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Monitoring committees for research participant protection

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Abstract

Of increasingly relevance in public health and research projects involving human beings, the topic of safety has been intensely discussed. Participants in clinical trials are subject to risks, physical or otherwise, that impact their integrity, rights, or autonomy. This study outlines and discusses the performance of the Data and Safety Monitoring Committee for research participant protection and risk minimization in clinical research. An integrative literature review was conducted to identify the committees' duties and role in protecting participants. Most of the analyzed articles confirm that the monitoring committees are mainly responsible for protecting research participants, as well as ensuring research integrity and credibility.

Keywords: Clinical trials data monitoring committees. Patient safety. Ethics, research.

Resumo

Comitês de monitoramento para a proteção de participantes de pesquisa

O tema segurança tem sido intensamente discutido, mostrando-se cada vez mais relevante na saúde pública e em projetos de pesquisa envolvendo seres humanos. Participantes de estudos clínicos estão sujeitos a riscos, físicos ou não, que impactam em sua integridade, direitos ou autonomia. Este trabalho apresenta e discute a atuação do Comitê de Monitoramento de Dados e de Segurança para a proteção do participante de pesquisa e minimização de riscos em pesquisa clínica. A metodologia consiste em revisão integrativa da literatura, realizada com o propósito de identificar as funções dos comitês e seu papel na proteção dos participantes. Identificou-se que grande parte das publicações analisadas confirmam que os comitês de monitoramento têm como responsabilidade principal a proteção do participante de pesquisa, além da garantia de integridade e credibilidade da pesquisa.

Palavras-chave: Comitês de monitoramento de dados de ensaios clínicos. Segurança do paciente. Ética em pesquisa.

Resumen

Comités de seguimiento para la protección de los participantes en investigación

La seguridad ha sido un tema muy discutido, por lo que muestra su relevancia para la salud pública y los proyectos de investigación que involucran a seres humanos. Los participantes en estudios clínicos están sujetos a riesgos físicos o de otro tipo, que impactarán su integridad, derechos o autonomía. Este texto realiza un debate sobre el desempeño del Comité de Seguimiento de Datos y Seguridad destinado a la protección de los participantes de investigación y la mitigación de los riesgos en investigación clínica. Se realizó una revisión integradora de la literatura, con el propósito de identificar las funciones de los comités y su rol en la protección de los participantes. La mayoría de las publicaciones analizadas confirman que los comités de seguimiento tienen como principal responsabilidad la protección del participante de la investigación, además de garantizar la integridad y credibilidad de la investigación.

Palabras clave: Comités de monitoreo de datos de ensayos clínicos. Seguridad del paciente. Ética en investigación.

Research

The authors declare no conflict of interest.

Patient safety has been discussed for decades by countless authors in the field of science and medicine, and also by regulatory agencies and bodies that work to ensure patient protection [1]. Increasingly relevant to medical practice and public health, some principles of modern medical ethics have been developed on this topic.

The World Health Organization (WHO), in a resolution approved in 2002 by the 55th World Health Assembly (WHA), defines patient safety as *the reduction to the minimum acceptable risk of unnecessary harm associated with health care* [2]. Years later, this concept was also adopted by the Brazilian Ministry of Health in its Ordinance 529/2013, which established the National Patient Safety Program to improve health care in all the country's health facilities [3].

Defining which risks are acceptable for an individual or group of individuals is not a trivial task. The search for safety—the moral compass of healthcare professionals in patient protection—is not present as an absolute value in the panorama of clinical practice. For every clinical intervention, there are risks to which patients are subjected [4].

Ensuring safety should always be prioritized, as it values the principle of non-maleficence, which requires avoiding harm to patients and avoiding whatever goes against the patients' wishes [5]. Non-maleficence ensures the prevention of risks and the minimization of possible harms, to which the benefits should stand out [6].

