have written procedures in place for the actions to be taken when the storage conditions are outside of the specified range.
11. Pharmacies should have an approved destruction policy that outlines the process for destroying; although some Sponsors may require unused, expired or returned CTIMP study medication to be returned to a Sponsor nominated central licensed facility for destruction.
12. Pharmacy files will be kept by the primary site and where requested, may develop additional accountability logs and files for satellite site usage.
13. Suitable archiving facilities will be required for pharmacy trial files. The system used for archiving must allow for prompt retrieval of any pharmacy study file or of non-study specific documentation (such as pharmacy standard operating procedures, original pharmacy temperature monitoring records and training records of pharmacy staff).
14. Pharmacy should receive funding for providing a clinical trial service. This funding should reflect the workload and cover costs involved and is separate to the prescription charge.
15. Procedures for unblinding must be made available to the satellite site in the case of an emergency.

The patient compliance with taking the medication will be monitored by the dispensing pharmacy, nursing and medical officers. During joint consultations, primary site clinicians can also reiterate to patients.

3.4.5. Pathology and radiology

Pathology and radiology requirements are dealt with at the feasibility questionnaire stage and arrangements agreed by Sponsors. Biopsy and biomarker and pharmacodynamic studies may require onsite centrifuge, processing and storage. If the satellite site does not have these capabilities, private pathology could be used and considered subcontractors or agents of the primary site in agreement with the Sponsor. Similar arrangement could be made for radiology requirements. For sites that have never participated in trials, the Sponsor may wish to conduct a site visit to assess these aspects.

3.5. Training

Training requirements are the same for both the primary and satellite site staff involved in clinical trials within a cluster.

3.5.1. Training for individual staff

All investigators and trial staff at each site are required to have undertaken GCP training and certification. Individual staff members should ensure GCP competence is commensurate with their roles and responsibilities in relation to the study protocol and the management of CTIMPs. Whilst it may be the case that some staff carry out trial-related tasks that are part of their normal role, they should be certified in the principles of GCP. A mentorship program would be of benefit where staff from the satellite sites have the opportunity to observe and have hands on experience at the primary site is one such example. Primary and satellite staff training is required to ensure that staff are competent to participate in the conduct of, or for providing the supporting and delegated activities of, a clinical trial. Both the primary and satellite sites must retain training records and signature logs for those staff involved in the clinical trial. These records should be readily available for inspection if required. GCP training can be accessed through the Australian Clinical Trials website: https://www.australianclinicaltrials.gov.au/researchers/good-clinical-practice-gcp-australia

3.5.2. Site initiation and trial update

Site initiation meetings and site staff training on the trial protocol for primary and satellite sites in a cluster could be undertaken via videoconferencing across a large geographical area. Site initiation meetings could also be used to reiterate the roles and responsibilities of staff across all sites. Joint consultations and regular trial meetings are also useful forums for discussing trial-related matters and updates.

3.6. Technology and support

A web-based system or videoconferencing equipment are required for interactive consultations. Availability of the electronic medical record (EMR) would enable seamless sharing of clinical data between sites. However, where the EMR is not available, source documents will need to be provided to the primary sites for data verification and trial monitoring purposes unless the Sponsor wishes to conduct trial monitoring visits themselves. While a tele-health approach may support the visit process both the primary and satellite sites need to understand the critical need for reliable source documents. In cases of technical failure, a secondary source of web-based technology should be available to ensure continuity of clinical encounters.

3.7. Participant screening and recruitment

It is expected that all processes and activities related to recruitment are coordinated by the primary site in communication with the satellite site. Satellite sites that have adequate resources could assist with screening and referral of patients for recruitment. Doctors, nurses and trial coordinators are able to identify patients, provide trial-related information and notify the primary sites, prior to participant consent being obtained.

NB: It is important to note that the National Statement has special requirements when enrolling special populations for example indigenous members of the community therefore sites need to ensure these requirements are met where appropriate.

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3.8. Obtaining participant consent

Patients from satellite sites are screened and recruited and provide consent for trial participation in collaboration with doctors and nurses at primary and satellite sites using video-link or on-site in a process approved by the Sponsor and the HREC.

3.8.1. Options for obtaining consent

The process for obtaining consent remotely via tele-health or onsite would be reviewed by the Sponsor and approved by the HREC. Satellite sites can be delegated responsibility to obtain informed consent.

For sites that do not have prior experience in clinical trials, it is important that the PI is directly involved in the trial consent process. In this option, the participants and the satellite site investigator sign the consent form, observed by an investigator at the primary site. This process is documented concurrently at both the primary site and satellite sites. At sites that have prior experience in trials, the satellite site investigator may be delegated to complete the consent process onsite. A copy of this final consent form can be given to the participant and stored in the medical record and in the primary trial site file. Mode of transfer for these documents (fax, emails and/or post) needs to be agreed by the Sponsor according to their privacy policies.

3.9. Medication handling

Sponsors may prefer to deliver CTIMP or devices directly to primary and satellite sites to reduce the cost of medication transport. At the request of the Sponsor, the primary site pharmacy may transfer clinical trial medication for administration or collection to satellite sites. Medications may include the investigational product and/or non-investigational medications related to the clinical trial. The following Sponsor approved medication could be managed in the following way:

a. Medication is dispensed and/or prepared according to protocol and accountability logs are completed.

b. Medication is sealed in a non-transparent bag clearly labelled with the patient details.

c. An acknowledgement of receipt form and a copy of the prescription are attached to the outside of the bag of medication.

d. The bag of medication is placed into a suitable container (e.g. box or padded envelope) and labelled and packaged for transport.

e. Cold pack and temperature monitor should be included for medication requiring refrigerated storage being transported from the primary site.

f. As per IB/Sponsor or manufacturers instruction.

g. Completed CTIMP containers being returned to the primary site are not required to be temperature-monitored. However, if a temperature-monitoring device is supplied by the Sponsor, the primary pharmacy will include it with the parcel with instructions to be followed by satellite site.

h. The pharmacy at the receiving satellite site is contacted by telephone to notify them of the delivery.

i. The courier service is contacted to arrange suitable pick-up/delivery.

j. The faxed signed copy of the Acknowledgement of Receipt from the satellite site is filed with the original prescription in the primary site Pharmacy folder.

k. In the event that the Acknowledgement of Receipt is not received by the primary site Pharmacy within 48 hours, the satellite site is contacted to check that the parcel has been received.

3.10. Managing and reporting adverse events (AEs) and serious adverse events (SAEs)

3.10.1. Management at routine clinics

During planned trial consultations, the history of AEs and SAEs is obtained. Clinical trial staff needs to be aware that drug intervention studies will require minimum reporting times and the occurrence of AEs/SAEs are to be reported to the primary site in the usual within 24 hour plan by any satellite staff, medical practitioner, nurse or data manager. SAEs are managed according to the protocol and documented in the EMR or medical charts by medical specialists/medical officers at satellite sites. If EMR is not available, certified copies of the source documents may be required and sent to the primary sites for monitoring purposes. Mode of transfer for these documents (fax, emails and/or post) needs to be agreed by the Sponsor according to their privacy policies. Upon notification of an AE or SAE, the trial coordinator at primary or satellite site will report SAEs to the Sponsor and follow the local procedure for documenting and reporting adverse events to the approving Human Research Ethics Committee (HREC) and local site governance office.

Roles of trial staff regarding this aspect of care need to be outlined in the site responsibility form, agreed upon by both primary and satellite sites and the Sponsor and incorporated into the contracts. Engagement with other specialists either via tele-health or onsite needs to be finalised according to the trial protocol. This is important for managing immune-related and unusual side effects of medications including trial medications.

3.10.2. Additional consideration for unplanned presentation during and after hours

In cases of presentation to hospital between medical consultations, the on-site investigator needs to be contacted by emergency staff who in turn will notify the primary site staff within 24 hours. Trial coordinators at the primary site and medical specialists are informed by any satellite staff who is the first to become aware and a joint review may be initiated using videoconferencing.

A 'trial patient alert' process would be useful for alerting the emergency staff or general practitioners that a patient is on a trial so that on-call specialists can be contacted. The name of the trial and contact details for the PI at both the primary and satellite sites needs to be included.

Patients and their families need to be educated of the need for seeking urgent medical attention and reporting to the primary and/or satellite site staff of their concerns. Patients could also be given letters or brochures for communication with clinicians in an emergency situation. Not all situations may be able to be managed at the satellite site. Inter-hospital transfers may be required in consultation between primary and satellite medical officers in some cases.

3.11. Patient reported outcomes (PROs)

Some trials will include PROs, including quality of life endpoints, usually as secondary endpoints, but sometimes as primary. It is a matter of equity that rural and remote patients have the opportunity to self-report aspects of their health and quality of life as specified in the trial protocol.

PROs are typically assessed with questionnaires, either handed out to trial participants by the research nurse or completed online. The specific questionnaires, mode(s) of administration, and timing relative to recruitment and treatment need to be followed as per trial protocols. It is also important to develop mechanisms to minimise missing data as far as possible and record reasons for missing data, so patient engagement is essential.

Many trials groups have reported success of centralised monitoring systems for maintaining high PRO completion rates. Staff should have access to ongoing training and written guidance and understand the importance of PROs.

3.12. Documentation and reporting

During trial consultations, a detailed patient history including the documentation of AEs and SAEs is obtained by doctors at primary or satellite sites or at both sites simultaneously. Results of investigations are available online at most centres. If results are not available online, the primary site will ensure certified copies are provided by the satellite site.

Physical examination may be performed by the doctor at the satellite site with or without observation by the primary site doctor and as per ICG-GCP the PI can only delegate to those with the necessary experience, training and qualifications. When joint medical consultations are conducted via tele-health, clinical encounters are documented at the site with the delegation to perform the specific study-related activity. If EMR is not available, certified copies of the source documents may be required and sent to the primary sites for monitoring purposes. Mode of transfer for these documents (fax, emails and/or post) needs to be agreed by the Sponsor according to their privacy policies.

3.13. Financial considerations

Consideration also needs to be given to how satellite sites will be reimbursed for undertaking trial specific procedures (e.g. blood tests; radiology procedures, etc.).

There are administrative efficiencies if the co-ordination of invoicing or journal transfers for trial-related expenses at satellites sites are coordinated by the primary site. Generally most of

the expenses related to staff will be covered by existing work contracts and funding mechanisms that exist for routine operations. Remuneration of sites for trial-related activities should equate to the proportion of work the site undertakes and should be negotiated between Sponsor, primary and satellite sites at the outset. Primary sites need to be renumerated for coordination of trial activities and preparation of regulatory documentations across clusters.

3.14. Regulatory considerations

Many of the regulatory aspects of clinical trials are governed by local and state jurisdictions and are therefore beyond the scope of this document. It is important to engage with health service executives, ethics committees and research governance officers to expedite approval processes within clusters. However, a simplified and streamlined approach at state and national level may reduce the cost and expedite the approval processes.

It is recommended that the primary site takes the responsibility for preparation and submission of documents related to ethics, contracts and site-specific assessment forms (SSAs) in order to streamline and expedite the trial approval processes. Contractual, ethical and governance processes can be expedited when common standards and strong collaboration are established between primary and satellite sites within clusters.

It is prudent for clinicians or cancer centre managers who wish to participate in this model to get the support of their managers and chief executive officers especially in developing trial clusters between centres located within other health service districts and states so that governance and contract processes can be streamlined.

