REVIEW ARTICLE

Ethical considerations and challenges in first-in-human research

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First-in-human (FIH) research is a translational process to move a new potential therapy from bench to bedside. Major ethical challenges of an FIH trial arise because of the indeterminate nature of the risks involved and the controversial risk-benefit justification. Severe adverse events and death of subjects who participated in FIH research in the past have led to an increased attention on ethical considerations in the design and conduct of such research. Furthermore, novel therapies in the current decade, such as molecular-targeted, gene transfer, and pluripotent stem cells therapies, have led to numerous emerging ethical challenges or different ethical assessment and justification frameworks for FIH research. This article presents, discusses, and interlinks ethical considerations and challenges in FIH research through a review of related ethical principles and their application to each ethical issue with given examples. Possible solutions to address each ethical challenge are presented. The scope of this article focuses on 4 major ethical issues in FIH research: risk-benefit assessment and justification for the conduct of research, selection of a suitable target population, informed consent, and conflict of interest. (Translational Research 2016;■:1–13)

Abbreviations: CFR = Code of Federal Regulations; COI = conflict of interest; EMEA = European Medicines Agency; FIH = first-in-human; GCP = good clinical practice; ICF = informed consent form; ICH = International Conference on Harmonization; IRB = institutional review board; LAR = legally acceptable representative; MABEL = minimal anticipated biological effect level; OTCD = ornithine transcarbamylase deficiency; SDM = surrogate decision maker; TM = therapeutic misconception; TMis = therapeutic misestimation

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INTRODUCTION

First-in-human (FIH) research is an important step of product development, provided that it is a transitional move of a new potential therapy from bench to bedside. However, the very nature of FIH research can prove burdensome to its own success. First, owing to the fact that the human body's responses to new therapies are often unpredictable, prioritization of safety concerns in FIH research can be a complex requirement. Second, limitations on the applicability of nonclinical data to human subjects can also complicate the risk-benefit assessment and justification for the conduct of an FIH trial. Precedent

cases of severe, life-threatening adverse events, including death, resulting from FIH research (eg, Jesse Gelsinger's death in 1999[1] and the tragedy of the TGN1412 trial in 2006[2]) have contributed to the increased attention on ethical considerations in the design and conduct of such research, leading to better protections for the human subjects involved. As Henry Beecher outlined half a century ago, "*an experiment is ethical or not at its inception*."[3] In other words, positive outcomes with no adverse events do not equate to ethical research and, conversely, occurrences of serious adverse events, including death, do not automatically make research unethical.[4,5] This article presents major ethical issues and challenges in FIH research through a review of related ethical principles with given examples. The application of ethical principles and possible solutions to address each ethical challenge are also discussed.

RISK-BENEFIT ASSESSMENT

In FIH research, major ethical challenges often arise because of the indeterminate nature of the risks involved and the controversial risk-benefit justification that must be made based on limited safety and efficacy data derived solely from nonclinical experiments.[6] Owing to its generally nontherapeutic design, FIH research tends to transgress on the tenets of the Declaration of Helsinki[7] and the International Conference on Harmonization (ICH) for good clinical practice (GCP)[8] that emphasize the precedence of the rights, safety, well-being, and interests of individual subjects over the purposes and interests of clinical research. The ethical justification for the conduct of a nontherapeutic trial with uncertain risks is thus challenging. According to the core ethical principle of beneficence specified in the Belmont report, risks and benefits must be extensively assessed with regard to minimization of the potential risks, maximization of the possible direct and indirect benefits, and justification for the design and conduct of research (Fig 1).[9]

Risk assessment. Risk assessment can consist of more than just the physical aspect. In addition to physical risks, one should also take into consideration psychological, financial, and social risks to the subjects and/or the society as well as the probability, duration, and magnitude of their effects.[10] Furthermore, some potential risks may be manageable, whereas certain harms may be irreversible. Risks arising from 'me too' drug FIH trials are fundamentally more predictable than that of innovative therapy FIH trials.[11] Failure to notice existing potential harms or emphasize well-defined risks could occur in complex protocols of novel therapies.[12] There is a constant

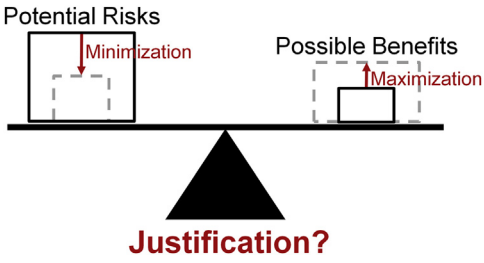

Fig 1. Risk-benefit assessment and justification.

challenge in FIH research on the quality and comprehensiveness of risk evaluation.

Interpretation of nonclinical results can, in some aspects, fail to predict human risks and to anticipate the outcomes of human research because of physiological differences among species and representative models.[11] The TGN1412 study, though uncommon,[13] demonstrates the complexity of risk determination in FIH research and the limitations of animal models to represent human responses. In 2006, all 6 healthy volunteers, who were administered with the first supposedly subtherapeutic dose of TGN1412 (a CD28 superagonist antibody), experienced severe systematic inflammatory responses that required cardiopulmonary support within a few hours after dose administration.[2] This life-threatening cytokine storm was completely unpredicted at the time since the test systems used (ie, an analogous rodent model, a primate model using TGN1412 at up to 500 times the dose given to the volunteers, and conventional human peripheral blood mononuclear cells cultures) all failed to exhibit this toxic potential.[14] This event led to the issuance of several reports on FIH studies[15-18] and significant changes in the regulations, released by the European Medicines Agency, for FIH trials with investigational medicinal products.[19] The revised regulations highlighted the need for the identification of the risk factors (ie, the mode of action, the nature of the target, and the relevance of animal models) and the application of risk mitigation strategies. Despite the increased attention on risk determination, it is worth noting that no matter how extensively a translational review has been done, the risks can never be wholly predicted. With the limitations of nonclinical data, existing methodologies for evaluating research risks systematically, which are based on the available data, may not be effectively applied to FIH research.[20,21]

It is also reasonable to assume the existence of publication bias among clinical and nonclinical data as some negative or neutral results may have remained unpublished. The analysis of the tragedy at Northwick Park Hospital in 2006, for example, later found that TGN1412 in fact works in quite similar ways to another cancer drug whose trial was conducted by Professor