In this context, the protection afforded to clinical research participants is also questioned to discuss their safety in the face of interventions foreseen in a clinical study. Unlike patients assisted by healthcare services (outpatient or hospital care, for example), clinical research participants face potentially greater risks, subjecting themselves to new therapies or new interventions. They are often exposed to unknown risks when accepting to participate in a clinical study, without fully understanding what they are actually exposing themselves to. On many occasions, they are also unaware that they would be entitled to the same benefit in routine health care [7].

To protect research participants and minimize the potential risks, the National Institutes of Health (NIH) created, in 1967, the data and safety monitoring boards (DSMB) [8], committees independent from research sponsors and researchers, designed to supervise and monitor clinical trials, with the primary purpose of protecting participants and ensuring research integrity. Since its creation, every multicenter, randomized clinical trial, with potential risk to participants sponsored by the NIH, has had the presence of these committees.

In Brazil, DSMB were officially instituted by the MS in 2008, via the Operational Guidelines for the Establishment and Operation of Data Monitoring and Safety Boards [9]. DSMB are necessary and particularly important in studies that require continuous and periodic monitoring of safety aspects to ensure research participant protection [9,10].

Resolution No. 466/2012 of the National Health Council (CNS) [11] addresses the system integrated by the National Commission of Ethics in Research (Conep) and by the Research Ethics Committees (REC, or CEP in the Portuguese acronym), known as the CEP/Conep System, stating:

All research with human beings involves risk of varying types and degrees. The greater and more evident the risks, the greater care must be taken to minimize them and the protection offered by the CEP/Conep System to participants. Possibilities of immediate or subsequent harm, at the individual or collective level, must be analyzed. Risk analysis is an essential component of ethical analysis, resulting in the monitoring plan that must be provided by the CEP/Conep System in each specific case [11].

Considering that all research with human beings involves risks and that ensuring safety for its participants is not absolute, the primary objective of this study is to discuss the role of DSMB in protecting research participants.

The secondary objectives include:

- To know the state of the art of the surveyed publications;
- To know the existing gaps when discussing the role of DSMB, the problems presented, the criteria used and their integration in research ethics regulations.

Method

An integrative literature review of the literature available in databases was conducted based on a systematic search. For understanding the study object and developing the research question and bibliographic review, in addition to indexed scientific literature, the authors used official documents, guidelines and manuals, national and international, published by bodies such as the Ministry of Health, Brazilian Health Regulatory Agency (Anvisa), Food and Drug Administration (FDA) and others. The Brazilian regulation on research with human beings was also consulted.

The integrative review is a research method that (...) *has the purpose of gathering and synthesizing research results on a delimited topic or issue, in a systematic and orderly manner, contributing to further knowledge on the investigated theme* [12] and comprises six steps:

1. Determining the research question;
2. Defining inclusion and exclusion criteria for the bibliographic search;
3. Categorizing the data extracted from the surveyed studies and organizing the obtained information;
4. Systematically analyzing the selected material and its collected data;
5. Interpreting the results;
6. Presenting evidence and conclusions.

Integrative review

The research question

As a research question for conducting the integrative review, we proposed to identify the functions of the DSMB and their role in monitoring research data.

Inclusion and exclusion criteria

For the integrative review, an exploratory and systematic search of indexed articles was conducted on the essential platforms: PubMed, Scopus, Web of Science and Virtual Health Library (VHL). Chart 1 summarizes the descriptors, their synonyms, and generic terms used in the bibliographic search.

All search keys were turned in unique terms, using the Boolean connectors "*and*" and *"or*." For all the terms in Chart 1, their Portuguese versions was used in the VHL database. The Scopus and Web of Science databases were accessed via the portal of the Coordination for the Improvement of Higher Education Personnel (Capes).