3.15. Indemnity, insurance and clinical trial agreements

Primary sites and the Sponsor assume responsibility for ensuring that criteria for safe care are met by all sites within a cluster. When undertaking investigator lead trials, both the primary and satellite are indemnified as per each state and territory health department provision. For industry-sponsored studies the indemnity is provided by the trial Sponsor (https://medicinesaustralia.com.au/policy/clinical-trials/indemity-and-compensation-guidelines/).

The Sponsor of a clinical trial takes overall responsibility for the conduct of the trial, including protocol design and the investigational product.

Agreements between sites within a cluster could be in the form of formal contracts, or overarching agreements such as Service Level Agreements (SLA). This matter needs to be solved at the local level between health services or at the state level through research and governance offices in collaboration with the Sponsors.

4. Conclusion and recommendations

System improvement using this model is unlikely to be achieved without added cost and additional resources for the Sponsors, hospitals and governments. Simplification and streamlining of site accreditation and selection processes, monitoring requirements, ethics, governance

and contractual matters are needed to reduce cost and workload, and to expedite approval processes.

4.1. Recommendations

1. Adoption of tele-trial models such as the Australasian Teletrial model as part of standard practice by cooperative trial groups, industry, researchers, governments, regulatory bodies, hospitals and insurers.
2. Inclusion of central review processes for site-specific authorisations within clusters.
3. Development of overarching contracts for the tele-trial model between sites within clusters in order to simplify the contract processes at local, state and national levels.
4. Development of a pre-accreditation process where the focus is on the capability of the site and the investigator at the satellite, well ahead of any trial. Once pre-accredited, a satellite should be able to recruit to any trial immediately or at short notice, if they have a candidate case. A pre-accredited satellite could then recruit to more than one primary site, provided that the trial of interest has been approved by the primary site governance and ethical approval processes. Any primary sites could pre-accredit a number of satellite sites even though different sites may be part of a cluster at different times.
5. Provision of incentives by funding bodies and government and non-government organisations for hospitals, industry or trials groups to accommodate innovative models such as the Australasian Tele-trial model in their trial protocols to improve access to clinical trials for rural and regional cancer patients.
6. Exploration of the feasibility of adopting remote monitoring systems by Sponsors and auditing authorities.

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References

[1] Hazin R, Qaddoumi I. Teleoncology: Current and future applications for improving cancer care globally. The Lancet Oncology. 2010;**11**(2):204-210

[2] Australian Institue of Health and Welfare. Cancer Survival and Prevalence in Australia: Cancers Diagnosed from 1982 to 2004. Canberra: AIHW; 2008. Cat.no. CAN38: p

[3] Jong KE, et al. Remoteness of residence and survival from cancer in New South Wales. Medical Journal of Australia. 2004;**180**:618-622

[4] Coory MD, Baade. PD. Urban–rural differences in prostate cancer mortality, radical prostatectomy and prostate-specific antigen testing in Australia. Medical Journal of Australia. 2005;**182**(3):112-115

[5] Sabesan S, Piliouras P. Disparity in cancer survival between urban and rural patients—how can clinicians help reduce it? Rural & Remote Health. 2009;**9**(3):1146

[6] Cancer Research UK (www.cancerresearchuk.org)

[7] Sabesan S, et al. Attitudes, knowledge and barriers to participation in cancer clinical trials among rural and remote patients. Asia-pacific Journal of Clinical Oncology. 2011;**7**(1):27-33

[8] Comis RL, et al. Systematic review of barriers to the recruitment of older patients with cancer on to clinical trials. Journal of Clinical Oncology. 2005;**23**:3112-3124

[9] Sabesan S, et al. Telemedicine for rural cancer care in north Queensland: Bringing cancer care home. Australian Journal of Rural Health. 2012;**20**(5):259-264

[10] Doolittle GC, Spaulding A. Providing access to oncology care for rural patients via telemedicine. Journal of Oncology Practice. 2006;**2**(5):228-230

[11] Palkhivala A. Canada develops models of teleoncology. Journal of the National Cancer Institute. 2011;**103**:1566-1568

[12] Weinerman B, et al. Can subspecialty cancer consultations be delivered to communities using modern technology?A pilot study. Telemedicine Journal and E-Health. 2005;**11**(5):608-615

[13] Sabesan S, Simcox K, Marr I. Medical oncology clinics through videoconferencing: An acceptable telehealth model for rural patients and health workers. Internal Medicine Journal. 2012;**42**(7):780-785

[14] Thaker D, et al. Cost savings from a telemedicine model of care in northern Queensland, Australia. Medical Journal of Australia. 2013;**199**(6):414-417

[15] Sabesan S, et al. Practical aspects of telehealth: Establishing Telehealth in an Institution. Internal Medicine Journal. 2014;**44**:202-205

[16] Doolittle GC, et al. A cost analysis of a tele-oncology practice. Journal of Telemedicine and Telecare. 1997;**3**(Suppl 1):20-22

[17] Chan B, et al. Do teleoncology models of care enbale safe delivery of supervised chemotherapy in rural towns? Medical Journal of Australia. 2015;**203**(10):406.e1-406.e6

[18] Sabesan S, et al. Timely access to specialist medical oncology services closer to home for rural patients: Experience from the Townsville Teleoncology Model. Australian Journal of Rural Health. 2014;**22**:156-159

[19] Queensland Health. Queensland Remote Chemotherapy Supervision Model & guide, Brisbane, Australia [Internet] 2014. Available from: https://www.health.qld.gov.au/__data/assets/pdf_file/0020/424532/qrecs-guide.pdf

[20] Jhaveri D, et al. Remote chemotherapy supervision model for rural cancer care: Perspectives of health professionals. European Journal of Cancer Care. 2015;**25**(1):93-98. DOI: 10.111/ecc.12309

[21] Sabesan S, Zalcberg J. Telehealth models could be extended to conducting clinical trials—A teletrial approach. European Journal of Cancer Care. 2016:1-4. DOI: 10.1111/ecc.12587

[22] Sabesan S. Medical models of teleoncology: Current status and future directions. Asia-Pacific Journal of Clinical Oncology. 2014;**10**(3):200-204. DOI:10.1111/ajco.1222s

[23] Doolittle GC, Allen A. Practising oncology via telemedicine. Journal of Telemedicine & Telecare. 1997;**3**(2):63-70

Chapter 11

Training Programs for Improving Communication about Medical Research and Clinical Trials: A Systematic Review

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Additional information is available at the end of the chapter

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Abstract

Objectives: The aim of this article is to provide recommendations on the structure, materials, and outcomes that should be adopted for communication training programs designed to improve clinical trial education for patients.

Methods: A systematic review of peer-reviewed articles was conducted. A total of 22 studies were included. Several dimensions were analyzed, such as program design, content development, pedagogical tools, content of the program, and the outcomes affected.

Results: The trainings described in the articles analyzed generally took the form of workshops and were developed by groups of heterogeneous experts. Trainings used a variety of educational materials and activities often developed by the research team hosting the training. The outcome measures and assessment methods were not consistent among the trainings, which hinders the ability to statistically synthetize findings.

Conclusions: Findings from the review point to a number of recommendations for the development of future clinical research communication training programs. Training programs should be developed by a team of experts with a range of expertise and should be organized in the form of workshops. Participants should be able to role-play newly acquired communication skills using standardized patients.

Keywords: clinical trials communication, training for recruiters, clinical trials recruitment, accrual, informed consent

1. Introduction

Clinical trials represent the first essential step toward the development of treatments targeting cancer and various diseases [1, 2], and allow researchers to Test the effectiveness of preventive

measures, treatments, screenings, and diagnostic techniques [3]. However, despite the evidence for the positive benefits of conducting clinical trials, and despite the overall agreement on the importance of clinical research (as evidenced by the Cancer Moonshot initiative and recent, highly funded efforts directed toward advancing precision medicine), researchers are limited by the low number of patients consenting to join clinical research studies [4, 5]. The most critical consequence of low accrual rates is that treatment effectiveness cannot be adequately assessed, even if a new regimen appears to be promising [6]. Research on the reasons for clinical trials' low accrual rates has identified several key barriers, which include a low rate of physicians' referral [7, 8]. Many physicians characterize discussions about research and clinical trials with patients as particularly challenging, a problem, which is rarely addressed, even by academic medical centers committed to the research enterprise [9].

Physicians are not the only professionals who face challenges when trying to communicate about clinical trials. In fact, clinical and medical research teams are typically composed of a heterogeneous group of professionals with specific skills and roles; these include study nurses, clinical research coordinators, research associates, nonstudy personnel, and professional recruiters [9]. Regardless of the role, however, good communication skills are necessary to meet the needs of both patients and PIs to ensure both information comprehension and accrual [10, 11]. Conversations with patients and their families intended to educate them about participation in clinical trials and research studies present unique challenges that differ significantly from typical exchanges in the provider-patient encounter. Discussions about clinical trial participation are quite challenging due to the uncertainty regarding the outcomes of clinical trials, and the complex nature of consent documents [12]. For example, a treatment recommendation that involves the possibility of enrolling in a clinical trial is fraught with uncertainty because patients are generally randomized into one of multiple treatment arms, and because the treatment itself is under study [13]. Thus, both the treatment outcomes and any possible side effects have yet to be defined. Additionally, recruiters (whether clinical research professionals, physicians, or study nurses) need to provide information through documents that are strictly governed by legal and ethical policies. The content and the structure of the consenting documents are complex and often difficult to understand for patients [14]. Many patients express concerns about the trustworthiness of the clinical research process and the experts involved [14, 15].

Because of the uncertainty associated with the treatment, the complexity of procedures and documents, the vulnerability of patients, and the often-negative attitudes of patients toward medical research, discussions about clinical trial participation can be difficult for both patients as well as clinical personnel. Because patients' intentions to enroll into a clinical trial are strongly related to the competency of communication by recruiters [16, 17], and because communication is a mediating variable in the decision process on whether or not enroll [14, 15, 18], it is essential for medical and clinical research professionals receive training on how to better communicate with patients about participating in clinical trials and research studies. Trainings specifically aimed at improving communication skills may help to increase the rate of patient accrual to clinical trials [10, 19].

Although there have been successful training programs focused on doctor-patient communication [20–25], there is little theoretical and empirical research on the best way to develop trainings for improving clinical trial communication. Previous studies of other types of communication training programs in health care environments have provided evidence that the structure of the training as well as the type of educational materials employed have dramatic consequences on

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the effectiveness of the trainings and the learning outcomes of participants [24, 26–28]. In the case of trainings to improve communication about clinical trials and research studies, there is no clear evidence about the best structure for trainings or the materials to be used. Therefore, this study aims to fill a gap in the literature by addressing the following research questions:

RQ1: How are clinical trials communication training programs structured?

RQ2: What type of content is included in communication skills training programs for those who recruit for clinical trials study?

RQ3: How are the outcomes of these trainings assessed?

2. Methods

2.1. Key terms and databases

A literature review was performed by using several databases, namely scholar.google.com, university library's database, MEDLINE, PsycINFO. The search terms used were "clinical trials training," "clinical trials recruiters training," "cancer trials training," "clinical trials recruiters' communication," and "clinical trials patients' recruitment." Second, an additional search was conducted by checking the references employed by the articles considered relevant for the purposes of the present study. This process yielded 22 articles on communication training programs designed to increase medical and nonmedical professionals' efficacy in recruiting potential participants for research studies and clinical trials.

