

Addressing the Ethical Challenges of First-in-Human Trials

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Abstract

Phase I clinical trials raise ethical challenges, particularly the Phase I trials that involve a novel therapy being tested in humans for the first time, usually termed first-in-human (FIH) trials. The ethical appropriateness of clinical research requires having a favorable risk-to-benefit ratio and protecting patients from excessive risk, but both of these standards may be difficult to assess and to achieve in Phase I trials. There are no widely accepted standards for judgments concerning risk, benefit, and value in Phase I trials. Also the question of how to conceptualize and compute benefit has been a subject of ethical debate, particularly for Phase I trials where the likelihood of therapeutic benefit to participants is very slight. Specifically, should regulators and institutional review boards approve Phase I trials in the absence of likely benefit to participants when these subjects are being exposed to an uncertain and potentially high level of risk. Then there is the question as to how to communicate accurate and meaningful information about the uncertainty, risk of adverse events, and the very limited, if any, prospect of therapeutic benefit to potential trial participants in order to promote a meaningful informed consent process. That FIH trials involving highly novel agents often enroll participants with serious unmet needs further complicates the process.

Very serious adverse reactions that occurred in the first-in-human trial of the monoclonal antibody TGN412 in Britain led to the issuing of several reports on first-in-human studies and the European Medicines Agency published a guideline on first-in-human trials shortly thereafter. In the past two years the (United States) Food and Drug Administration (FDA) has approved Investigational New Drug applications for three Phase I first-in-human clinical trials of candidate therapeutics derived from human embryonic stem cells (hESCs). Neither the FDA nor the National Institutes of Health have developed their own guidelines for the safety and ethics of first-in-human trials or guidelines for first-in-human trials with hESC derivatives.

The analysis in this paper highlights the need for more focused attention to the ethical issues that first-in-human, trials raise. The paper proposes identifying prerequisites for beginning trials with a novel and potentially high-risk intervention. Preferably, there should be clear-cut guidelines and/or review by a central body.

Keywords: Clinical trials; Novel therapy; First-in-human; Human experimentation; Therapeutic benefit; Human subject protections; Human embryonic stem cells

In March 2006, six healthy volunteers participating in a first-in-human trial of TGN1412, a monoclonal antibody that was being developed as a therapy to treat leukemia and autoimmune diseases, experienced a serious adverse reaction. Shortly after receiving an infusion of the agent in a private clinical research unit of a hospital in London, the six developed a cytokine release syndrome resulting in multi-organ failure. As is the case for all clinical trials in the United Kingdom, the design of this Phase I trial had been evaluated and authorized by the appropriate regulatory bodies. This event raised awareness of the risks of conducting FIH trials with novel and potentially risky candidate therapies. In response, the Secretary of State for Health for the UK set up an Expert Scientific Group on Phase One Clinical Trials which published its report later that year [1]. The Royal Statistical Society established an expert group of its own to assess the statistical issues that might be relevant to FIH trials, and also issued a report [2]. In addition, the BioIndustry Association and the Association of British Pharmaceutical Industry organized a taskforce to provide an industry perspective on these issues [3]. At the same time as these reports were being written, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency, the European counterpart to the U.S. Food and Drug Administration (FDA), developed a guideline on strategies to identify and mitigate risks for FIH clinical trials with investigational medicinal products [4].

A 2007 workshop report on rethinking early clinical testing organized in the UK by the International Institute for Regulatory Science, an industry supported agency, comments that “the world of

pharmaceutical research received an unpleasant ‘wake-up’ call when the TGN 1412 incident hit the headlines,” [5] but other incidents of harm, even death, to participants in Phase I trials, some then known and other unpublicized, had taken place. Phase I clinical trials often raise significant ethical and human subject protection challenges, particularly the Phase I trials that involve a novel therapy being tested in humans for the first time, usually termed first-in-human (FIH) trials. In contrast with later stage clinical trials, where it is possible to assess risks to human subjects based on data from earlier human trials, Phase I trials involve a transition from pre-clinical scientific studies and animal testing into clinical research on human subjects. Further complicating matters, FIH trials lack comparative human studies from which reviewers can glean data about risk and benefits. Reviewers have to make determinations about whether to initiate human clinical testing and then the risks and benefits to trial participants on the basis of *in vitro* studies of human tissue and animal research.

