ECRONICON OPEN ACCESS

DENTAL SCIENCE
Review Article

Ethical Considerations For A Multicenter Research

Navdeep Kaur[1]* and Daniel Kandelman[2]

[1]Department of Biomedical Sciences, Faculty of Medicine, Montreal University, Canada

[2]Department of Dental Medicine and Director of the International Centre for Prevention of Oral health diseases for specific needs populations, Montreal University, Canada

***Corresponding Author:** Navdeep Kaur, Department of Biomedical Sciences, Faculty of Medicine, Montreal University, Canada.

Received: November 09, 2015; **Published:** November 18, 2015

Abstract

Multicenter research is an effective paradigm for biomedical research and offers advantages such as large sample size, cost-effectiveness and enhances external validity. Concurrently, multicenter research may raise various ethical and practical concerns since practices vary across involved research centers primarily due to varied local laws and available technology. Although, there is a widespread debate about the ethical considerations for a multicenter research, yet limited literature exists on this topic. The main purpose of this paper is to review and summarize the existent literature on the topic of ethical considerations for multicenter research. Our search and review of the existent literature revealed that in general the main ethical considerations for a multicenter research are 1) ethics board review process, 2) informed consent process, 3) protection of confidentiality and vulnerability 4) data monitoring and 5) best practices. This paper concludes that each multicenter research situation is unique, so "one size fits all" approach is not possible to be prescriptive in how to conduct an ethically sound multicenter research. However, it is recommended to foster partnerships and have open communications among the involved researchers and ethics review boards to gain a clear understanding beforehand about the context specific and ambiguous local situations and issues to design and conduct an effective multicenter research.

Keywords: *Multicenter research; Ethical considerations; Best practices; Guidelines*

Introduction

"Multicenter research refers to a research conducted according to a single research protocol but at more than one site and is carried out by more than one investigator and may have its research centers located in the same country or in another country" [1]. Multicenter research has many advantages such as likelihood of having large sample size, is cost-effective and enhances external validity [2]. Concurrently, such research may raise various ethical and practical concerns since practices vary across involved research sites, due to variation in local laws and available technology [3-5].

Although four principal international ethical research documents; the Declaration of Helsinki [6], the Council for International Organizations of Medical Sciences (CIOMS) [7], Canada's Tri-council Policy Statement (TCPS2) [8] and the UNESCO's [9] universal declaration on bioethics and human rights have been generated yet there exists widespread debate about multicenter research guidelines [10]. Even if there is general agreement on basic key elements of multicenter research, the implementation policies of the involved research centers may vary considerably [10]. Furthermore, there is scarcity of literature pertaining to ethical considerations regarding multiple and complex features of multicenter research. The main purpose of this paper is to review and summarize the existent literature on the topic of ethical considerations for multicenter research.

Main ethical considerations for a multicenter research

Canada's three major granting agencies; the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC), and the Social Sciences and Humanities Research Council (SSHRC) have developed a Tri-Council Policy Statement (TCPS2) entitled "Ethical conduct for research involving humans" [11]. The chapter 8 of the TCPS2 on "Multi Jurisdictional Research" describes standards, procedures and considerations for governing research involving human participants (including the establishment of a research ethics board) at Canadian institutions and international multicenter research [8]. In this paper we have primarily focused on the Canadian ethical considerations concerning multicenter research. Our in depth search and review of existent literature has revealed that in general the main ethical considerations for a multicenter research are 1) ethics board review process, 2) informed consent process, 3) protection of confidentiality and vulnerability 4) data monitoring and 5) best practices. Following is brief description of the main issues and ethical considerations for multicenter research:

Ethics board review process

All research projects seeking approval from the Research Ethics Board (REB) need to submit a formal application along with other relevant documents such as research protocol, consent forms etc. The main role of the REB is to evaluate and ensure before providing approval that good ethical practices e.g. subjects remain informed, and their consent is valid etc. will be followed at research centers. For multicenter research, institutionally based REBs were put in place in order to protect the rights, safety and well-being of potential research participants, particularly in light of issues unique to geographically isolated populations. However, involved institutionally based REBs sometimes require minor or even major modifications depending on different concerns and interests of the involved board members [5-12]. Although it is critical yet getting approval from all the REB's involved in multicenter research is quite cumbersome and may pose challenges since it costs energy, time and money and may discourage researchers due to delays in starting their research activities.

At the provincial level within Canada, the Quebec Ministry of Health and Social Services has developed a mechanism for the ethical review and monitoring of multicenter research [13]. Recently, it is replaced by another document entitled, "Cadre de référence des établissements publics du réseau de la santé et des services sociaux pour l'autorisation d'une recherche menée dans plus d'un établissement [14]. Furthermore, the Ministère de la Santé et des Services Sociaux (MSSS) and the Fonds de recherche du Québec Santé (FRQS) and the four integrated university health networks (RUIS) maintain that any research project conducted at multicenter within the Health and Social Services network (RSSS) would undergo a single ethics review and that would be recognized by the other institutions involved in the project [14]. It is a useful document that provides detailed description of various elements to consider while determining which REB to ask to act as the primary REB [14]. The TCPS 2[8] has specified following 3 models for the ethics review involving multiple REBs in multicenter research:

A. The REBs at each involved center shall conduct an independent research ethics review and provide their separate decisions.
B. Two or more regional, provincial or national institutions may participate to create one joint REB or to appoint an external REB, to which may delegate as research ethics review.
C. Multiple institutions may enter into official agreements for the ethics review of research proposals.