2.2. Inclusion and exclusion criteria

In order to be included in this systematic review, the studies had to meet several criteria. First, they had to deliver and test educational trainings; second, participants in the trainings had to be health care professionals; third, the trainings had to provide instructions and educational materials or activities to improve clinical trial communication skills. After a careful review of the literature, 22 studies were found to be appropriate for the present systematic review. Further, in order to be considered in this systematic review, the studies had to meet the following inclusionary criteria: report on physicians' and medical personnel communication strategies to recruit patients; provide empirical evidence rather than theoretical assertions or recommendations (that is, qualitative or quantitative data had to be reported), and results had to be published in a peer-review journal.

2.3. Data extraction and analysis

Information from the studies selected for this project was summarized into tables and compared across studies. Key information that was retrieved included authors' names, year of publication, country where the trainings were conducted, journal in which the findings were published, theoretical background, methods adopted for the study, type of training, demographics, content development methodology, format of educational material, timing of the program, and learning assessment.

3. Results

From the search for relevant studies, the authors included a total of 22 studies conducted between 1998 and 2016. All of the articles included in the present study were published in peer-reviewed journals. The majority of the studies did not report using a theoretical framework as basis for the communication training program. Also, the majority of the studies did not provide exhaustive information about participants' demographics. When these data were available (7 studies out of 22), more participants were reported to be female, for a total of 275 females participating versus 212 total males participating. When data were available about the profession of participants (12 studies out of 22), Participants included 658 physicians, 373 nurses, 29 research coordinators, and only 1 person described as a professional recruiter, although all participants in these training programs were responsible for recruiting patients for clinical trials. Half of the studies assessed the effectiveness of training by using quasi-experimental designs; two of the remaining studies used survey as data collection methodology, and the other two studies used qualitative methodologies. Only 8 studies out of 22 reported whether the intervention was the first communication raining experience for participants, or not.

3.1. Design of training programs

With regard to the type of training developed and implemented, 18 studies out of the 22 analyzed employed a workshop format, while 1 training utilized coaching sections and peer-reviews [10]. Duration of the trainings varied across studies, ranging from a minimum of 3 hours, to a maximum of three days. Some trainings were spread over 2 days [29–31] or 3 days [46]. In the majority of the studies, participants selfselected into the training programs. Consistent with what has been observed in the literature on communication training in health care environments [32], the duration of the training programs seems to be an indicator of their effectiveness, with the longest trainings having the most positive outcomes. Information about the design of the trainings for each study is presented in **Table 1**.

3.2. Content development and pedagogic tools

The educational content of the trainings reviewed was varied, as was the source material used. Seventeen studies reported creating original content for their training, using source material that included the team's own original research, and collaborations with experts, such as oncologists, nurses, and clinical trials managers. One study explicitly reported the contributions of patients [30]. Another publication did not describe the process of developing the material, but reported that the training was done by instructors with previous experience in teaching communication skills to physicians. Similarly, the pedagogical tools adopted were varied. There was a general preference for the use of video materials, such as DVDs or videotaped scenarios, which were used in 10 training programs [29, 30, 33–40]. Other formats used included case studies, vignettes, instructional manuals, dummy referral letters, protocols, and didactic presentations. The majority of the trainings included role-playing activities, and/or review of real-world discussions among recruiters and patients (whether actual or standardized patients). In many cases, checklists were used to standardize the observation

Study	Design	Control group	Content development	Format educational material	Duration	Sensitive words explained
Fallowfield et al. [29]	Experiment	Yes	Authors, physicians and nurses	Workshop, five DVD-based scenarios + handbook, dummy referral letters outlining patients' histories, bibliography	8 h, 2 days	N/A
Jenkins et al. [30]	Experiment	N/A	Authors, recruiters physicians, nurses trial managers, and patients	Workshop, interactive exercise, didactic presentations, four DVD-based scenarios + handbook	8 h, 2 days	Yes, randomization and placebo
Fallowfield et al. [39]	Experiment	No	Authors	Workshop, exercise and activities: small groups critiques, SP*, video reviews; videotaped scenarios; case histories, comprehensive handbook; papers; annotated bibliography	3 day course	Yes
Brown et al. [37]	Survey and conversation	Yes	Previous research with experts from different fields	Workshop, strategies document, presentation of strategies, video model of ideal behavior, role-played (standardized patient)	1 day	N/A
Fallowfield et al. [40]	Experiment, survey and conversation	No	Authors	Workshop, exercise and activities: small groups critiques, SP, video reviews; videotaped scenarios; case histories, comprehensive handbook; papers; annotated bibliography	3 days or 1.5 days	No
Hietanen et al. [41]	Survey	No	Experts: oncologist-psychotherapists	Workshop, lecture, role-played with real patients	1 day	Yes, randomization
Mann et al. JAN. 2014	Interviews	Yes	Trial team	APEX trial protocol and research literature	N/A	Yes, randomization

Study	Design	Control group	Content development	Format educational material	Duration	Sensitive words explained
Paramasivan et al. T. 2011	Content, thematic, and conversation analysis	No	Previous research from the team	Workshop, lecture (face to face and teleconference)	N/A	Yes, randomization
Larson et al. [11]	Experiment	No	Authors and administrative offices	Workshop, lecture, vignettes, role-played	3 h	N/A
Cadman et al. [33]	Experiment	No	NIMH—no info on the development	Workshop, video, didactic lecture	N/A	No
Bernhard et al. [35]	Experiment	Yes	Authors based on the available literature	Workshop with didactic presentation and video, strategies document, feedback	7 h	No
Yap et al. [36]	Observation and interviews with patients	Yes	Authors using materials from previous projects	Workshop with didactic presentation, slides, pocket card, scientific article, audiotaped examples	N/A	Yes, randomization
Kendall et al. [43]	Quantitative: changes in recruitment rates	Yes	Not produced by authors. The source is unspecified (US based)	Didactic presentation and educational material	N/A	N/A
Jenkins et al. [31]	Experiment	No	Authors	Workshop with didactic presentation, trial planning, team-building exercise, role-playing, open discussion	1.5 days	N/A
Fallowfield et al. [44]	Experiment	No	Authors	Workshop	1 day	N/A
Donovan et al. [45]	Mixed method	No	Authors based on formative research	Workshop, document, feedback, role-playing	N/A	Yes, randomization
Mills et al. T 2014	Content and thematic analysis	No	N/A	Documents, individual and group discussions, role-play	N/A	Yes, randomization
Butow et al. HE 2015	Experiment	Yes	Authors using materials from previous projects	Workshop, video, role-play, individualized feedback	7 h	N/A

Study	Design	Control group	Content development	Format educational material	Duration	Sensitive words explained
Wuensch et al. EJoCC. 2011	Survey	No	Authors using formative research	Workshop, role-play, pocket card, feedback from experts & colleagues	17 h	Yes, randomization
Wells et al. [47]	Quasi-experiment	Yes	Authors using formative research	In-person and online training	N/A	N/A
Kimmick et al. [38]	Experiment	Yes	N/A	Educational symposium, lecture outline, videos, emails, checklists, case discussion seminar, bibliography, slides	N/A	No
Burnett et al. [48]	Experiment	No	Authors using formative research (literature review)	Workshop, reflective practice component	1 day	Yes, randomization

Table 1. Design and content of the training.

and analysis of such discussions. **Table 1** reports the role and profession of the people who developed the content and materials used in the trainings, as well as the formats used in each training.

3.3. Information conveyed

Several areas of focus for the trainings were reported. Six studies [10, 13, 29, 38, 42, 46], reported training participants on the importance of assessing the eligibility of patients for the clinical trials. Authors reported assessing participants' performance on how to offer the opportunity to participate in clinical trials (with the exception of [40], which does not explicitly mention it). Only six studies instructed participants how to address possible benefits and side effects associated with clinical trials participation [11, 29, 35, 37, 45, 46]. Generally, authors did not recommend different communication strategies for different phases of clinical trials. Seven trainings out of the 22 analyzed in this review instructed participants on how to check for patients' understanding of the information provided [10, 13, 29, 30, 34, 37, 42]. In this regard, Mann et al. [10] and Brown et al. [37] reported "summarizing" as a useful technique to check for patients' understanding. Other topics specifically addressed by the training programs included how to explain the aims of clinical trials [10, 13, 29, 30, 39, 41], the importance of informing patients about the voluntariness of their potential enrollment [10, 11, 29, 30, 33], or the importance of avoiding coercive behaviors and/or the importance of adopting a shared decision making process [34, 35, 37]. In some training, participants were instructed on strategies for clarifying key terms such as "randomization" and "placebo," which tend to be difficult for a large proportion of patients to understand or accept [10, 13, 30, 36, 39, 41, 42, 45, 46, 48]. Few studies explicitly addressed concerns and strategies to successfully deal with potential participants' struggle to manage uncertainty [29, 30, 36, 37, 42]. Ultimately, only 3 studies out of 22 specifically discussed the role that family members play in influencing patients' decisions on whether to enroll or not in clinical trials or provided training on how to better address family members' concerns [29, 30, 36, 40, 47]. A summary of the main information conveyed is shown in **Table 2**.

3.4. Assessments

Whether training programs had a concrete impact on the communication skills of the participants was assessed through several means. Consistent with the literature on trainings to improve physician-patient communication [27, 49, 50], one of the most widely adopted strategies (13 studies out of 22) consisted of an evaluation of audio recorded interactions of participants in the training programs with either real-world patients or standardized patients. Similarly, 16 studies reported having used self-assessments, although specific measures differed across studies. In one study [41], the self-assessment consisted in a qualitative description of the experience participants in the training program had when interacting with patients. Only three studies did not explicitly report any assessment of the outcomes [11, 38, 43]. Although similar methodologies were used, the outcomes of the trainings tended to differ significantly across studies. The strategies used to assess the communication trainings are shown in **Table 3**.