The level of risk to participants in Phase I trials often correlates with the innovativeness of the therapy under consideration. Early stage

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clinical trials with “me too” drugs modeled on existing medications or with already approved drugs being tested for new applications usually pose fewer risks than trials with more innovative therapies. Novel biological and cellular products are generally considered to be higher risk interventions than novel chemical entities. The European Medical Agency’s (EMA) guideline for first-in-human trials involving potentially high-risk products places clinical trials in this category when uncertainty exists regarding: (1) the mode of action; (2) the nature of the target; and/or (3) the relevance of animal models, each of which increases the possibility that participants will experience serious harm. The EMA cautions that “the higher the potential risk associated with the type of medicinal product and its pharmacological target, the greater the precautionary measures that should be exercised in the design of the first-in-human study [6].”

Many Institutional Review Boards (IRBs) struggle with evaluating and providing oversight for innovative FIH trials. Some of the reasons will be discussed in this paper. But it should also be noted that the regulatory systems providing oversight of clinical trials in the United States and in other developed countries often fail to offer sufficient guidance for the specific ethical issues raised by FIH trials with novel therapies. The Common Rule [7], which delineates basic protections for all human subject research conducted or supported by the U.S. federal government does not address how to apply these standards in FIH trials. Nor does the FDA’s human subject protection regulations [8] for clinical trials. Because the FDA considers the basis on which it makes determinations to authorize Investigational New Drug Applications to be confidential, it does not share its analysis with the IRBs reviewing applications to begin clinical trials with these agents. With the notable exception of gene transfer research, the National Institutes of Health (NIH) have not developed guidance documents for Phase I trials in general or FIH trials in particular.

This is not to claim that the FDA and the National Institutes of Health (NIH) are either unaware of or unconcerned about the complex ethical and human subject protection issues FIH trials raise. In response to social and scientific concern with the special ethical, scientific, and safety dimensions of gene transfer research (sometimes incorrectly referred to as gene therapy), the NIH established a Recombinant DNA Advisory Committee (RAC), a multidisciplinary group at the NIH, to review such trials. The RAC has issued a number of guidance documents, including its Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Research Participants (Points to Consider) [9] and the NIH Guidance on Informed Consent for Gene Transfer Research [10]. On the part of the FDA, the agency sponsored a public workshop in November 2010 that dealt with the ethical issues and regulatory challenges of FIH cell and gene transfer trials in pediatric populations [11].

Nevertheless, other novel and high risk FIH studies have not received comparable attention from either of the agencies. For example, the FDA has recently authorized Investigational New Drug (IND) applications for three high-risk trials of candidate therapies derived from human embryonic stem cells (hESCs). While the FIH clinical trials with hESC derivatives qualify on all three of the EMA’s criteria for high-risk FIH trials, the FDA did not develop guidelines for trials with hESC derivatives. Nor has the NIH established an expert ethical body to oversee the trials as it did for gene transfer/therapy oversight by the Recombinant DNA Advisory Committee (RAC).

This article explores some of the key ethical challenges of conducting FIH trials from the perspective of local review and evaluation. It

focuses on the ethical issues and not on the mechanisms involved with oversight of the trials. The concluding section of the paper offers a series of recommendations.

Evaluating preclinical data

In contrast with later phases of clinical trials, for which there are human subject data available, the justification for proceeding with Phase I clinical trials of an investigational agent relies entirely on the quality and efficacy of the preclinical evidence. The Council for International Organizations of Medical Sciences states that “clinical testing must be preceded by adequate laboratory or animal experimentation to demonstrate a reasonable probability of success without undue risk [12].”