Chart 1. List of descriptors, their synonyms, and generic terms used in the bibliographic search

Problem-elements contained in the questions	DeCS/MeSH Structure		Terms that were not removed from the controlled vocabulary
Term	DeCS/MeSH	Synonyms (PubMed=entry terms)	Generic terms
DSMB	*Comitês de monitoramento de dados de ensaios clínicos* (Clinical trials data monitoring committees)	Data monitoring committees; Safety monitoring boards; Data and safety; Monitoring boards.	DSMB Monitoring committee
Patient safety	*Segurança do paciente* (Patient safety)	Patient safeties	Participant safety Subject safety

DSMB: Data and Safety Monitoring Boards; DeCS/MeSH: Health Sciences Descriptors/Medical Subject Headings

As search filters, the following tools were used for designing the bibliographic research, when available in the databases (no temporal filters were used for the search):

- Articles published only in Spanish, English, or Portuguese;
- Articles only related to the human species.

Once completed, the bibliographic search identified 1,245 articles, which were saved in the EndNote reference management tool. Before reading the collected material, duplicate references were excluded, with the aid of EndNote, resulting in a final sample of 479 articles to be analyzed. Chart 2 summarizes the articles found in each bibliographic search platform used.

Chart 2. Total articles found in the different search platforms used in this study

Bibliographic search platform used	Articles found	Total articles after applying filters
PubMed	285	244
Scopus	328	322
Web of Science	71	71
Virtual Health Library	806	608
Total articles: 1,245		

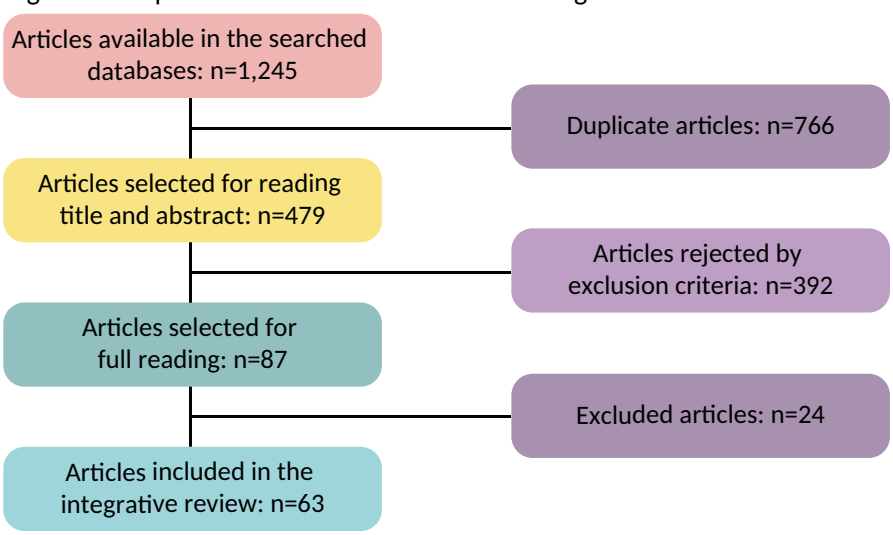
Inclusion criterion consisted of articles that discussed DSMB and their importance, functions or attributions in protecting research participants. Articles that only briefly mentioned the existence of a monitoring committee or its resolutions, without describing the basis of its opinion, its importance, functions or attributions in protecting research participants were excluded.

Seeking to avoid bias during article selection, two evaluators read the titles and abstracts of all the material collected. After reaching a consensus regarding the inclusion and exclusion criteria, the evaluators selected the articles of interest.

After reading the titles and abstracts and applying the inclusion criteria, 87 articles were selected for full reading, which was carried out by one evaluator, to then proceed with the integrative review and categorization of the achieved results.

Among the 87 articles selected for full reading, 24 were excluded for the following reasons: 10 papers were review articles; 7 were not available in full; and 7 did not discuss the importance of DSMB, their functions or attributions in protecting research participants. Finally, a total of 63 articles were included in the subsequent steps of the integrative review, and only 28 were used as a reference for the review. Figure 1 illustrates the steps taken for selecting the articles included in the integrative review.

Figure 1. Diagram of steps taken to select articles for the integrative review



Data categorization

Data categorization required extensive reading of the 63 articles included in the integrative review.

First, we created a bibliographic record for all the articles fully read to record the data that supported the inclusion criteria.