Study	Key information offered	Scenarios	Patient is suitable	Participation offered
Fallowfield et al. [29]	Scenarios portraying different trials, tumor sites, and patient characteristics; communicating risks; checking for understanding	Stressed person communication demands; talking about innovativeness of the treatment; interacting with family members; communication difficulties when dealing with failing tests; communication for Phase II; study retention	Yes	Yes
Jenkins et al. [30]	Scenarios portraying how to structure trial discussions; how to describe treatments available; process of randomization; checking for understanding	(1) Introduction to trials, concept of randomization, difficulties associated with trials (use of different perspectives); (2) adjuvant treatment and uncertainty; (3) distressed patients, dealing with questions; (4) dealing with patients with preference for a specific study arm	No	Yes
Fallowfield et al. [39]	Skills development; knowledge acquisition; personal awareness	N/A	No	Yes
Brown et al. [37]	Scenarios informing on shared decision making; structuring consultations, risks & benefits; checking for understanding; providing clear & comprehensive information; avoiding coercion	Patient with stage II breast cancer	N/A	Yes
Fallowfield et al. [40]	Breaking bad news; discussing therapeutic options; informed consent; talking with relatives; psychosocial concerns	N/A	N/A	N/A
Hietanen et al. [41]	Articles and checklist published on information about CT and informed consent	N/A	No	Yes
Mann et al. JAN. 2014	APEX trial protocol and research literature; checking for understanding	Interviews considered effective	Yes	Yes
Paramavisan et al. T 2011	Lecture (face-to-face and teleconference); checking for understanding	N/A	Yes	Yes
Larson et al. [11]	Personal experience; principles of ethical conduct; key elements of consent process; risks and benefits of participation; voluntary nature of research; purpose of research	N/A	No	No

Study	Key information offered	Scenarios	Patient is suitable	Participation offered
Cadman et al. [33]	Communication skills (style, use of plain language, body language, tone of voice, eye-contact); contextual elements (environment); relevant elements of informed consent; importance of relationship building	Mental health, but authors suggest that the video can be used to improve informed consent in general; study presentation; risks & benefits; alternative treatments; confidentiality & patients' rights; voluntariness of participation	No	N/A
Bernhard et al. [35]	Shared decision making; sequential information disclosure; clarity; disclosing controversial information; avoiding coercive communication	Breast cancer patients	N/A	N/A
Yap et al. [36]	Communication skills (positive and negative examples); importance of considering emotional preparedness of patients & family members; metaphors to explain randomization; stressed person communication demands; literacy concerns	Children and their family members	N/A	Yes
Kendall et al. [43]	Specifically tailored to the needs of the recruitment site	N/A	N/A	N/A
Jenkins et al. [31]	Team-specific involvement in research; patients' attitudes; problematic trials; interpersonal communication with team members; planning strategies; identification of potential issues in the patient sheet	Cancer teams in UK	N/A	Yes
Fallowfield et al. [44]	Tailored to the needs of the site; trials planning; quality of patient sheet; interpersonal communication; time management	Breast cancer teams	N/A	Yes (actual recruitment)
Donovan et al. [45]	Tips for recruitment; case studies; informed consent process; risks/benefits; importance of randomization	N/A	N/A	Yes
Mills et al. T 2014	Importance of eliciting and exploring treatments preferences; strategies to explain randomization; importance of balance of arms	N/A	Yes	Yes

Study	Key information offered	Scenarios	Patient is suitable	Participation offered
Butow et al. HE 2015	Shared decision making framework; correctly sequence information; ensure clarity; avoid coercion	Breast cancer trials	N/A	Yes
Wuensch et al. EJoCC 2011	Opening of discussion; disclosing risks and benefits; offering participation; clarifying meaning of randomization	Oncology clinical trials	Yes	Yes
Wells et al. [47]	Barriers, beliefs, social norms, myths of African Americans and Hispanics about clinical trial enrollment	Radiation therapy	No	No
Kimmick et al. [38]	Importance of mental status assessment; assess depression, cognition, comorbidity	Geriatric oncology clinical trials	Yes	No
Burnett et al. [48]	Importance of clinical trials; types of clinical trials; benefits; randomization; answer questions; provide screening recommendations, barriers	Nursing oncology clinical trials	N/A	N/A

Table 2. Information conveyed.

3.5. Improved outcomes

Clinical trial communication training programs influenced several outcomes. In seven studies, participants reported increased confidence in their ability to better interact with and educate patients. However, in terms of better communication of clinical trials, only a few studies reported strong effects [29, 30, 33, 36, 41], with only one article reporting modest but significant changes [39]. A study by Brown et al. [37] reported no significant improvement in participants' ability to provide clinical information, nor did they report differences in the way participants structured their consultations. However, the authors reported improvements in shared-decision making behaviors, and in refraining from using coercive behaviors [37]. Fallowfield et al. [40] demonstrated improvements in participants' communication and information provision skills as a result of the training, even if communication about clinical trials specifically was not significantly affected by training. In one study [10], participants reported increased knowledge of trial design, and an improved ability to adhere to the study protocol after receiving the training. Mills et al. [13] observed that after the training participants improved in their ability to address patients' preferences. Only three studies assessed and obtained improvements in accrual rates [38, 43, 47]. The positive changes associated with training participation are shown in **Table 3**.

Study	Audio-taped assessment	Patient simulator assessment	Participants generate list of optimal points	Strategies/key points document	Subjective assessment/survey	Outcomes considered
Fallowfield et al. [29]	Yes	Yes	Yes	Yes	Yes	Self-confidence; communication of trial entry; voluntariness; questions asking; discussion of symptom control; permit time for consideration; discussion of aims
Jenkins et al. [30]	Yes	Yes	Yes	Yes	Yes	Communication of trials; use of key words; check patient understanding; self-confidence
Fallowfield et al. [39]	Yes	Yes	N/A	N/A	Yes	Quality of the course material; expression of empathy; communication skills
Brown et al. [37]	Yes	Yes	No	Yes	Yes	Shared decision-making behavior; reduction of coercive behaviors. Patients' attitudes; Physicians' behavior
Fallowfield et al. [40]	Yes	Yes	No	No	Yes	Confidence; discussion of clinical trials; communication skills; self-awareness; improvement in the consent process
Hietanen et al. [41]	No but voice feedback	Yes	No	No	No but description of personal experience	Psychosocial reaction; interviewing techniques; patients' needs when receiving info about CT
Mann et al. JAN 2014	Yes	No	No	No	Yes	Protocol adherence; knowledge of trial design; acceptability of the training; communication skills

Study	Audio-taped assessment	Patient simulator assessment	Participants generate list of optimal points	Strategies/key points document	Subjective assessment/survey	Outcomes considered
Paramavisan et al. T 2011	No	No	N/A	Yes (tips)	Yes (from interviews)	Confidence; addressing patients' preferences/ concerns; knowledge of informed consent elements
Larson et al. [11]	N/A	Yes	N/A	N/A	N/A	Enthusiasm and surprise about the perceived improvement
Cadman et al. [33]	No	No	No	No	Yes	Knowledge of informed consent elements; communication; contextual factors
Bernhard et al. [35]	Yes	No	No	Yes	Yes	Reduction of patients' decisional conflict; patients' involvement; reduction of patients' anxiety
Yap et al. [36]	Yes	No	No	No	Yes, completed by patients	Adoption of a sequence approach; eliciting questions; clarifying concepts
Kendall et al. [43]	No	No	No	No	No	Accrual
Jenkins et al. [31]	No	No	No	No	Yes	N* of patients approached; professionals' involvement with the trial; awareness; confidence
Fallowfield et al. [44]	No	No but used role-play	No	No	Yes	Awareness of other members' roles; confidence; facilitation of the workshop; role-play; planning
Donovan et al. [45]	Yes	Yes	No	No	No	Use of right documents; completion of informed consent; accrual

Study	Audio-taped assessment	Patient simulator assessment	Participants generate list of optimal points	Strategies/key points document	Subjective assessment/survey	Outcomes considered
Mills et al. T 2014	Yes	No	No	No	No	Addressing patients' treatments' preferences; improvement in informed consent process
Butow et al. HE. 2014	Yes	Yes	No	No	Yes	Shared decision-making; high satisfaction
Wuensch et al. EJoCC. 2011	Yes	Yes	No	No	Yes	Acceptance of the training; relevance of the training; appreciation of the training
Wells et al. [47]	No	No	No	No	Yes	Accrual; knowledge; attitudes
Kimmick et al. [38]	No	No	No	No	No	Accrual; accrual per type of treatment
Burnett et al. [48]	No	No	No	No	Yes	Knowledge; attitudes; confidence; format of the workshop; atmosphere; usefulness; and quality of the workshop

Table 3. Assessment and improved outcomes.

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4. Discussion

This study presents a systematic review of published articles on trainings to improve communication about clinical trials with patients. From the review, it appeared that the majority of the trainings followed the format of a workshop, as also observed in a previous review [51]. The duration of the trainings ranged from 3 hours to 3 days. According to literature on communication training programs for physicians (not specifically aimed at improving clinical trial communication), the optimal length for a training workshop seems to be 3 days [32]. However, currently there are not enough data to confirm these results in a clinical trial communication context.

In the majority of the articles reviewed, the educational materials used in the trainings were developed through the collaborative efforts of several experts with diverse backgrounds, including oncologists, clinical trial coordinators, researchers, and nurses. Having an interdisciplinary team seems to be a common strategy for successfully developing trainings to improve clinical trial communication. In order to further enhance educational materials and messages' effectiveness, appeal, and clarity, it may be beneficial to include communication researchers in the team.

The pedagogical materials were quite varied across trainings; despite this, there seemed to be a preference for visual forms of communication such as videos and vignettes, and role-playing [52, 53]. Many training programs used checklists in order to help both participants and educators to assess the outcomes of recruiters-patient interactions (both when the conversation was reproduced in videos, as well as during role-playing). These checklists were described as useful educational tools by all the studies and should be included in future training protocols, even if specific details on the content of these checklists are only approximately reported in the articles. Trainings themselves focused on several topics. A portion of this information is consistent with the recommendations provided by the literature on clinical trials accrual [5, 9, 54]. However, the choice of topics differed across the trainings, and not all key areas were reported as having been covered. Research teams generally collected preliminary data to provide better targeted information; this strategy is consistent with recommendations from previous studies focusing on communication trainings for physicians [55, 56], which encouraged trainers to consider contextual factors and characteristics of the organizations in which participants operate. However, future programs should provide content that is consistent with research on the barriers faced by potential participants in order to develop well-design trainings that are geared toward effective patient education. A first step toward this goal would be establishing an agreement on the outcomes that should be obtained through communication trainings to improve clinical trial accrual. In addition, only few studies reported positive, significant changes in participants' recruiting skills, although all participants reported increased confidence and satisfaction with the training. This is in line with findings from Townsend et al. [51]. Unfortunately, the fact that outcomes differed by study hindered our ability to statistically analyze results from the entire body of literature.

The articles synthetized in this paper represent an important effort toward the improvement of patient education about participation in clinical trials and research studies, and potentially, an increase in accrual rates. However, despite having conducted an extensive literature search, only 22 studies were found as adequate to be included in this systematic review. In our opinion, this finding alone is sufficient to call for additional studies aimed at evaluating the efficacy

of trainings for improving clinical trial communication and subsequently, patient satisfaction with the enrollment/consent process as well as improved accrual rates for clinical trials.

This study contributes to the emerging literature on clinical trial communication, and to the literature addressing clinical trials planning processes. Despite its contributions, this systematic review presents certain limitations. Only peer-reviewed studies were included; there is the possibility that other teams have conducted training programs to improve clinical trial communication and have disseminated findings in formats other than peer-reviewed journals. Future reviews should search for such materials and include them in their analysis. In addition, only materials in English were included, but it is possible that studies have been published in other languages.

5. Conclusion

Despite the wide diffusion of communication trainings for physician and medical personnel, only a few studies were retrieved with regard to specific trainings on communication about clinical trials. These studies demonstrated significant impact on outcomes such as participants' satisfaction, self-confidence, and understanding of the design of clinical trials. However, few training demonstrated any significant improvement in participants' recruiting skills. In light of the urgency of the need to increase clinical trial accrual, improved communication training may be an effective way to support recruitment goals. Researchers should further define the most effective strategies to meet the educational needs of professional recruiters, research coordinators, and study personnel, with the ultimate goal of improving accrual rates and the quality of patients' experience while enrolled in clinical trials and research studies.