The key to determine which of the above mentioned model shall be context sensitive. It is responsibility of researchers to ensure that the reviewing REB is provided with as much context concerning the local situation where research will be conducted since not all REB members may be familiar with the location.

Informed consent process

Globally, to obtain free and informed consent from research participants is central to the ethical research practice and there is a consensus about its components. According to the TCPS 2 Article 4.1 particularly, in cases where written consent is not possible (especially among populations having limited literacy) it is crucial to specify the procedure of how will consent be obtained. However, sometimes its application may be challenging particularly when, multicenter research is conducted across different cultures and the participants

speak different language than researchers [4]. Interestingly, in 2001, a study was conducted in Bangladesh to examine participants understanding of iron supplementation in a community-based study. This study showed that even if informed consent was obtained after a detailed explanation of the study, many participants did not fully understand that they were free to refuse to participate, or they could choose to leave the study, about half thought that participation was part of a health care routine [15]. The results of this study raises a question about the use of the doctrine of informed consent that whether the word "informed" is indeed applied in actions in research involving different cultures and languages?

Furthermore, the concept of autonomy may differ across locales, rendering it more difficult to decide who must be involved in the informed consent process and whose consent to participate must be sought [4]. Depending upon the sites at which the study is to be conducted, involved researchers may require the consent of local leaders or family elder in addition to that of the individual. Also, in certain cases if the research is based on publically available information and does not pose any privacy risk and for observational studies conducted for evaluation and improvement purposes. Despite of taking all necessary measures another challenge concerning informed consent could arise since some words of informed consent may be difficult to translate exactly from one language to other [4]. An option is to hire or arrange for a translator and ensure that that the translator is unbiased (so that they will provide accurate translated information without altering the sense intended by the research study participant). Also ensure that the translator holds the information in confidence and signs a non-disclosure agreement. Thus, it is primary responsibility of researcher to ensure that the participants have completely understood and are completely "informed" about everything in the consent form [4].

Protection of confidentiality and vulnerability

Researchers are ethically obligated to protect confidentiality and vulnerability of the study participants. The procedure to protect the confidentiality of the database and the privacy of the participants varies across centres due to protection procedures afforded by local law and available technology. Consequently, the risks of participation in a given study may also vary across different centres. For example, in United States (US) a certificate of confidentiality protects the identity of individuals participating in studies in which highly personal information is gathered (e.g. drug, alcohol use and sexual behavior) [16]. A certificate of confidentiality protects such data from being accessed by attorneys, courts, and law enforcement officials for use in civil, criminal, and administrative proceedings [16]. However, a multicenter study which includes centers outside US may not have this privilege to provide such protection of database having personal information.

While any breach of confidentiality is serious, a breach of confidentiality in highly stigmatized populations (e.g. HIV-positive study participants) can lead to significantly increased vulnerability. In addition, women in strongly patriarchal societies can be put at serious risk if their male partners take offense about their study participation or learn of negative health issues about her due to her study participation. Behavioral and social science research may cause emotional and psychological distress among subjects who learn negative information about their health status particularly in developing countries among vulnerable population groups (e.g. low levels of literacy, economically depressed or disadvantaged, ethnic/religious/cultural minority, children, etc.). Thus, understanding, protection of confidentiality and vulnerability should be an issue of concern for researchers working with such vulnerable groups.

Data monitoring

According to the TCPS 2 article 5.7, researchers must first obtain approval from the REB for the data linkage [17]. The fundamental reason to establish a data and safety monitoring plan is to enhance subject safety, confidentiality and data credibility. In order for a study to be REB approved, the research plan must make adequate provisions for monitoring the data collected to ensure the safety and confidentiality of subjects [18]. It is important to specify that who will be responsible for data and safety monitoring for example a data monitoring committee can be useful [19]. Furthermore, clear description of the number of people who will be responsible for data monitoring and data collection and analysis plan is essential [18-19]. It is also critical to describe the study stopping rules regarding the potential outcomes of the study that are likely to have a major impact on the rights or welfare of research participants . If there is a potential for conflicts of interest (financial or otherwise) that might bias the data-monitoring process, state how will they be managed or eliminated [13]. On May 5-8 May 2013 in Montreal, the world conferences on research integrity were organized to promote exchange of

information and to discuss ways to promote research integrity and harmonize efforts to foster responsible research practices [20]. The draft statement sets out 20 responsibilities for individual and institutional partners, including agreeing goals and avoiding "agreements that unduly or unnecessarily restrict dissemination of data, findings, or other research products" [20].

