STATISTICS AND RESEARCH NOTES

Multicenter studies in clinical research: benefits, challenges, and recommendations for effective management

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ABSTRACT

In clinical research, multicenter studies represent a key tool for collecting data from multiple centers, thus increasing the external validity and generalizability of results. The fact that they are conducted simultaneously in several institutions, localities, provinces, or even countries allows for a larger and more diverse sample, which favors representativeness and makes the information applicable to different populations and settings.

This narrative review highlights their advantages and disadvantages and explores in depth the main challenges they entail (ethical, methodological, logistical, and operational). It also analyzes real and relevant examples that illustrate their impact on the generation of robust clinical evidence. Finally, conclusions and practical recommendations for the effective management of these projects are presented, emphasizing the importance of leadership, coordination between centers, the commitment of the research team, and rigorous adherence to ethical and methodological standards.

Keywords: epidemiologic studies, biomedical research, multicenter studies as topic, data management, reproducibility of results, Argentina.

RESUMEN

En la investigación clínica, los estudios multicéntricos representan una herramienta clave para recolectar datos de centros múltiples, aumentando así la validez externa y la generalización de los resultados. El hecho de que se lleven a cabo simultáneamente en varias instituciones, localidades, provincias o incluso países permite conformar una muestra más amplia y diversa, lo que favorece la representatividad, haciendo que la información resulte aplicable a diferentes poblaciones y escenarios.

Esta revisión narrativa destaca ventajas y desventajas, y explora en profundidad los principales retos que conllevan (éticos, metodológicos, logísticos y operativos para considerar). Asimismo, se analizan ejemplos reales y relevantes que ilustran su impacto en la generación de evidencia clínica robusta. Finalmente, se presentan conclusiones y recomendaciones prácticas para una gestión eficaz de estos proyectos, con énfasis en la importancia del liderazgo, la coordinación entre centros, el compromiso del equipo investigador y el cumplimiento riguroso de estándares éticos y metodológicos.

Palabras clave: estudios epidemiológicos, investigación biomédica, estudios multicéntricos como asunto, gestión de datos, reproducibilidad de los resultados, Argentina.

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INTRODUCTION

Multicenter studies are research investigations conducted simultaneously across multiple centers or institutions, generally located in different cities, provinces, or even countries.[1] Their primary objective is to collect data from a larger and more diverse sample, thereby increasing the representativeness and external validity of the findings.[2]

Although the terms “multicenter” and “multisite” are often used interchangeably, they are not strictly synonymous. Important distinctions exist between them, as outlined below (Table 1).

ADVANTAGES

Multicenter studies offer numerous methodological and operational benefits that make them a highly effective strategy in clinical and epidemiologic research. First, they optimize recruitment timelines by enabling the enrollment of a larger number of participants within shorter periods. In addition, they enhance sample representativeness by including broader and more diverse populations, thereby increasing external validity and allowing findings to be generalized across different healthcare settings.

Furthermore, larger sample sizes increase statistical power, facilitating the detection of smaller effects and improving the precision of estimates. In addition, the implementation of standardized protocols across multiple centers can improve data quality. However, this may also be a disadvantage, as it requires substantial operational and logistical effort (e.g., variability in the variables collected; despite the use of uniform operational definitions, centers may employ different kits or measurement instruments, or have access to different resources).

Finally, multicenter studies are often more attractive to funding agencies, thereby increasing opportunities for grants and research funding, and they promote the development of academic collaborative networks, strengthening scientific output.[4]

REAL-WORLD EXAMPLES

The following section presents three relevant local examples that illustrate the impact of multicenter studies on the generation of robust clinical evidence.

The Inter-American Society of Cardiology promoted the Inter-American Registry of Influenza and Pneumococcal Vaccination (CorVacc Study).[5] This was a cross-sectional study that included outpatients older than 18 years who provided informed consent to participate in a 34-item online survey administered through Google Forms. A total of 19 Latin American countries were represented by cardiologists who enrolled as participating investigators.