Because FIH trials rest on the foundation of the appropriateness and quality of preclinical research, it is disturbing that there is a growing literature documenting problems with the preclinical data used to support initiating Phase I trials. Deficiencies noted include inadequate measures to control bias, absence of measures for random treatment allocation and blinded outcome assessment in the animal studies, and failure to account for missing data. Yet another issue is that FIH trials may be initiated before data have received adequate peer review. Financial incentives may also contribute to premature entry into clinical trials [13]. Preclinical literature also shows evidence of publication bias, that is, neutral or negative animal studies may be more likely to remain unpublished than successful studies [14].

Many IRBs have difficulty evaluating the preclinical research. The designs of some clinical trials have failed to take into account the limitations of efficacy observed in animal data [14] as well as discounting the risks. These shortcomings may result from a variety of factors. Because of issues related to the proprietary nature of the data submitted to the FDA and the confidentiality of the FDA review, the FDA does not make its assessment of the preclinical data available to IRBs. IRB members may lack the technical competence to be able to conduct their own review and many institutions do not have specialized scientific bodies to which the IRB can refer the data for assistance with the analysis. Many IRB members may be reluctant to question the quality of the scientific data and their potential social value [15]. Instead, they may be inclined to defer to the judgment of the FDA and other regulatory bodies rather than carefully scrutinizing the quality, integrity, and appropriateness of the preclinical models in the science being presented [16].

Assessing risk

The ethical appropriateness of clinical research requires achieving a favorable risk-to-benefit ratio and protecting subjects from excessive risk, but these standards are difficult to achieve in FIH trials which involve the greatest degree of uncertainty at any point in the drug development process [17]. Nor is there agreement on the acceptable level of risk to begin clinical testing on an investigational agent. Moreover, parties to the risk assessment process – investigators, IRB members, potential subjects – often have diverging views about a study’s risks [18].

Analysis of risk in clinical trials frequently differentiates between interventions with a therapeutic warrant and those performed strictly for scientific purposes. Risks in the case of the former are deemed “acceptable” if an intervention can reasonably be considered consistent with the best medical interests of the subject while in the latter case the standard is whether the scientific value justifies the risk imposed on the subject [19]. This dichotomy, however, assumes that some Phase I trials

offer a clear therapeutic benefit – which for reasons reviewed later in this article is contested by many ethicists. Also it is difficult to anticipate the scientific value of new agents based solely on laboratory and animal studies. Moreover, if the value of acquiring the scientific information were to be considered sufficiently great, it could theoretically justify exposing participants who would not personally benefit to a very high level of risk [20].

Given the centrality of risk analysis, it is worrying that several recent articles contend that no systematic framework exists for assessing whether research risks are acceptable or excessive. James Anderson and Jonathan Kimmelman argue that there are no widely accepted standards for judgments concerning risk, benefit, and value in Phase I trials [21]. This is also a theme in a 2010 article written Annette Rid, Ezekiel Emanuel and David Wendler. These authors, all of the Department of Bioethics at the NIH Clinical Center, assert that as a result, investigators and review boards often rely on intuitive judgments in making decisions. Doing so is problematic because intuitive judgments fail to take into account relevant empirical data and are subject to well-documented cognitive biases. In addition, intuitive judgments about which research risks are acceptable are likely to vary widely and lack transparency [22].

In addition, as Anderson and Kimmelman demonstrate, the principle of clinical equipoise, widely used for evaluating risk in late phase trials involving human subjects, cannot usually be extended to FIH trials as a standard for assessing the ratio of risk to benefit. This is because the principle of clinical equipoise is grounded in a research context in which subjects are being randomly assigned to one of two arms in a trial in which a new therapy is being compared with an existing therapy and there is uncertainty regarding the comparative therapeutic merits of each arm. However, FIH studies are rarely designed to compare an experimental treatment against a standard therapy (unless no therapy is considered such an option). Instead, the goal in most first-in-human trials is to determine the safety and dose levels for subsequent trials. Moreover, FIH typically do not involve randomization [23].