5.1. Practice implications

Training programs for improving communication with patients about participation in clinical trials and research studies should be developed based on the insights from several experts, including social scientists focused on communication. These trainings should be organized in the form of workshops, where participants can receive both didactic education and the opportunity to role-play new communication skills. Role-playing exercises may prove to be particularly effective with standardized patients, if such a resource is available. The use of checklists during observations of role-plays is recommended as an objective test of behavioral outcomes. The long-term outcomes of the training on patient satisfaction with the enrollment and consenting process as well as study accrual rates should be carefully defined and assessed.

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References

[1] Friedman DB, Kim SH, Tanner A, Bergeron CD, Foster C, General K. How are we communicating about clinical trials? An assessment of the content and readability of recruitment resources. Contemporary Clinical Trials. 2014;**38**:275-283. DOI: 10.1016/j.cct.2014.05.004

[2] Quinn GP, McIntyre J, Gonzalez LE, Antonia TM, Antolino P, Wells KJ. Improving awareness of cancer clinical trials among Hispanic patients and families: Audience segmentation decisions for a media intervention. Journal of Health Communication. 2013;**18**:1131-1147. DOI: 10.1080/10810730.2013.768723

[3] Langford A, Resnicow K, An L. Clinical trial awareness among racial/ethnic minorities in HINTS 2007: Sociodemographic, attitudinal, and knowledge correlates. Journal of Health Communication. 2010;**15**:92-101. DOI: 10.1080/10810730.2010.525296

[4] Haddad RI, Chan ATC, Vermorken JB. Barriers to clinical trial recruitment in head and neck cancer. Oral Oncology. 2015;**51**:203-211. DOI: 10.1016/j.oraloncology.2014.12.007

[5] Albrecht TL, Eggly SS, Gleason MEJ, Harper FWK, Foster TS, Peterson AM, Orom H, Penner LA, Ruckdeschel JC. Influence of clinical communication on patients' decision making on participation in clinical trials. Journal of Clinical Oncology. 2008;**26**:2666-2673. DOI: 10.1200/JCO.2007.14.8114

[6] Carter RE, Sonny SC, Brady KT. Practical considerations for estimating clinical trial accrual periods: Application to a multi-center effectiveness study. BMC Medical research Methodology. 2005;**5**:1-5. DOI: 10.1186/1471-2288-5-11

[7] Kaplan CP, Nápoles AM, Dohan D, Hwang ES, Melisko M, Nickleach D, Quinn JA, Haas J. Clinical trial discussion, referral, and recruitment: Physician, patient, and system factors. Cancer Causes & Control. 2013;**24**:979-988. DOI: 10.1007/s10552-013-0173-5

[8] Foley JF, Moertel CG. Improving accrual into cancer clinical trials. Journal of Cancer Education. 1991;**6**:165-173. DOI: 10.1080/08858199109528114

[9] Parreco LK, DeJoice RW, Massett HA, Padberg RM, Thakkar SS. Power of an effective clinical conversation: Improving accrual onto clinical trials. Journal of Oncology Practice. 2012;**8**:282-286. DOI: 10.1200/JOP.2011.000478

[10] Mann C, Delgado D, Horwood J. Evaluation of internal peer-review to train nurses recruiting to a randomized controlled trial–Internal Peer-review for Recruitment Training in Trials (InterPReTiT). Journal of Advanced Nursing. 2014;**70**:777-790. DOI: 10.1111/jan.12254

[11] Larson EL, Cohn EG, Meyer DD, Boden-Albala B. Consent administrator training to reduce disparities in research participation. Journal of Nursing Scholarship. 2009;**41**:95-103. DOI: 10.1111/j.1547-5069.2009.01256.x

[12] Krieger JL, Palmer-Wackerly A, Dailey PM, Krok-Schoen JL, Schoenberg NE, Paskett ED. Comprehension of randomization and uncertainty in cancer clinical trials decision making

among rural, Appalachian patients. Journal of Cancer Education. 2015;**30**:743-748. DOI: 10.1007/s13187-015-0789-0

[13] Mills N, Blazeby JM, Hamdy FC, Neal DE, Campbell B, Wilson C, Paramasivan S, & Donovan JL. Training recruiters to randomized trials to facilitate recruitment and informed consent by exploring patients' treatment preferences. Trials, 2014;**15**:1-13

[14] Albrecht TL, Ruckdeschel JC, Riddle DL, Blanchard CG, Penner LA, Coovert MD, Quinn G. Communication and consumer decision making about cancer clinical trials. Patient Education and Counselling. 2003;**50**:39-42. DOI: http://dx.doi.org/10.1016/S0738-3991(03)00078-8

[15] Albrecht TL, Blanchard C, Ruckdeschel JC, Coovert M, Strongbow R. Strategic physician communication and oncology clinical trials. Journal of Clinical Oncology. 1999;**17**:3324-3332

[16] Morgan SE, Mouton A, Occa A, Potter J. Clinical trial and research study recruiters' verbal communication behaviors. Journal of Health Communication. 2016;**21**:1-8. DOI: http://dx.doi.org/10.1080/10810730.2016.1157654

[17] Morgan SE, Occa A, Mouton A, Potter J. The role of nonverbal communication behaviors in clinical trial and research study recruitment. Health Communication. 2016;**32**:1-9. DOI: http://dx.doi.org/10.1080/10410236.2016.1140266

[18] Morgan SE, Mouton A. Improving patient accrual to research studies through communication design interventions. In: Harrison TH, Williams E, editors. Organizations, Communication, and Health. New York, NY: Routledge. 2015;82-100

[19] Fletcher B, Gheorghe A, Moore D, Wilson S, Damery S. Improving the recruitment activity of clinicians in randomised controlled trials: A systematic review. BMJ Open. 2012;**2**:e000496. DOI: 10.1136/bmjopen-2011-000496

[20] Cegala DJ. Patient communication skills training: A review with implications for cancer patients. Patient Education and Counselling. 2003;**50**:1-94. DOI: http://dx.doi.org/10.1016/S0738-3991(03)00087-9

[21] Cegala DJ, Lenzmeier BS. Physician communication skills training: A review of theoretical backgrounds, objectives and skills. Medical Education. 2002;**36**:1004-1016. DOI: 10.1046/j.1365-2923.2002.01331.x

[22] Cegala DJ, McClure L, Marinelli TM, Post DM. The effects of communication skills training on patients' participation during medical interviews. Patient Education and Counselling. 2000;**41**:209-222. DOI: http://dx.doi.org/10.1016/S0738-3991(00)00093-8

[23] van Dalen J. Communication skills in context: Trends and perspectives. Patient Education and Counselling. 2013;**92**:292-295. DOI: http://dx.doi.org/10.1016/j.pec.2013.05.020

[24] Berkhof M, van Rijssen HJ, Schellart AJ, Anema JR, van der Beek AJ. Effective training strategies for teaching communication skills to physicians: An overview of systematic reviews. Patient Education and Counselling. 2011;**84**:152-162. DOI: http://dx.doi.org/10.1016/j.pec.2010.06.010

[25] Ammentorp J, Sabroe S, Kofoed PE, Mainz J. The effect of training in communication skills on medical doctors' and nurses' self-efficacy: A randomized controlled trial. Patient Education and Counselling. 2007;**66**:270-277. DOI: http://dx.doi.org/10.1016/j.pec.2006.12.012

[26] Sarbaz M, Kimiafar K, Taherzadeh Z, Naderi H, Eslami S. Effect of modifying the information and training structure on the occupational safety of health care workers in exposure to blood and body fluids: A quasi-experimental study. American Journal of Infection Control. 2016;**45**:80-82. DOI: http://dx.doi.org/10.1016/j.ajic.2016.05.023

[27] Lane C, Rollnick S. The use of simulated patients and role-play in communication skills training: A review of the literature to August 2005. Patient Education and Counselling. 2007;**67**:13-20. DOI: http://dx.doi.org/10.1016/j.pec.2007.02.011

[28] Aspegren K. BEME Guide No. 2: Teaching and learning communication skills in medicine-a review with quality grading of articles. Medical Teacher. 1999;**21**:563-570

[29] Fallowfield LJ, Solis-Trapala I, Jenkins VA. Evaluation of an educational program to improve communication with patients about early-phase trial participation. The Oncologist. 2012;**17**:377-383. DOI: 10.1634/theoncologist.2011-0271

[30] Jenkins V, Fallowfield L, Solis-Trapala I, Langridge C, Farewell V. Discussing randomised clinical trials of cancer therapy: Evaluation of a Cancer Research UK training programme. British Medical Journal. 2005;**330**:1-6. DOI: 10.1136/bmj.38366.562685.8F

[31] Jenkins VA, Farewell D, Farewell V, Batt L, Wagstaff J, Langridge C, Fallowfield LJ, Teams Talking Trials Steering Committee. Teams talking trials: Results of an RCT to improve the communication of cancer teams about treatment trials. Contemporary Clinical Trials. 2013;**35**:43-51

[32] Stiefel F, Barth J, Bensing J, Fallowfield L, Jost L, Razavi D, Kiss A. Communication skills training in oncology: A position paper based on a consensus meeting among European experts in 2009. Annals of Oncology. 2010;**21**:204-207. DOI: 10.1093/annonc/mdp564

[33] Cadman ME, Murphy JH, Brintnall-Karabelas J, Squires C, Whorton K, Pao M. A training program for improving the informed consent discussion between clinical researchers and their subjects. Journal of Empirical Research on Human Research Ethics. 2014;**9**:71-75

[34] Butow P, Brown R, Aldridge J, Juraskova I, Zoller P, Boyle F,… Bernhard J. Can consultation skills training change doctors' behaviour to increase involvement of patients in making decisions about standard treatment and clinical trials: A randomized controlled trial. Health Expectations. 2015;**18**:2570-2583

[35] Bernhard J, Butow P, Aldridge J, Juraskova I, Ribi K, Brown R. Communication about standard treatment options and clinical trials: Can we teach doctors new skills to improve patient outcomes? Psycho-Oncology. 2012;**21**:1265-1274

[36] Yap TY, Yamokoski A, Noll R, Drotar D, Zyzanski S, Kodish ED, Multi-site Intervention Study to Improve Consent Research Team. A physician-directed intervention: Teaching and measuring better informed consent. Academic Medicine. 2009;**84**:1036-1042

[37] Brown RF, Butow PN, Boyle F, Tattersall MHN. Seeking informed consent to cancer clinical trials; Evaluating the efficacy of doctor communication skills training. Psycho-Oncology. 2007;**16**:507-516. DOI: 10.1002/pon.1095

[38] Kimmick GG, Peterson BL, Kornblith AB, Mandelblatt J, Johnson JL, Wheeler J,… Muss HB. Improving accrual of older persons to cancer treatment trials: A randomized trial comparing an educational intervention with standard information: CALGB 360001. Journal of Clinical Oncology. 2005;**23**:2201-2207

[39] Fallowfield L, Jenkins V, Farewell V, Saul J, Duffy A, Eves R. Efficacy of a Cancer Research UK communication skills training model for oncologists: A randomised controlled trial. The Lancet. 2002;**359**:650-656. DOI: 10.1016/S0140-6736(02)07810-8

[40] Fallowfield L, Lipkin M, Hall A. Teaching senior oncologists communication skills: Results from phase I of a comprehensive longitudinal program in the United Kingdom. Journal of Clinical Oncology. 1998;**16**:1961-1968

[41] Hietanen PS, Aro AR, Holli KA, Schreck M, Peura A, Joensuu HT. A short communication course for physicians improves the quality of patient information in a clinical trial. Acta Oncologica. 2007;**46**:42-48. DOI: 10.1080/02841860600849067