We then categorized the recorded data by topics of interest for the study. The following themes were identified:

1. Themes related to the functioning of the DSMB:
   a. Theme 1: conceptualization and composition of DSMB;
   b. Theme 2: methods used to protect research participants;
   c. Theme 3: DSMB relationship with REC, researchers, and sponsors.
2. Themes related to other ethical issues identified while reading the articles:
   a. Theme 4: conflicts of interest and confidentiality;
   b. Theme 5: other relevant ethical issues.

Finally, categories that fit the aforementioned themes were proposed for a better understanding of the surveyed articles. Categories identified in each theme, together with the frequency of mention in the publications included in the integrative review, are presented below.

Theme 1

Categories related to the conceptualization and composition of DSMB (articles that conceptualize the DSMB and describe the minimum composition for their constitution):

- Concept of DSMB, their attributions and functions (39.7%);
- Presence of (bio)ethicists recommended or mandatory for constituting DSMB (47.6%);
- Difficulties in identifying experienced members to compose DSMB (14.3%).

Theme 2

Category related to research participant protection (articles that describe the monitoring of safety aspects for proper protection of research participants):

- Monitoring of adverse events and risk/benefit assessment as a mechanism for research participant protection (61.9%).

Theme 3

Categories related to the relationship of DSMB with REC, researchers, and sponsors (articles that state that DSMB have a complementary function to REC, in addition to functions shared with researchers and research sponsors):

- Relationship with REC (15.9%);
- Concern about other research participants and future patients (23.8%).

Theme 4

Categories related to conflicts of interest and confidentiality (articles that describe possible conflicts of interest between DSMB members and between DSMB and other entities, in addition to issues related to research data and information confidentiality):

- Questions raised about DSMB resolutions (28.6%);
- Payment to DSMB members (19.0%).

Theme 5

Categories related to other relevant ethical issues (articles that explain some ethical discussion regarding the role of DSMB in protecting research participants):

- DSMB are responsible for maintaining clinical equipoise (4.8%);
- DSMB must act according to principles of beneficence, non-maleficence, justice, and autonomy (3.2%);
- Early completion of clinical studies (27.0%).

The themes and categories previously presented are discussed in depth in the following topics.

Systematic analysis and interpretation of results

After carrying out the bibliographic record of the articles and identifying the categories according to the themes of interest, we conducted an initial systematic analysis to verify the frequency with which the categories were repeated in the surveyed articles and the possible relationship between them.

Definition and composition of the data and safety monitoring boards

Only 39.7% of the articles offer a conceptualization of DSMB, generally defining these committees as multidisciplinary bodies

composed of professionals with experience in conducting clinical studies independent of sponsors and researchers, with the main purpose of ensuring participant protection and guaranteeing the research's ethical and scientific integrity.

Still regarding the conceptualization of the committees, studies differ as to the scope of DSMB action. From the total sample, 16% point to the demand for the presence of DSMB in all clinical studies—and not just in studies with potential risk to research participants, as mentioned in other articles and advocated, for example, by the NHI policy [8,13] implemented in 1998, or by the 2008 Ministry of Health guidelines for constituting DSMB [9].

Approximately 75% of the analyzed articles describe, even if succinctly, how DSMB should be composed, but without much consensus: 47.6% of the articles argue that the presence of a (bio)ethicist in the DSMB is strongly recommended, and even mandatory. According to Asplund [14], although the presence of a professional bioethicist is not mandatory, it is generally favorable and important during the development of the study, according to the DSMB regulations.

The presence of a professional with knowledge of ethics/bioethics is necessary, especially for studies on vulnerable populations or high-risk interventions [15]; sometimes, to provide the DSMB with a broader analysis perspective [16]; or for the advocacy of the research participants, being also important for protecting their rights and interests [17].

Still regarding the composition of DSMB, 14.3% of the articles pinpoint some difficulty in recruiting members with experience in conducting activities, monitoring data, and protecting research participants. Some studies mention the difficulty in finding members with expertise in conducting clinical trials in neonatal pediatrics, a context that requires adequate knowledge for proper moral judgment [18]. It is necessary to know the characteristics and needs of the population to be studied, including its peculiarities, for proper data monitoring and complete participant protection [10].