A major factor complicating risk analysis in FIH trials is the difficulty of making accurate predictions from preclinical laboratory research on human tissues and animal studies of the likely effect of the investigational agent on humans. According to Rebecca Dresser, risk analysis based on preclinical research can fall short in three ways. It may fail to predict human risks, leading to adverse effects in human trials – one example being the TGN1412 trial. It may predict clinical benefits that then fail to materialize for human subjects. And it may predict nonexistent risks in humans with the result that a potentially useful agent is discarded [24].

Extrapolating from laboratory and animal studies is a complex process under all circumstances, but even more so in proposed FIH trials which usually lack data from comparator studies in humans to help guide the analysis. Although an effort is usually made to choose species based on their similarities to the human biological response under study, there may not be appropriate animal models that accurately replicate the human disease. Moreover, there are significant differences between human and animal physiology. Given the limitations of animal models of many diseases and differences between human and animal physiology, toxicological studies in animals may be poor at predicting toxicity in humans [25]. For similar reasons, the ability to show proof-of-principle in preclinical research, whether in the *in vitro* or the animal studies, does not provide a therapeutic warrant for humans [26].

The severe adverse reaction that TGN1412 engendered in human volunteers after being safely administered at a much higher equivalent dose in rhesus and macaque monkeys for four consecutive weeks provides one example of the limitation of animal models. The investigation of the Expert Scientific Group concluded that the adverse incident did not involve errors in the manufacture of the agent or its formulations, dilution, or administration to the trial participants. Instead it placed the cause of the cytokine storm the volunteers experienced in an unpredicted biological action of the drug in humans [27]. One theory is that the catastrophic effects of the trial were mediated by memory B cells which were either absent or under developed in the laboratory animals [28].

To lower risk in Phase I trials, subjects usually receive a low dose of the investigational agent, and if that level of exposure appears safe, then the dose is gradually increased with each cohort until investigators determine the maximum tolerated dose. This approach, however, is not risk-free, especially when the trials recruit seriously ill patients. A review of all non-pediatric Phase I trials conducted by the National Cancer Institute between 1991 and 2002, a total of 460 trials involving 11,935 participants, about one quarter of which were FIH trials, found that 15 percent of subjects in trials of single chemotherapy agents experienced serious but nonfatal toxic events. There were 58 deaths (a death rate of .49 percent) that were determined to be at least possibly related to the treatment. The toxicity related death rate in these trials was 0.26 percent. Rates of response and toxicity varied among the various types of Phase I oncology trials but the data for FIH trials were not separately computed [29]. It is difficult to know whether these data can be generalized to other types of trials.

Given the centrality of risk analysis to the clinical trials enterprise, the development of more systematic approaches is critical. To address this need, Rid, Emanuel, and Wendler propose a four step method they term “the systematic evaluation of research risks” (SERR). The method involves delineating, quantifying, and comparing the risks of research interventions with the risks posed by appropriate comparator activities [30]. It will require empirical evaluation to know whether the method or a modified version can be applied to FIH trials.

Conceptualizing and computing potential benefit

U.S. federal regulations stipulate that IRBs must ensure that “risks to subjects are reasonable in relation to anticipated benefits [31].” The implication is that the more unknown, likely, or severe the potential risks are, as in the case of Phase I FIH trials, the greater in likelihood and magnitude the corresponding potential benefits should be. Part of the problem in making such a determination is how to conceptualize or compute benefits, especially in FIH studies. There has been ethical debate on a number of topics including what benefit entails, how to make assessments, who the appropriate beneficiary is, how to balance risk to the trial participant with potential benefits to society, and how all of this relates to the concept of justice.

