ENSAYO

Equipoise e incertidumbre, o el dilema ético de los ensayos clínicos aleatorios

Equipoise and uncertainty, or the ethical dilema of randomized clinical trials / Equipoise e incertezas, ou o dilema ético dos ensaios clínicos aleatórios

Fabián Jaimes[1]

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RESUMEN

El ensayo clínico controlado es considerado como el mejor diseño para evaluar la eficacia de una intervención. La investigación clínica que emplea este diseño, sin embargo, plantea un dilema ético. Por un lado, cada paciente debería tener el tratamiento que mejor se ajusta a sus necesidades, según el acuerdo entre el juicio del médico y los requerimientos individuales. Y, por otra parte, el ensayo clínico necesita que el cuidado de cada paciente no sea decidido ni por el juicio clínico ni por la elección del individuo, sino por una asignación aleatoria. Esta tensión puede ser descrita, en un sentido genérico, como un conflicto entre los intereses terapéuticos de los pacientes individuales y el interés de la población total que podría beneficiarse de los avances en el conocimiento médico y la investigación. En esta revisión, se mostrará algo de la historia de la ética de la investigación desde 1970, y la forma como dos aproximaciones éticas, aparentemente opuestas, han intentado resolver las preocupaciones acerca de la diferencia entre investigación y terapia. Esta diferencia, finalmente, se supone que es la pregunta subyacente en la investigación clínica terapéutica.

Palabras clave: ética; ensayos clínicos controlados aleatorios como asunto; equipoise terapéutico; incertidumbre; terapéutica

ABSTRACT

Randomized controlled trials (RCT) are considered the best design for testing the efficacy of an intervention. Clinical research employing this design has been considered to pose an ethical dilemma. On one hand, each patient requires the treatment that best meets his or her needs, as judged by his or her doctor in agreement with the patient's requirements. On the other hand, the randomized trial necessitates that each patient's care is decided neither by the physician nor the patient but instead by random assignment. The tension may be described, in a generic sense, as a conflict between the therapeutic interests of individual patients and the interests of the whole population that would benefit from advances in medical understanding and research. This manuscript covers some of the history of research ethics since 1970, and how two apparently opposite ethical approaches have tried to solve these concerns about the distinction between research and therapy; which, at the end, is supposed to be the underlying question in therapeutic clinical research.

Keywords: trials; ethics; equipoise; uncertainty; therapeutics

RESUMO

O ensaio clínico controlado é considerado o melhor desenho para avaliar a eficácia de uma intervenção. A investigação clínica que emprega este desenho se considerou

1. Médico, internista, MSc., Ph.D. Profesor Facultad de Medicina, Universidad de Antioquia. Investigador Asociado, Unidad de Investigaciones, Hospital Pablo Tobón Uribe. Medellín, Colombia.

Dirección de correspondencia: abián Jaimes. Correo electrónico: fjaimes@udea.edu.co.

que propõe um dilema ético. Por um lado, cada paciente deveria ter o tratamento que melhor se ajusta a suas necessidades, segundo o acordo entre o juízo do médico e os requerimentos individuais. E por outra parte, o ensaio clínico precisa que o cuidado que cada paciente não seja decidido nem pelo juízo clínico nem pela eleição do indivíduo, senão por uma atribuição aleatória. Esta tensão pode ser descrita, num sentido genérico, como um conflito entre os interesses terapêuticos dos pacientes individuais e o interesse da população total que poderia beneficiar-se dos avanços no conhecimento médico e a investigação. Nesta revisão se mostrará um pouco de a história da ética da investigação desde 1970, e a forma como duas aproximações éticas aparentemente opostas tentaram resolver as preocupações a respeito da diferença entre investigação e terapia. Esta diferença, finalmente, supõe-se que é a pergunta subjacente na investigação clínica terapêutica.
Palavras chave: ética; ensaios clínicos controlados aleatórios como assunto; equipolência terapêutica; incerteza; terapêutica

INTRODUCTION

Randomized controlled trials (RCT) are considered the best design for testing the efficacy of an intervention[1]. Clinical research employing this design has been considered to pose an ethical dilemma. On one hand, each patient requires the treatment that best meets his or her needs, as judged by his or her doctor in agreement with the patient's requirements. On the other hand, the randomized trial necessitates that each patient's care is decided neither by the physician nor the patient but instead by random assignment[2]. The tension may be described, in a generic sense, as a conflict between the therapeutic interests of individual patients and the interests of the whole population that would benefit from advances in medical understanding and research.