Best practices

The Good Clinical Practice (GCP) guidelines, developed by an International Conference on Harmonization(ICH) group [21] covers aspects of designing, conducting, recording and reporting trials that involve the participation of human subjects. The guidelines were developed in consideration of good clinical practices of the European Union, Japan, and the United States, Australia, Canada, the Nordic countries and the World Health Organization (WHO) and thus the GCP guidelines have been adopted by many countries [21]. Its main goal is to protect the rights, safety and well-being of research subjects and is consistent with the principles that have their origin in the Declaration of Helsinki. It also includes the process of free and informed consent by subjects taking part in research projects; the scientific integrity of the protocol and research data; the knowledge, qualifications and expertise of the research team; the confidentiality of records and data regarding subjects; quality assurance [21].

Conclusion

Each research situation is unique, so "one size fits all" approach is not possible to be prescriptive in how to design and conduct ethically sound multicenter research. In general, it is recommended to foster participation [22] and have open communications amongst researchers and local REB's involved at multi-centers to come to an agreement at the outset regarding research protocol [23] about the use, management, sharing and ownership of data, intellectual property, informed consent and research records. Thus it is critical for involved researchers and members of local REB to gain beforehand a clear understanding about the context specific and ambiguous local situations and issues to design and conduct an effective multicenter research.

Acknowledgement

Authors thank Dr. Florina Moldovan, Professor, Department of Stomatology, Faculty of Dental Medicine, Université de Montréal for the inspiration of this article.

Conflict of Interest

Authors of this article declare having no conflict of interest.

Bibliography

1. International Conference on Harmonization, Guidance E6: Good Clinical Practice - Consolidated Guideline 1996, adopted by Health Canada in 1997.
2. Weinberger M., *et al*. "Multisite randomized controlled trials in health services research: scientific challenges and operational issues". *Medical Care* 39.6 (2001): 627-634.
3. Gold J L and C S Dewa. "Institutional Review Boards and Multisite Studies in Health Services Research: Is There a Better Way?" *Health Services Research* 40.1 (2005): 291-308.
4. Sana Loue J. "Ethical Issues in Multicenter Studies. 2008: Department of Epidemiology and Biostatistics,Case Western Reserve University, Cleveland, Ohio.
5. Stair T O., *et al*. "Variation in institutional review board responses to a standard protocol for a multicenter clinical trial". *Academic Emergency Medicine* 8.6 (2001): 636-641.
6. WMA and Declaration of Helsinki "Ethical principles for medical research involving human subjects. 2008, World Medical Association.
7. WHO. "Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects" (2002). CIOMS: Geneva.
8. Ethics Review of Research in Multiple Settings and/or Involving Multiple REBs (Previously Multicentred Ethics Review) A Discussion Paper and Recommendations (2008).

9. UNESCO (United Nations Education, S.a.C.O., Universal declaration on bioethics and human rights. 2005: Paris.
10. Udo Schüklenk DH. "Ethical issues in international researchand multicentre studies". *Electronic Journal of Communication, Information & Innovation in Health* 2008.
11. About the TCPS.
12. Dwyer JM. "Special considerations for multicenter research in Diversity in health care research, L.A.H. Joellen W. Hawkins, Editor. 2003, Springer Publishing Company, Inc.: New York. (2003): 71.
13. Jones M., et al. "Oral health literacy among adult patients seeking dental care". *The Journal of the American Dental Association* 138.9 (2007): 1199-1208.
14. Cadre de référence des établissements publics du réseau de la santé et des services sociaux pour l'autorisation d'une recherche menée dans plus d'un établissement. 2014, Ministère de la Santé et des Services sociaux.
15. Lynoe N "Obtaining Informed Consent in Bangladesh (To the editor)". *The New England Journal of Medicine* 344.6 (2001): 460-461.
16. Certificates of Confidentiality - Frequently Asked Questions.
17. Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans, 2nd edition (TCPS 2). Article 5.7-Data linkage 2014.
18. Arthur JD and Keith RM. "Ethics Guidelines for International,Multicenter Research Involving People with Intellectual Disabilities". *Journal of Policy and Practice in Intellectual Disabilities* 1.2 (2004): 57-70.
19. Friedman L and D DeMets "The Data Monitoring Committee: How It Operates and Why". *IRB: Ethics and Human Research* 3.4 (1981): 6-8.
20. Montreal Statement on Research Integrity in Cross-Boundary Research Collaborations by World Conference on Research integrity. 2015.
21. ICH Guidelines. 1997.
22. Dewa C S., *et al*. "Considering a multisite study? How to take the leap and have a soft landing". *Journal of Community Psychology* 30.2 (2002): 173-187.
23. Matheson L A., *et al.* "Ethics application protocols for multicentre clinical studies in Canada:a paediatric rheumatology experience". *Paediatrics and Child Health* 17.6 (2012): 313-316.

Volume 3 Issue 2 November 2015