Case Report

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Key Concepts of Clinical Trials

Abstract

The renewed focus on comparative effectiveness research by the federal government serves as a timely reminder of the value of clinical trials for the practice of evidence-based medicine and health care reform. Clinical trials have an impact on society as a whole by boosting the level of care, as well as on the individual patient by increasing the possibilities for effective therapies. Inaccurate information gathered through flawed clinical trials may unintentionally harm patients, and clinical studies also have the potential to pose unknown risks for the participants. Although conducting a well-designed clinical study may appear straightforward, it requires precise technique and oversight that are constrained by basic ethical principles. We provide a summary of the moral values that underpin this study.

Keywords: Phase I • Phase II • Phase III • Phase IV studies for drugs • randomized controlled trials

Hasan Mahmud*

CAR-T R&D Scientist, University of Oklahoma, United States of America

*Author for correspondence:
Mahmud.hasan@gmail.com

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Introduction

The rise in health care costs in the United States has recently generated major public health care spending to identify the medical treatments with the best value. In order to evaluate "clinical outcomes, effectiveness, and appropriateness of items, services, and procedures that are used to prevent, diagnose, or treat diseases, disorders, and other health conditions," the American Recovery and Reinvestment Act of 2009 specifically allotted $1.1 billion for "comparative effectiveness" research. Randomised controlled trials (RCTs), in particular, continue to be the gold standard for comparing disease therapy, even though a variety of study designs can accomplish these goals. Executing a clinical study, however, necessitates a thorough plan based on ethical, moral, and legal considerations. Consequently, it is crucial that medical professionals comprehend the principles. [1]

Materials and Methods

This narrative review, which is based on a clinical trials course developed by one of the authors, also includes a PubMed search performed before January 2011 using the keywords "randomised controlled trial," "patient/clinical research," "ethics," "phase IV," "data and safety monitoring board," and "surrogate endpoint" (DJM).

The Ethical Foundation of Clinical Trials

Despite the fact that James Lind's "A Treatise of the Scurvy" from 1753 detailed the earliest known contemporary clinical trial, it wasn't until the middle of the 20th century that ethical issues in human research were addressed. The Nuremberg Code was created in 1949 as a response to the Nazis' illegal use of human subjects for medical research during World War II. It consists of 10 fundamental guidelines for human research. [2] The World Medical Association accepted this guideline in 1964, expanding it to cover the whole world as The Declaration of Helsinki. Notably, it promoted the moral idea of "clinical equipoise," which was first used in 1987 to refer to the professional medical community's ambiguity about

the relative efficacy of several therapies that were the subject of a clinical study. [3] The clinical investigator is guided by this ethical principle in executing comparative trials without violating the Hippocratic Oath.

The 1979 Belmont Report5, which was commissioned by the US government in response to the Tuskegee syphilis experiment, furthered the ideas of respect for individuals, beneficence (to act in the best interests of the patient), and justice. 6 These ideas were applied in this paper to the procedures for obtaining informed permission, weighing the risks and rewards, and selecting research volunteers fairly. Importantly, the distinction between activities involving "physicians and their patients" and those involving "investigators and their subjects" was made, establishing clearer lines between clinical practise and research. This definition of research as "an activity meant to test a hypothesis...to generate or contribute to generalizable knowledge" is obvious. [4]

- In reaction to the Tuskegee syphilis experiment, the US government commissioned the 1979 Belmont Report5, which advanced the concepts of justice, beneficence (acting in the patient's best interests), and respect for people. 6 The methods for getting informed consent, balancing the benefits and hazards, and equitably choosing study subjects were all addressed in this work using these concepts. Importantly, the line between clinical practise and research was drawn clearly, separating actions involving "physicians and their patients" from those involving "investigators and their subjects." Research, according to this definition, is "an activity intended to test a hypothesis...to develop or contribute to generalizable information."
- Participation is purely optional.
- The level of secrecy that will be upheld.
- Contact information with any queries or issues.
- It's interesting to note that this fundamental protection in patient research has certain shortcomings. Since this is ironically the goal of the study, the investigator really has little knowledge about the dangers and advantages of an intervention. Insufficient research participant comprehension and self-reported unhappiness with the procedure serve as examples of the difficulties that still exist in providing informed consent [5]. Explorations to increase participant comprehension of consent papers and processes have been sparked by this [6].
- Title 45, Part 46 of the Code of Federal Regulations, which is titled "Protection of Human Subjects," is the culmination of the ethical ideas from these foundational books and was published in 1991.
- 7 It governs everybody and is referred to as the "Common Rule."

Overview of Trial Design

Clinical trials are intended to monitor patient outcomes under "experimental" circumstances that are within the scientist's control in their most basic form. In contrast, no interventional study designs (such as cohort and case-control studies) allow the researcher to quantify the exposure of interest without having any effect over it. Because it enables randomization of the intervention, a clinical trial design is frequently preferred because it effectively eliminates the selection bias brought on by an imbalance of unmeasured/unknown confounders. It is possible to demonstrate causation in an RCT thanks to its inherent strength [7]. However, there are still issues with randomised clinical trials, including contamination, misclassification or information bias of the outcome or exposure, co-interventions (where one arm receives an additional intervention more frequently than the other), and information bias of the outcome or exposure (where a proportion of subjects assigned to the control arm receive the intervention outside of the study).

The choice of an adequate study population is necessary for the execution of a strong clinical trial. Despite the fact that all participants gave their informed permission for the intervention, it's possible that the cohort that was enrolled will not be exactly like the group they were selected from. The so-called "volunteer bias" in selection might result from things like research eligibility requirements, intrinsic subject characteristics (such as RCTs aim to achieve internal validity by enrolling a relatively homogeneous population in accordance with predefined characteristics), narrow inclusion and

exclusion criteria may restrict their external validity (or "generalizability") to a limited degree. These factors include geographic distance from the study site, health status, attitudes and beliefs, education, and socioeconomic status. This topic emphasises the fact that an experimental treatment's "efficacy" (a measurement of an intervention's success in a controlled environment) may not translate into its "effectiveness" (a measurement of its worth when used in the "real world"). Efforts to increase generalizability and patient recruitment utilising free As long as the incentives are not excessively forceful, providing medical care, receiving financial compensation, and developing communication tactics are all regarded ethical [8].

Conclusion

It is critical to comprehend the fundamental ideas involved in conducting clinical trials in order to provide patients with the most efficient and secure treatments. This issue is highlighted by the media's focus on safety-based drug withdrawal, which has involved 1.5 medications on average annually since 199351. Key stakeholders may be better prepared to address future research conundrums both domestically and internationally if they understand the ethical principles and rules behind trial designs. Clinical trials that are properly planned and carried out can also make a substantial contribution to the national drive to enhance the efficacy and efficiency of healthcare in the United States. Physicians and patients can continue to have faith in the recommended therapy by using strict procedures for innovative medication research and approval [9].

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Conflict of Interest

None

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