This manuscript covers some of the history of research ethics since 1970, and how two apparently opposite ethical approaches have tried to solve these concerns about the distinction between research and therapy; which, at the end, is supposed to be the underlying question in therapeutic clinical research.

A first approach

According to Miller and Brody, the book *Medical Experimentation: Personal Integrity and Social Policy* by Charles Fried published in 1974 launched a "similarity position" within bioethics[3]. Fried assumed that answers to ethical dilemmas in research would have to be found within the same ethics of therapeutic medicine. Fried apparently was the first one who coined the term "equipoise" to describe the ethically necessary condition for conducting an RCT: physician-investigators must be indifferent to the therapeutic value of the experimental and controls treatment evaluated in the trial. However, what Fried objected primarily in RCTs was not randomization per se, but the fact that no informed consent had been obtained. Because his concern was about an ingredient of both medical research and therapeutic medicine – the informed consent – he did not discriminate any potential difference between the ethics of medical therapy and the ethics of medical research. From this point, the same ethical and conceptual framework seemed to be useful for medical research as well as for medical practice.

The emergence of clinical equipoise

In a landmark article in 1987, Benjamin Freedman offered a solution to the RCT's dilemma that gained widespread acceptance within bioethics[4]. He argued that the tension between ethically legitimate scientific experimentation and the therapeutic obligation of physicians could be overcome by the principle of "clinical equipoise".

Freedman called Fried's original concept "theoretical" or "individual" equipoise, and contrasted it with his own

definition of "collective" (clinical) equipoise. In the latter case, any individual investigator might have reasons to believe that one arm of the RCT offers a therapeutic benefit over the other arm, but the medical profession as a whole remains divided. Freedman argued that collective equipoise should be used as the only justification for entering patients into RCTs. If, the medical profession has no clear preference for one treatment over another, an RCT is needed to clarify this situation. Freedman considered that individual equipoise is too "fragile" to be used as a basis for trial entry. It is subject to change for many reasons, including peer pressure, results of imperfect studies, and the influence of advertising. He concluded that collective equipoise is a far more stable entity than individual equipoise, because shifts in one direction by some people are compensated by changes in the opposite direction by others, and only significant trial results will dispel collective equipoise.

The scientific community perceived Freedman's concept of clinical equipoise as both a theoretical and a practical advantage[5]. It appeared to offer a more compelling argument than Fried's formulation, and it would permit RCTs that would otherwise be ethically proscribed. Since it appeared to solve the ethical dilemma by accommodating the conduct of clinical trials with the therapeutic obligation of physicians to offer optimal medical care, clinical equipoise gained wide acceptance as a fundamental concept to the ethics of clinical trials.

This attractive presentation, however, diverted attention from the fact that clinical equipoise, in the same way that "individual" equipoise, collapsed the original distinction between research and therapy[3]. Moreover, some harsh critics consider that even if the community, physicians, and patients were to be in a true state of equipoise regarding what therapy is best, such equipoise would not resolve the ethical dilemma posed by the RCTs[6].

Problems with equipoise argument and the origin of uncertainty principle as an alternative

Some opponents of the equipoise construct argue that it has three fatal flaws[7]. First, it does not exist in real life: it is rarely the case, if ever, that reasons to favor one therapy are in fact evenly balanced among the medical community by reasons to favor an alternative. In fact, new studies are initiated precisely because a new therapy appears strongly promising. Second, it treats the individual preferences that construct the collective equipoise as point-estimates or certainties, and ignores the natural uncertainty with which those "hunches" are held. Third, equipoise is almost never formally considered by trialists or explored in a systematic manner by ethics committees.