Potential benefit to an individual subject is usually conceptualized in the form of an improvement in health status derived from the agent being tested, but often there is disagreement as to what kinds of milestones constitute a therapeutic benefit. For oncology patients, for example, does an improvement in the quality of life qualify or does benefit require a clinically relevant shrinkage in the size of the tumor, a remission, or an extension in life expectancy? To provide greater precision, Nancy Kass proposes that analysis include magnitude of benefit as well as likelihood of benefit. For example, a reference to the benefit of a potential extension in life expectancy would specify the length of time [32].

Benefit for a society, on the other hand, is generally understood to be in the form of the generalizable knowledge generated by the research that can lead to the future development of medical therapies. Progress in health research is considered to be a social good that generates knowledge that potentially contributes to relief of suffering, treatment of and cures for diseases, and the prolongation of life [33]. But medical research may be motivated by factors other than compassion for human suffering or the search for improved treatment for human diseases. Medical research in the 21st century is increasingly a commercial activity driven by the desire to maximize profits. Research may also reflect the pursuit of knowledge for personal curiosity, career advancement, and prestige. These considerations, particularly the commercialization of medical research, increasingly affect the questions asked and the solutions found [34].

Healthy volunteers for clinical trials do not have any prospect of direct benefit from the agent being tested, but they may decide to participate in order to receive other types of benefits, for example, remuneration or to gain access to health services they would otherwise not be able to qualify for or afford. Similarly, some patients enrolled in clinical trials receive the collateral benefit of improved health care. Should these benefits be taken into account in making risk/benefit calculations? In a much cited article addressing "What Makes Clinical Research Ethical?" the authors, Ezekiel Emanuel, David Wendler, and Christine Grady, caution that extraneous benefits such as payment or adjunctive medical services that might benefit individual participants cannot be considered when conducting a risk-benefit analysis. One reason is that provision of health services is not the purpose of clinical research. More fundamentally, including these extraneous benefits would skew the risk-benefit calculus: it would mean that simply increasing payment or including additional medical services could make the benefits outweigh even very risky research [35].

Similarly, Gillian Nycum and Lynette Reid argue that indirect or collateral affective benefits, such as the experience of hope or altruism, should not be a proxy for direct medical benefit in the context of risk-benefit calculations. The opportunity to exercise altruism, to act on behalf of benefitting others, is sometimes claimed as a collateral benefit for participation in early clinical trials. According to this line of reasoning, participants experience a feeling of accomplishment or meaning for their lives by contributing to the advancement of knowledge. But as Nycum and Reid point out, the claim that participants receive affective benefits does away with altruism as a motivating principle and substitutes a feeling of personal gratification. To protect altruistic motives from exploitation by trial directors, they recommend that ethics review should ensure there is significant content to the promise of a social benefit proportionate to the burdens or harm in question [36].

Whether trial participants, particularly those who are patients, should have a reasonable prospect of benefit has given rise to ethical controversy. As noted, healthy volunteers have no possibility of direct benefit to balance against the risks the trial entails, and the likelihood of therapeutic benefit to patients in Phase I trials is also very slight at best. In a standard Phase I design, the dose administered is too low to produce a therapeutic effect. Meta-analyses of Phase I cancer trials, for example, demonstrate that at best some five percent of those in FIH trials of an oncology agent have some shrinkage of their tumor, and this shrinkage may not have a clinical impact [37]. Given the emphasis on toxicity and dosing in Phase I trials, critics, usually bioethicists, have questioned whether Phase I trials can ever be considered to have therapeutic content [38]. According to Nancy King, for example, "in

many early-phase clinical trials, the prospect of direct benefit may be too small, too attenuated, too unlikely, too uncertain to hold out as reasonable to expect [39]." In contrast, "benefit enthusiasts," mainly drawn from scientific researchers, view Phase I trials as motivated by "therapeutic intent" as well as by scientific purpose. They counter that given even a small chance for benefit, Phase I trials should still be considered therapeutic research interventions [40]. Steven Joffe and Franklin Miller argue that while the potential for benefit in these trials exists, the data are not available to support any definitive estimate of a clinical benefit rate [41].