[42] Paramasivan S, Huddart R, Hall E, Lewis R, Birtle A, Donovan JL. Key issues in recruitment to randomised controlled trials with very different interventions: A qualitative investigation of recruitment to the SPARE trial (CRUK/07/011). Trials. 2011;**12**:1-15. DOI: 10.1186/1745-6215-12-78

[43] Kendall B, Städeli R, Schegg B, Olbrich M, Chen E, Harmelin-Kadouri R, Aurup P, Hildemann SK. Clinical Trial Educator program—A novel approach to accelerate enrollment in a phase III International Acute Coronary Syndrome Trial. Clinical Trials. 2012;**9**:358-366

[44] Fallowfield L, Langridge C, Jenkins V. Communication skills training for breast cancer teams talking about trials. The Breast. 2014;**23**:193-197

[45] Donovan JL, Lane JA, Peters TJ, Brindle L, Salter E, Gillatt D,… ProtecT Study Group. Development of a complex intervention improved randomization and informed consent in a randomized controlled trial. Journal of Clinical Epidemiology. 2009;**62**:29-36

[46] Wuensch A, Goelz T, Bertz H, Wirsching M, Fritzsche K. Disclosing information about randomised controlled trials in oncology: Training concept and evaluation of an individualised communication skills training for physicians COM-ON-rct. European Journal of Cancer Care. 2011;**20**:570-576

[47] Wells JS, Pugh S, Boparai K, Rearden J, Yeager KA, Bruner DW. Cultural competency training to increase minority enrollment into radiation therapy clinical trials—An NRG oncology RTOG study. Journal of Cancer Education. 2016;1-7

[48] Burnett C, Bullock L, Collins CA, Hauser L. Evaluation of a clinical cancer trial research training workshop: Helping nurses build capacity in Southwest Virginia. Public Health Nursing. 2016;**33**:565-572

[49] Colletti L, Gruppen L, Barclay M, Stern D. Teaching students to break bad news. The American Journal of Surgery. 2001;**18**:220-223. DOI: http://dx.doi.org/10.1016/S0002-9610(01)00651-1

[50] Haist SA, Wilson JF, Pursley HG, Jessup ML, Gibson JS, Kwolek DG, Stratton TD, Griffith CH. Domestic violence: Increasing knowledge and improving skills with a four-hour workshop using standardized patients. Academic Medicine. 2003;**78**:S24-26

[51] Townsend D, Mills N, Savović J, Donovan JL. A systematic review of training programmes for recruiters to randomised controlled trials. Trials. 2015;**16**:432

[52] Chant S, Jenkinson TIM, Randle J, Russell G. Communication skills: Some problems in nursing education and practice. Journal of Clinical Nursing. 2002;**11**:12-21. DOI: 10.1046/j.1365-2702.2002.00553.x

[53] Wilkinson S, Roberts A, Aldridge J. Nurse–patient communication in palliative care: An evaluation of a communication skills programme. Palliative Medicine. 1998;**12**:13-22. DOI: 10.1191/026921698675034697

[54] Fleisher L, Ruggieri DG, Miller SM, Manne S, Albrecht T, Buzaglo J, Collins MA, Katz M, Kinzy TG, Liu T, Mannig C, Charap ES, Millard J, Miller DM, Poole D, Raivitch S, Roach N, Ross EA, & Meropol NJ. Application support tools: The preparatory education about clinical trials (PRE-ACT) study. Patient Education and Counseling. 2014;**96**:63-71

[55] Uitterhoeve RJ, Bensing JM, Grol RP, Demulder PHM, van Achterberg T. The effect of communication skills training on patient outcomes in cancer care: A systematic review of the literature. European Journal of Cancer Care. 2010;**19**:442-457. DOI: 10.1111/j.1365-2354.2009.01082.x

[56] Baldwin TT, Ford JK. Transfer of training: A review and directions for future research. Personnel Psychology. 1988;**41**:63-105. DOI: 10.1111/j.1744-6570.1988.tb00632.x

Chapter 12

Assessing Communication Practice during Clinical Trial Recruitment and Consent: The Clinical Trial Communication Inventory (CTCI)

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Additional information is available at the end of the chapter

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Abstract

The development and evaluation of training programs with the potential to improve informed consent and accrual to clinical trials depend heavily on the ability to measure outcomes of these trainings. In this chapter, we present the development of an instrument, the clinical trial communication inventory (CTCI). Data were collected from 87 clinical research professionals at three academic medical centers, which were analyzed using factor analytic methods and reliability testing procedures. This testing resulted in eight subscales representing verbal, nonverbal, and privacy protection behaviors. While the final CTCI instrument would benefit from further validity testing, it represents a resource that can be used to evaluate future trainings of research professionals.

Keywords: clinical trial communication, accrual, verbal & nonverbal communication, informed consent, measures

1. Introduction

The abysmal rate of accrual to clinical trials, particularly among members of minority and underserved populations, has impeded medical and scientific progress [1]. Ironically, when members of marginalized populations do not participate in numbers that allow the medical community to draw conclusions about the efficacy of new treatments for members of

these communities, health disparities are deepened further [2]. This makes the participation of members of marginalized communities in clinical trials and research studies increasingly urgent.

There is growing evidence that the communication behaviors exhibited by medical and nonmedical professionals tasked with approaching and consenting patients impacts eventual enrollment [3–6]. Most research on clinical trial communication has focused on general guidelines for communication practice. These guidelines include making sure that the type and amount of information are appropriate for the patient [7], using plain language to explain a trial [5, 8, 9] and being open to answering potential participants' questions [3, 8, 10]. Additionally, recruiters are exhorted to be "warm" and respectful with patients [8, 11].

It is important, however, to examine the specific communication behaviors that lead to more effective recruitment, consent, and retention. A study of 63 medical professionals in two diverse U.S. cities indicates that both verbal and nonverbal communication practices support effective recruitment and consent processes [12–15]. Specific verbal communication behaviors that are associated with effective patient recruitment and consent include translating and simplifying information through the use of lay language and examples; reframing information through the use of metaphors, analogies, and storytelling; balancing discussions of risks with benefits; and encouraging potential participants to ask questions [12].

Nonverbal communication behaviors may be even more important, given the central role of nonverbal communication in the process of meaning generation [16]. However, this topic has received little attention by researchers studying factors that impact clinical trial accrual. In the recruitment and consent process, nonverbal communication behaviors that appear to be particularly important include the ability to "read" patients' state of mind before approaching them to participate in a study; the willingness to adapt to a patients' mood and communication preferences; mirroring patients' body posture, tone, and rate of speech; using eye contact, touch, and smiling in situationally and culturally appropriate ways; and being conscious of the impact of physical appearance [13]. Importantly, both verbal and nonverbal communication function to create a sense of relational connection which, in turn, creates both trust and the motivation required for patients to process often-complicated study information [14].

It should be noted that while these verbal and nonverbal communication behaviors are necessary (but not sufficient) for increasing enrollment in clinical trials, the goal of clinical trial communication interventions should not simply focus on accrual but rather improve informed decision making by potential participants. Thus, whether patients consent or do not consent is beside the point. All patients, we believe, should be (1) offered the opportunity to contribute to medical knowledge through study participation and (2) provided study information in language (and a format) that they understand so they can make an informed decision about whether to participate.

Contrary to popular belief, good communication skills come naturally to very few people. Just as public speaking abilities can be developed through professional training, the specific interpersonal verbal and nonverbal practices that foster positive interactions with

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patients in a clinical trial recruitment context can be taught [17]. The content of clinical trial communication training programs varies considerably (as do outcomes), but most programs appear to be successful in improving the confidence of those who recruit for studies [18].

While clinical trial communication training programs are not yet widely available, there are some laudable examples that warrant discussion. Fallowfield and colleagues [19–21] have been among the first to develop communication training programs specifically focused on clinical trial recruitment and consent issues. Their training programs provided information on common communication issues and ethical concerns and were primarily directed toward physicians and nurses with clinical trial management roles. The main outcomes from these trainings were improved knowledge of clinical trials and increased confidence in their ability to recruit and consent patients. Similarly, Wells and colleagues [22] developed a training program to improve professionals' communication abilities but focused largely on developing increased cultural competency by focusing on barriers and beliefs of African Americans and Latinos. The program focused on outcomes related to knowledge and attitudes of minority patients' cultural needs. Another communication training program, developed and piloted at the University of Miami, focused on educating research coordinators on specific verbal and nonverbal communication skills to improve clinical trial recruitment and informed consent discussions. This communication training program consisted of five modules and adopted several educational strategies including a didactic presentation, in-group discussions, live demos, and role play activities [17].

One issue that has troubled virtually all existing clinical trial communication programs is the actual assessment of training outcomes. This may be a symptom of a larger problem in that there seems to be little consensus about what the goal should be for communication trainings. We assert that there should be two central goals: (1) increasing the willingness and ability of recruiters to use "best practices" in communication about clinical trial participation, with the ultimate goal of (2) increasing informed decision making among potential participants. Whether patients and other potential participants provide informed consent to enroll in a study or make an informed decision to decline the opportunity to participate, we believe that all patients should be presented with the choice to advance knowledge relevant to their health conditions wherever such opportunities exist. The burden is on us to communicate well in order to maximize the patients' comprehension of all factors that are relevant to their decisions.

Current assessments of the quality of communication practice as an outcome of clinical trial communication training has focused on several tools: (1) surveys of training participants' knowledge, attitudes, and perceived self-efficacy; (2) role-plays to practice skills; (3) videotaping participants to provide individualized feedback, and (4) the use of check lists to assess recruiters' behaviors when interacting with potential participants [18]. While all of these assessment strategies are valuable, none of these approaches has been validated, including the self-report survey, which is the most commonly used tool [18]. The development and evaluation of more effective training programs depend heavily on the use of validated and, preferably, triangulated outcome measures.

Toward this end, we have developed a self-report questionnaire that focuses on communication behaviors that are critical for effective clinical trial recruitment and consent. The measure is grounded in the empirical literature on clinical trial communication, particularly the work of Morgan and colleagues, who identified verbal and nonverbal communication behaviors that recruiters themselves associate with effective recruitment and consent processes [12–15]. We created an initial pool of 138* items which corresponded to a wide variety of communication behaviors including eye contact; conversational style; protection of patient privacy; tone of voice; ability to "read" patients; ability to adapt to patient communication preferences; mirroring patient communication behaviors; smiling and friendliness; body positioning; the use of touch; physical appearance; simplifying/"translating" medical and technical information into lay language; reframing or using metaphors and analogies to explain difficult concepts; encouraging question asking; balancing the presentation of risks and benefits of study participation; describing the benefits to self and society of study participation; and other communication behaviors that ensure that potential participants comprehend information that is relevant to the decision to participate in a research study or clinical trial.

2. Methods

2.1. Procedures

All survey items were entered into online formats including REDCap and Qualtrics for dissemination. Following institutional review board (IRB) approval, the survey was distributed to research professionals at three academic medical centers: University of Miami, University of Florida, and University of Texas Health Science Center. Because of a technical error, data from the University of Texas Health Science Center (n = 16 surveys) could not be retained for the study.