Predominantly endorsed in the United Kingdom and Europe[8], the uncertainty principle rejects the indifference of equipoise and builds on the notion that clinicians and patients are often uncertain whether their hunches about a treatment's effectiveness are true. It is not that the members of the medical profession as a whole have no preferences and are indifferent to the alternative treatments, it is that they are uncertain about whether their hunches are correct. When the uncertainty boundaries of a group of clinicians and patients include or cross zero, such that they recognize that the treatment they prefer might be useless or even harmful, "it is time for a trial and that trial is ethical"[9-11].

In an elegant sentence, a clinical epidemiologist and obstetrician from McMaster University summarized the tenets behind the uncertainty principle[9]: "moral principles are intellectually attractive but ethically deceptive. Sometimes they are in conflict, and sometimes – like all evidence-based guidelines – they may not be appropriate. When we are morally certain, we know what to do. When we are uncertain, a controlled trial may help to resolve our uncertainty".

Uncertainty about clinical equipoise or the critique of the "similarity position"

In the philosophical realm, some authors consider that the debate about the usage of equipoise versus the uncertainty principle as an entry criterion for a RCT is misplaced. Accordingly, these are not mutually exclusive concepts, and equipoise simply represents the point or distribution of maximum uncertainty[12].

Furthermore, both of them reflect the same "therapeutic misconception" about the ethics of clinical trials, whereby the latter rests on the same moral considerations that underlie the ethics of therapeutic medicine[3].

Clinical equipoise and the uncertainty principle make sense as a normative requirement for clinical trials only on the assumption that investigators have a therapeutic obligation to the research participants. According to Miller and Brody, "the presumption that RCTs must be compatible with the ethics of the physician-patient relationship erroneously assumes that the RCT is a form of therapy, thus inappropriately applying the principles of therapeutic beneficence and nonmaleficence that govern clinical medicine to the fundamentally different practice of clinical research"[3].

If considered as coming from different teleological approaches, the more reasonable conclusion is that RCTs also should be governed by ethical norms appropriate to clinical research, which are distinct from the therapeutic

principles (i.e., beneficence and nonmaleficence) that support the medical practice.

An alternative ethical framework

The most recent treatment of human research ethics, which aims to minimize the possibility of exploitation by ensuring that research subjects are not merely used but are treated with respect while they contribute to scientific knowledge, has been developed by Emanuel E, and coworkers[13]. They proposed seven requirements that systematically elucidate a coherent framework for evaluating the ethics of clinical research studies:

- Social or scientific value: evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge
- Scientific validity: use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data
- Fair subject selection: selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful are not favored for potentially beneficial research
- Favorable risk-benefit ratio: minimization of risks, enhancement of potential benefits, risks to the subject are proportionate to the benefits to the subject and society
- Independent review: review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research
- Informed consent: provision of information to subjects about purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individuals understand this information and can make a voluntary decision whether to enroll and continue to participate
- Respect for potential and enrolled subjects: respect subjects by:
  - Permitting withdrawal from the research
  - Protecting privacy through confidentiality
  - Informing subjects about *newly* discovered risks or benefits
  - Informing subjects of clinical research results
  - Maintaining welfare of subjects

This framework is built on the difference between research and therapy and on the core value of protecting research participants from exploitation[13]. Fulfilling all seven requirements is necessary and sufficient to make clinical research ethical.

These requirements are universal, although they must be adapted to the health, economic, cultural, and technological conditions in which clinical research is conducted.

In summary, an alternative framework seems to provide accurate ethical guidance concerning clinical research without assuming that the ethics of therapeutic medicine should govern clinical trials. The most important next step for research ethics is to develop it systematically in a way that avoids any confusion of clinical research with medical care. ■

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