The Cardiovascular Imaging Society conducted a prospective, observational, multicenter study that included 1,435 hospitalized patients with COVID-19 from 12 high-complexity centers across nine Latin American countries.[6]

The Argentine Society of Internal Medicine led a prospective, multicenter registry of adults hospitalized with COVID-19, including data from 4,776 patients enrolled between March and October 2020 across 37 healthcare centers in Argentina.[7]

As illustrated by these examples, the organizational structure of a scientific society facilitates the coordination of multicenter studies because it typically provides access to already established professional networks, readily identifies potential participating centers, and encourages investigators to become involved. Undoubtedly, this support not only ensures broader geographic reach and greater representativeness but also enhances academic credibility and, consequently, often increases the impact of dissemination and publication efforts.

Although multicenter studies coordinated through scientific societies may appear easier to conduct in many respects, this does not mean they are free of challenges. These studies remain complex; however:

a) the coordination burden is reduced because it is centralized within an experienced scientific society;

Table 1. Differences Between Multicenter and Multisite Studies

Study tipe	MULTICENTER	MULTISITE
Definition	Several centers from different institutions (including different countries) coordinated by a lead center.	Multiple sites within the same institution under a common organizational structure
Organization	Coordinating center designs the protocol, oversees implementation, and centralizes data analysis.	Single organization with standardized procedures and integrated data.
Principal Investigator (PI)	One PI per center, responsible for local compliance	A single central PI who coordinates all participating sites.
Example	International clinical trial involving centers in different countries (Argentina and Uruguay), coordinated by a lead institution	Multiple-site study within the same healthcare network (e.g., Mayo Clinic campuses in Rochester, Minnesota; Scottsdale/Phoenix, Arizona; and Jacksonville, Florida) during a defined study period.[3]

b) logistics are streamlined through preexisting structures (e.g., scientific committees, access to research platforms, and funding for publication costs); and

c) methodological standards (e.g., ethical review and data quality assurance) are maintained, ensuring harmonization of the data collection process and enhancing regional or international visibility.

DISADVANTAGES

As early as 1980, Charles L. Meinert noted that multicenter clinical trials “are difficult to organize and expensive to conduct”.[8] Despite their value in generating robust evidence, these studies present important limitations that must be carefully considered during both the planning and implementation phases.[9] Even when they involve a relatively small number of centers, they pose substantially greater logistical, methodological, and operational challenges than single-center studies.

First, organizational complexity is often considerable, as multicenter studies require broader governance structures, multiple committees, and effective central coordination. With regard to protocol design and development, the involvement of numerous investigators with diverse interests and backgrounds may hinder consensus-building, often resulting in delays in ethical approval. These difficulties may be further exacerbated by differences in review criteria, the need for multiple protocol versions, and heterogeneity in institutional or jurisdictional regulations.

In addition, patient recruitment may be adversely affected when protocols are excessively complex or overly ambitious, creating a greater data collection burden and potentially increasing the risk of participant dropout. Finally, quality control and monitoring represent additional challenges, as variations may exist across centers in terms of procedures, available technologies, and staff training. Such differences increase the risk of bias and make the comparison and reproducibility of results more difficult.

ETHICAL CHALLENGES

The participation of multiple centers in a study requires review and approval by several institutional ethics committees[1] which may result in significant delays in project initiation. In some cases, one committee may require modifications that are not requested by others, complicating the implementation of a common protocol. The time required to obtain approvals can vary considerably; reports in the literature have documented delays of up to 18-24 months.[10]

Each participating center must prepare documentation for submission to its corresponding ethics committee, and this process of multiple reviews, together with the need to comply with different regulatory and administrative requirements (local regulations may vary across countries or provinces), often prolongs study start-up timelines compared with single-center studies.

It is essential to ensure that all participants receive the same level of protection, regardless of the country or center in which they are enrolled. Whenever informed consent is required, consent forms should be adapted to the cultural and linguistic characteristics of the populations being studied at each center (e.g., language), ensuring that the information is communicated clearly and comprehensibly to participants.[11]

The sharing of information across multiple centers increases the risk of breaches of confidentiality. Robust systems must therefore be implemented to protect