The eligibility criteria for participation were broad: Any employee whose job duties regularly involved recruiting and/or consenting patients for clinical trials or research studies could participate in the study. The survey was distributed via email link by managers within each academic medical center. No compensation for participation was offered. A total of 71 people who completed the survey were included in the analyses. Respondents had an average of 6 years of experience (M = 5.93, SD = 4.20). The demographic and professional characteristics of our sample appear in **Table 1**.

2.2. Measures

In addition to the items assessing communication behaviors in clinical trial contexts, demographic questions, the nature of their work, and their level of experience, we asked research professionals about how they feel about their jobs, their motivation levels, and their self-assessment of their competence in recruiting for clinical trials and research studies. These items were used to explore the relationship between responses to these questions and self-reported communication behaviors as a way to test the capacity of the clinical trial communication inventory (CTCI) to discriminate different audience characteristics.

Variable	n	(%)
Gender		
Male	14	(19.7)
Female	54	(76.1)
Not reported	3	(4.2)
Race		
American Indian	0	(0)
Asian	4	(5.6)
Pacific Islander	0	(0)
Black or African American	4	(5.6)
Middle Eastern	0	(0)
White or Caucasian	60	(84.5)
Not reported	3	(4.2)
Ethnicity		
Hispanic	32	(45.1)
Education		
High school–less than bachelors	8	(11.3)
Bachelor	23	(32.4)
Master	23	(32.4)
PhD	6	(8.5)
MD	11	(15.5)
Institution		
University of Miami	40	(57.1)
University of Florida	28	(40)
Both UM and UF	1	(1.4)
Other	1	(1.4)
Not reported	1	(1.4)
Type of trial*		
Drug	44	(62)
Device	11	(15.5)
Behavioral/social	30	(42.3)
Medical intervention/procedure	16	(22.5)

*Some individuals reported recruiting for more than one type of trial.

Table 1. Characteristics of the sample.

3. Results

Because of the high ratio of survey items to number of participants, an exploratory factor analysis that included all survey items did not yield meaningful results. Breaking the survey down into smaller groups of conceptually linked items proved to be a more useful strategy. All reported exploratory factor analyses used an oblimin rotation because items representing, for example, different dimensions of nonverbal communication necessarily have a strong relationship with each other. An item was considered to be an indicator of a factor if it had a loading of .5 and a loading of no more than .4 on any other factor. The results of the exploratory factor analyses for four sets of items appear in **Table 2** (nonverbal communication), **Table 3** (translation, simplification, and lay language), **Table 4** (reframing medical information), and **Table 5** (fostering understanding of medical research). Appendix A contains the items retained for each scale.

The results of the factor analyses (where viable results were obtained) were used to construct final versions of the scales. Descriptive statistics for each of the final subscales and Cronbach's alpha appear as **Table 6**. Pearson correlations between all of the CTCI subscales appear in **Table 7**.

The relationships between the final CTCI subscales and other variables in the survey were examined. Specifically, we sought to look for possible difference in responses by gender, race/

Item	1	2	3
I usually mirror a patient's body posture when I'm discussing a study with them.	**.85**	−.14	.25
I try to adjust my facial expressions to reflect the current situation they are in.	**.75**	.12	.13
When I am discussing study participation, if a patient appears relaxed, I relax my body too.	**.74**	−.23	.06
I often mimic a patient's mannerisms when I talk about a study.	**.74**	−.07	.18
Based on my first impressions of a patient, I adapt how I talk about a study.	**.69**	.00	.07
Whether a person talks loud and fast or softly and slowly, I adjust the way I speak about a study to how they talk.	**.69**	−.05	.18
I slip into the same style and manner of speech as the person I am talking to about a study.	**.68**	−.13	.20
I think it's more important to be warm and friendly with patients than to maintain professional distance	**.67**	.02	−.45
When I walk into the exam room (or waiting area) with patients, I try to figure out what kind of mood they are in.	.46	.36	−.54
I am very good at 'reading' a patient before I start talking about study details.	.42	.38	−.6
I always maintain a highly professional tone and demeanor when I talk to a patient.	.06	.77	.32
I act the same way with every patient regardless of their mood.	−.03	.67	.40

Table 2. Nonverbal communication (reading, adapting, mirroring) factor loadings for exploratory factor analysis with oblimin rotation.

Item	1	2	3	4
I 'translate' information about a study to help patients	**.69**	.00	.38	−.18
I find ways of using lay language	**.67**	−.08	.31	−.21
I believe that members of some minority/ethnic populations have specific preferences for words or research-related terminology	**.68**	.10	−.45	.18
I try to avoid certain words or medical terms when talking with members of certain cultural groups	**.73**	.30	−.44	.06
I try to use language that I think would be received well by members of the cultural group to which they belong	**.78**	.01	−.42	−.02
When going through a consent form with a patient, I often say something like, 'so this means…' followed by a lay explanation	**.70**	.03	−.02	−.38
Based on what I know about the educational level of the patient, I adapt my explanation of a study	**.75**	−.16	−.04	−.24
I break down the study protocol into smaller steps to make the prospect of participating in the study less intimidating	.59	−.15	.41	−.22
I simplify the language of the consent form	.58	−.25	.28	.56
I substitute simple words for complicated medical terminology	.54	−.38	.11	.58
I make sure that all of my explanations of a study can be found directly on the consent form	.15	.71	.50	.18
Because the consent form must be approved by the IRB, I keep to the language that is specified in the consent form	.08	.84	.12	.04
I do not diverge from the information and explanations offered in the consent form even when I understand a study well	.16	.82	−.11	.11

Table 3. Translation, simplification, and lay language use item factor loadings for exploratory factor analysis with oblimin rotation.

ethnicity, and type of trial recruited for. We also looked for correlations between responses to the CTCI subscales and job satisfaction and years of experience. None of these analyses produced a significant pattern of results except for years of experience. The number of years of experience as a research professional correlated significantly with use of eye contact ($r(62) = .45$, $p < .001$); efforts to preserve patient privacy ($r(61) = .47$, $p < .001$); translation of medical and research terminology into lay language ($r(56) = .55$, $p < .001$); the use of reframing to explain research ($r(51) = .52$, $p < .001$); fostering understanding of research concepts ($r(49) = .43$, $p = .002$); and attitudes toward answering patient questions ($r(54) = .67$, $p < .001$). The correlation between years of experience and fostering understanding of medical research was nearly significant, $r(52) = .27$, $p = .06$. However, correlations between years of experience and the measure of mirroring and adapting to patients' nonverbal communication was nonsignificant, $r(54) = -.05$, p = n.s.

Item	1	2	3
I frame unfamiliar or potentially scary concepts in terms that are more familiar or acceptable to patients	**.84**	−.04	−.02
I frequently use examples as a way to explain technical information about a study	**.78**	.30	.19
I often use metaphors and analogies to explain randomization or other study concepts	**.76**	−.29	−.24
I use analogies to explain potentially scary tests or concepts	**.76**	−.41	−.31
If it's a complex study, I often reframe information in medical terms that are more familiar to them	**.71**	−.32	.30
I often give specific examples of what will happen to a patient if they join a study	**.69**	.09	.37
I find that I often use analogies (that aren't part of the consent form) when explaining a study	**.66**	.14	−.21
Patients like to hear stories about other patient's experiences with research participation	.51	.51	−.10
I make sure that patients know that the consent form is not a contract	.42	.42	−.30
I often use predetermined and rehearsed stories to clarify difficult concepts	.44	.32	.60
I find it difficult to explain how randomization works in the context of the trial being offered	.31	−.57	.54

Table 4. Reframing medical information factor loadings for exploratory factor analysis with oblimin rotation.

Item	1	2
I always begin a discussion with a patient by explaining the purpose of our conversation	**.51**	−.24
Before getting a patient's signature on a consent form, I always check their understanding of the study information	**.69**	−.44
I ask patients to 'teach back' (or summarize for me) the key points of a study to me before they consent to being in a study	**.68**	−.26
I offer patients the option of delaying their decision about study participation	**.59**	.19
I explain to patients that the research study is being conducted to improve scientific knowledge about a particular disease, condition, or treatment	**.75**	−.15
I explain the general rationale for a randomized clinical trial (when appropriate)	**.60**	−.50
When offering patients the opportunity to participate in a research study, I explain the researchers' motivations for conducting the study	**.70**	−.38
When offering patients the opportunity to participate in a research study, I tell them that all trials have to receive approval from ethics committees	**.75**	−.08
When offering patients the opportunity to participate in a research study, I acknowledge the uncertainty of treatment benefits	**.73**	.16
I explain the concept of equipoise (trials are conducted only when there is collective uncertainty that the benefit of an experimental treatment is better than the current best practice standard treatment)	.62	.49
I explain the concept of beneficence (trials are conducted to determine whether there is a significant additional benefit from the experimental treatment)	.58	.60
I explain the concept of non-maleficence (there is evidence to suggest that being involved in a clinical trial will in no way worsen the patient's chances)	.68	.71

Table 5. Fostering understanding of medical research factor loadings for exploratory factor analysis with oblimin rotation.

	Mean	SD	Cronbach's alpha
Eye contact (3 items)	4.10	.55	.69
Maintaining patient privacy (4 items)	3.34	.72	.76
Translation of medical and technical information (7 items)	3.55	.60	.86
Reframing medical and technical information (7 items)	3.50	.71	.86
Fostering understanding of research (9 items)	4.29	.59	.86
Explaining specific research concepts (3 items)	3.96	1.13	.88
Nonverbal communication (reading, adapting, mirroring) (8 items)	3.12	.57	.90
Question answering (3 items)	3.25	.54	.83

Table 6. Means, standard deviations, and reliabilities of Clinical Trial Communication Inventory subscales.

	1	2	3	4	5	6	7
1. Eye contact	–						
2. Privacy	.53*** (70)	–					
3. Translation	.51*** (64)	.60*** (64)	–				
4. Reframing	.53*** (59)	.41** (59)	.70*** (58)	–			
5. Understanding	.11 (50)	.13 (57)	.23 (56)	.23 (54)	–		
6. Explaining	.19 (60)	.01 (60)	.14 (58)	.26 (55)	.46*** (56)	–	
7. Nonverbal	.59*** (61)	.56*** (61)	.56*** (59)	.41** (54)	.04 (52)	.13 (54)	–
8. Questions	.37** (62)	.41** (62)	.53*** (61)	.50*** (.59)	.36** (56)	.08 (58)	.17 (57)

*p = .05.
**p = .01.
***p < .001.

Table 7. Pearson correlations of Clinical Trial Communication Inventory subscales.

4. Discussion

This chapter presents the development and analysis of an instrument designed to evaluate the communication behaviors of professionals who recruit for clinical trials and research studies. Of the original 133 items, 44 items were retained in 8 subscales. These subscales include maintaining patient privacy; translation of medical and technical information; reframing medical and technical information; fostering understanding of research; explaining specific research concepts; question answering; nonverbal communication, including reading patients, adapting to patients' communication, their state of mind, and preferences, mirroring behaviors; and eye contact.