Research participant protection

As expected, according to what is provided for in current regulations and normative instructions, most articles make DSMB responsible for protecting participants and guaranteeing research integrity and credibility [19-26]. Thus, 96.8% of the articles state that DSMB have as its main responsibility protect the participant; 84.1% state that DSMB must guarantee research integrity and credibility by ensuring reliable and quality data. The committees are assigned the role of protecting participants during the clinical trial, even if this implies changes in its scope and development [27].

Moreover, 13% of the articles highlight that the functions of DSMB fall into the category of ethical responsibility [28] and assume the duty of protecting the participant and guaranteeing their safety and rights. According to Fleming [22], assuming these responsibilities is an ethical imperative for monitoring committees to function.

Of the analyzed articles, 61.9% define research participant protection as the main attribution of DSMB, citing the monitoring of adverse events and other safety data and the assessment of study risks and benefits as ways of ensuring it. These procedures mainly apply to verification of criteria that can determine the completion of the study [28,29].

According to Conwit and collaborators [16], DSMB are responsible for reviewing safety data to ensure that participants are not exposed to unacceptable risks. One can even recommend the suspension or alteration of the natural course of the study if preliminary results show risks, harms, or absence of benefits to the participants [30].

Relationship with research ethics committees

About 16% of the analyzed articles highlight that DSMB have a complementary function to REC. Despite being independent and having different responsibilities, DSMB and REC complement each other regarding their roles and activities in monitoring clinical trials [31]. Besides approving the DSMB regulations, the REC must also be informed about their resolutions to take action and provide technical support during the ethical evaluation of a study, from beginning to end [32,33].

Moreover, REC face the dilemma of being co-responsible for monitoring participant safety in a study in the absence of an infrastructure that allows DSMB to fulfill such attribution,

whether due to the composition and experience of their members or for administrative reasons [34].

In 23.8% of the articles, the authors mention that DSMB should also be concerned with participants in other studies, in addition to future patients, considered potential users of the interventions tested. Accordingly, Eckstein [20] discusses the principle of collective ethics, capable of protecting future patients (and not only the study participants).

DSMB may interrupt a study due to safety reasons. Shah and collaborators [35] point to the importance of discussing whether or not the committee should share the results of its analyses, deciding on the interruption of the study beyond the clinical trial in question. According to the authors, any action taken would be ethically justified by the protection of participants in other studies and future patients: after all, monitoring committees and sponsors have ethical obligations to protect their participants and other individuals from any potential risk.

Confidentiality

During any communication between DSMB, sponsors, researchers, ethics committees, and research participants, the terms, contracts, and agreements executed between monitoring committees and sponsors must be considered, as the signature of these documents is a prerequisite for DSMB members to receive and analyze research data. According to Shah and collaborators [35], monitoring committees should prioritize minimizing risks and preventing harms to participants, even in other studies.

Conversely, some articles point out that DSMB must guarantee the confidentiality of the data received and analyzed as well as the content of their resolutions sent to sponsors and researchers. Eckstein [20], for instance, states that confidentiality is important for DSMB to maintain their function of promoting scientific integrity.

Regarding the issuance of resolutions by DSMB to sponsors and researchers as a way of protecting research participants, 28.6% of the analyzed articles address this category. DSMB resolutions can include suggestions for suspending the study, interrupting the recruitment of participants or, still, ending the study as a measure of safety and protection of research participants [24,36].

Ball, Piller, and Silverman [27] also point out that DSMB must consider ethical aspects for their resolutions—and not just scientific and statistical aspects, as the data analysis plans of several clinical trials are traditionally composed. For the authors, the statistical guidelines and criteria proposed in a data analysis plan should not be an obstacle to ethical decision-making, but rather proposals to improve the interaction between scientific and ethical outcomes in research.

Satisfying criteria for early interruption of studies or issuing opinions unfavorable to the continuity of an intervention should provoke assertive resolutions for the study to be completed. In these cases, proceeding with the research would be considered unethical [27].