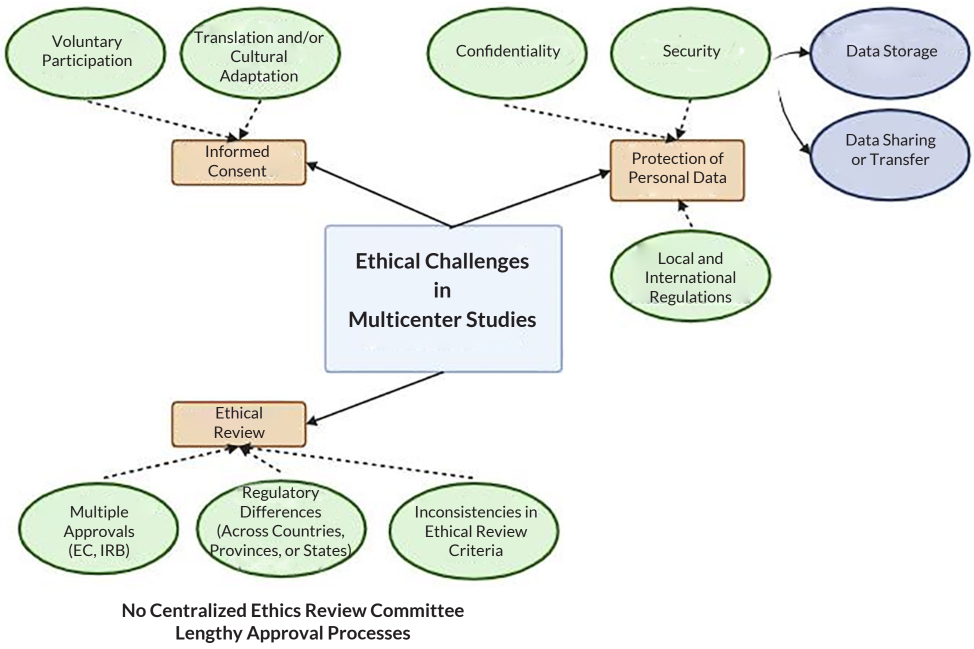

Figure 1. Ethical Challenges Associated With Multicenter Clinical Research Studies. Source: Prepared by the authors.

personal and clinical health data in compliance with local and international regulations.[12] Figure 1 summarizes the main ethical challenges associated with multicenter clinical research studies.

RECOMMENDATIONS

The following section presents several key recommendations for the effective management of multicenter studies. These recommendations are intended to guide the planning, implementation, and oversight of such projects.[13-14]

1. A collaborative team composed of investigators from each participating center, local coordinators, the Data Coordinating Center (DCC; Data Coordinating Center-which is not always available in Argentina and whose responsibilities often fall to a single individual, the Principal Investigator [PI], who may simultaneously serve as site coordinator, auditor coordinator, trainer, and data analyst), and mentors (when more than one person is involved in data entry).

2. A clear communication and decision-making structure. The steering committee, composed of the principal investigator and site co-investigators, oversees the overall progress of the study. The operations committee –consisting of the principal investigator, DCC members, and local coordinators– manages the operational aspects of the study. Authorship policies should also be clearly defined, as they are generally established in advance (e.g., the number of authors eligible for inclusion in the scientific publication may be determined according to the number of patients enrolled by each center).

3. Strict protocol adherence is essential to ensure data quality. In addition, all regulatory requirements must be fulfilled, including ethics approvals, budgetary approvals, and data-sharing agreements.

4. Trained personnel, provided with adequate training and clear instructions to ensure compliance with the standardized protocol. The key consideration is not only having trained personnel, but also ensuring that training is directed specifically toward those who will perform these roles (e.g., principal investigators [PIs] and data entry personnel). Pilot testing of the database is strongly recommended, beginning data entry with a fictitious “test patient” to identify potential issues before study implementation.

5. An initial meeting with the study team, which helps strengthen communication and ensure regulatory compliance.

6. Monitoring the performance of each participating center is crucial. The steering committee should oversee recruitment through study records and issue periodic reports on data quality, including errors, missing data, and inconsistencies.

7. Maintain regular communication with participating centers (e.g., through teleconferences, email, or newsletters). Actively foster the engagement of all personnel involved, as their participation is essential to achieving the study objectives.

8. Strictly adhere to the statistical analysis plan as originally designed and approved. The DCC is responsible for centralizing the study database and conducting the statistical analyses.

CONCLUSIONS

Multicenter studies constitute a fundamental research strategy for generating robust, representative evidence that is applicable across diverse clinical settings. However, their successful implementation depends on rigorous management capable of anticipating and addressing the multiple methodological, logistical, and ethical challenges inherent to these projects. The complexity associated with coordinating multiple sites, research teams, and methodological processes requires the adoption of specific project management strategies to ensure study quality, integrity, and overall success.

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