It has been suggested that clinical research that presents no potential benefits to individual subjects depend on a different type of evaluation, which Charles Weijer terms a "risk-knowledge calculus." This approach assesses whether societal benefits, calculated in terms of knowledge, justify the risks to individual participants in the trial [42]. Regulators and IRBs have usually been willing to go forward with Phase I trials in the absence of likely benefit to participants if the research has the prospect of contributing to generalizable scientific knowledge for social benefit, but the prospect of the trial doing so may be difficult to assess. Though IRBs engage routinely in the analysis of such a trade-off, there are no agreed upon methodologies for doing so. Emanuel and his colleagues acknowledge "There is no settled framework for how potential social benefits should be balanced against individual risks [43]." Nancy King goes further in her critique. She contends that there is a tendency for investigators and IRBs to indulge in "benefit creep:" to ensure that research considered beneficial to society is able to go forward, they may exaggerate or even invent benefit to subjects [44].

In such situations participants bear the risk of harm while society gains the potential benefit. Some ethicists have termed this arrangement a "bad deal" trial [45]. Here it should be noted that an ethical principle expressed in the Declaration of Helsinki is that "in medical research on individual subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society [46]." In response to this situation Wing Kong argues that a robust conception of justice needs to be factored into the ethical assessment of risk and benefit in Phase I trials involving competent patients. He is critical of current practices among research ethics committees in the UK and IRBs in the U.S. which focus on consent and assume that individual participants are motivated by beneficence. Instead, he proposes that the legitimacy and decency of what is requested of would-be research participants need to be examined in the broader context of societal obligations and principles of justice. According to Kong, even if potential participants fulfill the requirements for autonomy, justice still limits what society can appropriately ask them to do and to what they can give consent. The moral legitimacy of medical research for Kong depends on the demonstration of sufficiently compelling societal benefits and fair limits on what we can ask of others [47].

Kong offers an important insight on the importance of factoring a robust conception of justice into the ethical assessment of risk and benefit in Phase I trials, particularly FIH trials. Some IRBs try to incorporate justice considerations in their deliberations but the absence of clear standards as to what constitutes compelling societal benefit and fair limits makes it difficult for them to do so. Clearly some clinical trials of potentially promising therapeutics are premature and others too risky for any type of volunteers. The decision to go forward in 2011 with clinical trials of agents derived from human embryonic stem cells likely falls into this category [48]. The key to factoring in justice setting an appropriate guideline will be conceptualizing and

reaching consensus on what constitutes compelling societal benefits and fair limits. This will be a difficult task, but it is important to begin conversations.

Determining the appropriate subjects for a FIH trial

Fair subject selection, a key dimension of making clinical research ethical, encompasses both decisions about who should be eligible for inclusion in a trial and who should be excluded from recruitment. Both of these decisions depend on the balance of risks and benefits as well as the scientific goals of a particular study. Making these calculations more complex, subject selection can itself affect the calculation of risks and benefits of a study. To reduce risks, fair subject selection requires that subjects who may otherwise fit the scientific criteria, but are at substantially higher risk of being harmed or of experiencing more severe harm, should be excluded from participation. Conversely, to enhance benefits, considerations should assess which subjects will maximize the benefit or value of the information obtained, as for example, including a wide range of groups for whom the investigational drug could be prescribed if found safe [49].

Like most clinical research, research directors of FIH trials generally prefer to recruit healthy volunteers. Healthy subjects provide the “cleanest” data that are not compromised by underlying conditions or the effects of medications. There is also concern that drug toxicity could exacerbate patients’ existing medical problems. Other downsides noted of using patients are that the homogeneity of the data may be prejudiced and operational efficiencies compromised by the greater difficulty and likely higher costs of recruitment [50]. Additionally, it is thought that healthy people can usually tolerate adverse reactions from experimental interventions better than persons already suffering from a serious medical problem.