The results of supplemental analyses demonstrate that there are statistically significant relationships between all but one of the subscales of the instrument (including all of the verbal communication measures) and years of experience. This may indicate that as research professionals gain experience, they acquire knowledge about effective strategies to communicate about complex medical and scientific concepts. In fact, the fact that the measure of nonverbal communication (behaviors which are often described as something akin to "instinctual" or innate in the published studies of Morgan and colleagues) has a correlation of nearly zero may indicate that many individuals who are drawn to this type of research position may naturally be "people-people" who may nonetheless benefit from training programs with an emphasis on verbal communication techniques when recruiting and consenting potential research participants. Tentative validity testing of several items and subscales of the instrument described here was performed in early 2017. The results of this early pilot testing demonstrated that items contained in the Clinical Trial Communication Inventory can be used to assess the pre- to post-test impact of a clinical trial communication training (see Ref. [17] for full results of the evaluation).

While the CTCI is likely to prove useful to evaluate efforts in clinical trial communication training, it should be noted that with a relatively small sample, the validity of factor analytic strategies used to construct some of the initial scales may be limited, although the scales we created based on these results showed strong reliability. Future research should further develop this instrument by testing its robustness with a larger sample of research coordinators and validate it with other types of medical professionals who recruit for clinical trials, including physicians and study nurses. Additionally, it is vitally important for this instrument to be evaluated through convergent validity testing. The question remains whether the Clinical Trial Communication Inventory reflects real-world communication practice and indeed, whether these communication behaviors predict increased informed decision making or improved rates of clinical trial accrual. Convergent validity can be established through a variety of strategies, including checklists of exhibited communication behaviors during role plays and video recordings of actual recruitment and consent behaviors with patients. Predictive validity could be established by demonstrating that communication training results in changed scores on the CTCI from pre- to post-test, and more importantly, that scores post-training reflect improvements to informed consent with patients, which can be evaluated through patient "teach-backs" and an increased number of accurate responses to a set of study-related knowledge questions.

5. Conclusion

Improvement of low accrual to clinical trials and research studies is urgently needed, particularly for members of minority populations. Research has demonstrated that communication behaviors play an important role in the recruitment and consent processes. While communication behaviors can (and should) be developed through professional seminars and workshops, there are few available instruments to conduct evaluations of the outcomes of those trainings. In this chapter, we outline the development and testing of a measure of communication in clinical trial contexts: the Clinical Trial Communication Inventory. While additional

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testing needs to be conducted to more thoroughly establish convergent and predictive validity with multiple professional groups, we believe that this instrument will help advance the development of clinical trial communication training programs.

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Appendix A: Subscales of the Clinical Trial Communication Inventory

Use of eye contact

I use eye contact to try to figure out whether a patient understands a study through eye contact.

I use eye contact to assess a patient's state of mind while I talk with them about a study.

I find that most patients do not want to make eye contact when discussing study participation.

Maintaining patient privacy

If the patient is comfortable discussing a study in an area where privacy cannot be secured, I will still consent the patient.

Most patients don't care about being consented in a private location.

It is not practical to always consent patients in a private location.

If a private location in unavailable, I talk in a quiet voice to enhance a sense of privacy when discussing a study.

Translation of medical and technical information

I 'translate' information about a study to help patients.

I find ways of using lay language.

I believe that members of some minority/ethnic populations have specific preferences for words or research-related terminology.

I try to avoid certain words or medical terms when talking with members of certain cultural groups.

I try to use language that I think would be received well by members of the cultural group to which they belong.

When going through a consent form with a patient, I often say something like, 'so this means…' followed by a lay explanation.

Based on what I know about the educational level of the patient, I adapt my explanation of a study.

Reframing medical and technical information

If it's a complex study, I often reframe information in medical terms that are more familiar to them.

I find that I often use analogies (that aren't part of the consent form) when explaining a study.

I frequently use examples as a way to explain technical information about a study.

I often give specific examples of what will happen to a patient if they join a study.

I frame unfamiliar or potentially scary concepts in terms that are more familiar or acceptable to patients.

I often use metaphors and analogies to explain randomization or other study concepts.

I use analogies to explain potentially scary tests or concepts.

Fostering understanding of research

I always begin a discussion with a patient by explaining the purpose of our conversation.

Before getting a patient's signature on a consent form, I always check their understanding of the study information.

I ask patients to 'teach back' (or summarize for me) the key points of a study to me before they consent to being in a study.

I offer patients the option of delaying their decision about study participation.

I explain to patients that the research study is being conducted to improve scientific knowledge about a particular disease, condition, or treatment.

I explain the general rationale for a randomized clinical trial (when appropriate).

When offering patients the opportunity to participate in a research study, I explain the researchers' motivations for conducting the study.

When offering patients the opportunity to participate in a research study, I tell them that all trials have to receive approval from ethics committees.

When offering patients the opportunity to participate in a research study, I acknowledge the uncertainty of treatment benefits.

Explaining specific research concepts

I explain the concept of equipoise (trials are conducted only when there is collective uncertainty that the benefit of an experimental treatment is better than the current best practice standard treatment).

I explain the concept of beneficence (trials are conducted to determine whether there is a significant additional benefit from the experimental treatment).

I explain the concept of non-maleficence (there is evidence to suggest that being involved in a clinical trial will in no way worsen the patient's chances).

Nonverbal communication (reading, adapting, mirroring)

I think it is more important to be warm and friendly with patients than to maintain a professional distance.

I slip into the same style and manner of speech as the person I am talking to about a study.

Whether a person talks loud and fast or softly and slowly, I adjust the way I speak about a study to how they talk.

I usually mirror a patient's body posture when I's discussing a study with them.

When I am discussing a study participation, if a patient appears relaxed, I relax my body, too.

I often mimic a patient's mannerisms when I talk about a study.

Based on my first impressions of a patient, I adapt how I talk about a study.

I try to adjust my facial expressions to reflect the current situation they are in.

Question answering

I enjoy answering a patient's questions about a study.

I always invite patients to ask questions about a study.

I make sure to give a patient the names of who to contact if they have additional questions about the trial

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References

[1] Heller C, Balls-Berry JE, Nery JD, Erwin PJ, Littleton D, Kim M, Kuo WP. Strategies addressing barriers to clinical trial enrollment of underrepresented populations: A systematic review. Contemporary Clinical Trials. 2014;**39**:169-182. DOI: 10.1016/j.cct.2014.08.004

[2] Underwood SM. Minorities, women, and clinical cancer research: The charge, promise, and challenge. Annals of Epidemiology. 2000;**10**:S3-S12

[3] Albrecht TL, Blanchard C, Ruckdeschel JC, Coovert M, Strongbow R. Strategic physician communication and oncology clinical trials. Journal of Clinical Oncology. 1999; **17**:3324-3332

[4] Byrne MM, Kornfeld J, Vanderpool R, Belanger M. Discussions of cancer clinical trials with the National Cancer Institute's Cancer Information Service. Journal of Health Communication. 2012;**17**:319-337. DOI: 10.1080/10810730.2011.626500

[5] Eggly S, Albrecht TL, Harper FW, Foster T, Franks MM, Ruckdeschel JC. Oncologists' recommendations of clinical trial participation to patients. Patient Education and Counselling. 2008;**70**:143-148

[6] Siminoff LA, Fetting JH. Factors affecting treatment decisions for a life-threatening illness: The case of medical treatment of breast cancer. Social Science & Medicine. 1991;**32**:813-818

[7] Stevens T, Ahmedzai SH. Why do breast cancer patients decline entry into randomised trials and how do they feel about their decision later: A prospective, longitudinal, in-depth interview study. Patient Education and Counselling. 2004;**52**:341-348

[8] McSweeney J, Pettey C, Fischer E, Spellman A. Going the distance: Overcoming challenges in recruitment and retention of Black and White women in multisite, longitudinal study of predictors of coronary heart disease. Research in Gerontological Nursing. 2009;**2**:256-264

[9] Siminoff LA, Step MM. A communication model of shared decision making: Accounting for cancer treatment decisions. Health Psychology. 2005;**24**:S99-S105

[10] Siminoff LA, Colabianchi N, Saunders Sturm CM, Shen Q. Factors that predict the referral of breast cancer patients onto clinical trials by their surgeons and medical oncologists. Journal of Clinical Oncology. 2000;**18**:1203-1211

[11] Harrigan R, Perez MH, Beaudry S, Johnson C, Sil P, Mead K, Apau-Ludlum N. Recruitment and retention of under-represented groups with health disparities into clinical trials: A formative approach. Minority Health. 2014;**16**:898-903. DOI: 10.1007/s10903-013-9786-8

[12] Morgan SE, Mouton A, Occa A, Potter J. Clinical trial and research study recruiters' verbal communication behaviors. Journal of Health Communication. 2016;**21**:765-772

[13] Morgan SE, Occa A, Mouton A, Potter J. The role of nonverbal communication behaviors in clinical trial and research study recruitment. Health Communication. 2016;**32**:461-469

[14] Morgan SE, Occa A, Potter J, Mouton A, Peter M. "You need to be a good listener": Recruiters' use of relational communication behaviors to recruit and consent participants for clinical trials and research studies. Journal of Health Communication. 2017;**22**:95-101

[15] Occa A, Morgan SE, Potter J. Underrepresentation of Hispanics and other minorities in clinical trials: Recruiters' perspectives. Journal of Racial and Ethnic Health Disparities. 2017;1-11

[16] Knapp ML. Nonverbal Communication in Human Interaction. New York: Holt, Rinehart, and Winston; 1972

[17] Occa A, Morgan SE, McFarlane SJ, Peng W, Potter J. A pilot training to improve medical professionals' verbal and nonverbal communication about clinical trials and research studies. In: Presented at the National Communication Association Conference; November 2017; Dallas, TX

[18] Occa A, Morgan SE. Training programs for improving communication about medical research and clinical trials: A systematic review. In: Prostran M, editor, Serbia. Clinical Trials in Vulnerable Populations. InTech; 2017

[19] Fallowfield L, Lipkin M, Hall A. Teaching senior oncologists communication skills: Results from phase I of a comprehensive longitudinal program in the United Kingdom. Journal of Clinical Oncology. 1998;**16**:1961-1968. DOI: http://dx.doi.org/10.1200/JCO.1998.16.5.1961

[20] Fallowfield L, Jenkins V, Farewell V, Saul J, Duffy A, Eves R. Efficacy of a Cancer Research UK communication skills training model for oncologists: A randomised controlled trial. The Lancet. 2002;**359**:650-656. DOI: 10.1016/S0140-6736(02)07810-8

[21] Fallowfield LJ, Solis-Trapala I, Jenkins VA. Evaluation of an educational program to improve communication with patients about early-phase trial participation. The Oncologist. 2012;**17**:377-383. DOI: 10.1634/theoncologist.2011-027

[22] Wells JS, Pugh S, Boparai K, Rearden J, Yeager KA, Bruner DW. Cultural competency training to increase minority enrollment into radiation therapy clinical trials—An NRG Oncology RTOG study. Journal of Cancer Education. 2016;1-7. DOI: 10.1007/s13187-016-1051-0

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This book Clinical Trials in Vulnerable Populations has 12 chapters divided into 4 sections: Minority Patients, Women, Medically Compromised Patients and Clinical Trials. Contributing authors came from several countries, from Serbia to Turkey. The book was edited by Professor Milica Prostran MD, Ph.D., specialist in Clinical Pharmacology. The potential reader is shown a modern approach to clinical trials in vulnerable populations, from different points of view. The chapters deal at length and clarity with their topics. Finally, I believe, that this book I edited and reviewed with dedication will capture the attention of many readers, from medical students to practicing doctors and pharmacists. All of whom must consider this very important field of medicine: clinical trials in vulnerable patients.

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