Conflict of interests

Seeking to minimize and avoid some conflicts of interest between the professionals who compose the monitoring committees and the study researchers and sponsors, 19% of the articles emphasize that there should not be any type of payment to DSMB members, who must be independent of the researchers and, mainly, the study sponsors, without professional or financial ties [37,38].

Other relevant ethical issues

About 4.8% of the articles describe some ethical discussion regarding the clinical equipoise of the study, for which DSMB must be responsible. One must maintain the uncertainty that a treatment or intervention is better than another for the continuity of studies and participant recruitment—unless the study outcomes have been definitively answered, thus justifying its completion. Thus, when clinical equipoise is no longer sustained, there is a criterion for early interruption of the study [25].

Some articles (about 3.2%) conduct an ethical discussion based on principlism to support the DSMB actions. These studies defend the participants' autonomy, beneficence, non-maleficence, and justice as pillars of medical ethics; however, according to

Davis and collaborators [39], decision-making by sponsors and/or DSMB members can be paternalistic, going against the principle of autonomy. This occurs when a false interpretation of beneficence can provide participants with something unwanted that does not, in fact, bring them benefits [39].

A total of 27% of the articles state that early interruption of the study, when recommended by DSMB, produces an ethical dilemma. According to DeMets and collaborators [40], this is because early interruption could deprive some patients of access to new interventions and treatments, with potential benefits. But interrupting a study prematurely also prevents exposing more patients to risks and harms caused during research. Thus, the balance between risk and benefit of any intervention must be evaluated before deciding on its interruption or continuation [40].

Final considerations

Data and safety monitoring boards are important agents in the conduction of clinical research projects, as they ensure due protection to participants. As discussed, all research can pose risks and harms to its participants, in several types and degrees; in this scenario, the proper work of monitoring committees becomes especially relevant.

As shown, the functions of DSMB may be complementary to those of the REC. And, as much as there are ethics committees for assessing research projects and ethical evaluation, DSMB are essential for continuous monitoring of efficacy and safety data, and for the ethical evaluation of criteria necessary for the continuation or early interruption of a study.

From beginning to end of a study, DSMB act by reviewing and approving its protocols, even before starting any intervention with the research participants. Moreover, these committees evaluate interim data, clinical outcomes, efficacy and, mainly, safety assessments. Continuous monitoring of adverse events and other aspects is important for a global view of the safety data of an intervention and its results.

DSMB resolutions must be assertive and encourage decision-making that determines the continuity or interruption of a study. Assessing the risks to which participants are exposed is necessary, even if there are direct benefits. The risks must be managed and, preferably, mitigated, so there is no harm to the participants. Therefore, DSMB monitoring of safety data is essential for the follow-up of research participants and their exposure to real and potential risks in a clinical trial.

Since 2008, the Ministry of Health has been establishing regulations and guidelines for the operation of monitoring committees. More recently, in 2015, Anvisa also highlighted the need for monitoring committees to conduct research projects. Resolution No. 9/2015 of the Collegiate Board of Anvisa (RDC), which regulates clinical trials with drugs in Brazil, establishes that every phase III clinical trial must be monitored by DSMB and determines that their resolutions be reported to Anvisa [41].

Brazil has a connected ethical-regulatory system, which has Conep and hundreds of REC spread throughout the country. Unlike in other countries, these bodies are connected under a coordinated articulation.

Ethics committees follow guidelines published by Conep for monitoring research involving human beings, aiming to protect the safety and well-being of research participants. Besides monitoring committees, this structure offers a structured and organized network to ensure that its resolutions are met and, especially, that research participants are protected.

Finally, Brazil has been moving towards making monitoring committees a requirement for conducting clinical studies with human beings. But this is not enough: we must qualify and train professionals and demand the presence of bioethicists as differential members in the composition of monitoring committees. We must propose methodologies for data analysis that include adequate criteria for interruption or suspension of a study. We must make ethical thinking the determining factor in project evaluation and monitoring. We must care about research participants. We must protect them.

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