Nevertheless, there is a division of opinion about the appropriateness of the practice of recruiting healthy volunteers in clinical trials. To provide an incentive to participate, clinical trials usually remunerate healthy participants. There is concern that monetary incentives, especially when combined with economic need, might incline potential recruits to conceal information that could disqualify them from trial enrolment, as for example, about their health status or use of alcohol, cigarettes, and drugs that could then bias outcomes. Payment can also complicate efforts to protect participants from undue risk: criteria which exclude individuals with specific physical conditions, habits, and prior study exposures may do so because these conditions make them unusually vulnerable to harm. Yet another issue is whether financial incentives result in a disproportionate share of the exploratory research burdens being placed on low-income people. Some critics claim this constitutes a form of exploitation because it results in poor people assuming risks to develop better health care interventions likely to be used for higher-income people [51].

Patients are often considered to be more appropriate subjects for trials testing investigational agents targeting their particular medical problem. It has been a practice to recruit seriously ill patients who have exhausted standard treatment options for some risky trials, for example, oncology trials of potential chemotherapy drugs as well as many of the FIH trials involving highly novel biological, cell, and gene transfer agents. Doing so is justified on the grounds that these patients have the advantage of potentially receiving a direct or indirect benefit.

Sometimes recruitment distinguishes between patients whose diseases can be managed with standard therapies and those who cannot. Because stable patients exposed to investigational agents face a higher relative risk, some ethicists argue there should be stronger

evidentiary justification for FIH trials involving this group, and this caution seems appropriate. The choice of stable patients constituted one source of the controversy surrounding the gene transfer trial that resulted in the death of Jesse Gelsinger [52].

There are several sources of disagreement over which types of subjects are appropriate to recruit for FIH trials. One issue is whether FIH studies with serious risks should ever be conducted on healthy recruits. Some analysts oppose doing so on the grounds that healthy volunteers have more to lose than patients already compromised by illness or injury. Consistent with this mind set, the Working Party of the Royal Statistical Society criticized the decision to recruit healthy volunteers for the TGN1412 trial arguing that the principle of non-maleficence, the obligation not to inflict harm intentionally, requires not exposing healthy recruits to a significant level of harm. Their reasoning was that it is unethical to do so because healthy volunteers cannot receive a compensating health benefit from the agent [53]. Similarly participants in a 2007 workshop sponsored by the CMR Institute maintained that in circumstances where there are known toxicities studies should only be conducted in patients. Another point was that longer-term risks to healthy volunteers, as for example, an agent altering the immune system, might not always be obvious in healthy volunteers [54]. Since the participants in this workshop were primarily drawn from industry, it is possible there may have also been some unstated concerns with liability issues.

Some ethicists have questioned the judgment that higher risks are acceptable in FIH trials involving people who face lethal or serious risks from a pre-existing disease. Wing Kong, for example, takes issue with the proposal that research that is unethical to attempt in a fit young adult becomes ethical because the patient is dying. He proposes that the dying have as much right not to be harmed or used as the healthy. Although it is assumed that terminally ill patients who participate in clinical research are motivated by altruism, Kong points out that evidence suggests that these patients often participate in research primarily out of desperation and a mistaken belief of likely therapeutic benefit [55]. Rebecca Dresser notes that even patients with untreatable life-threatening disease can experience serious losses and receive no personal benefit from participation in a FIH trial [56].

Although all of these cautions are ethically justified, the dilemma is that accepting all of them would leave FIH trial organizers without any category of subjects to recruit. This means that difficult choices need to be made, preferably on a case by case basis related to the agent being tested and the specific types of risks the trial entails. Recruitment of patients for a trial of a potential intervention specifically targeting their disorder seems unavoidable, and if the trial is risky, to focus on advanced rather than stable patients. Otherwise it would be less problematic to recruit healthy volunteers. In all cases it would be important to bear in mind Rebecca Dresser’s observation that all participants in FIH studies qualify as vulnerable subjects because they can be harmed or wronged in distinct ways. She points out that FIH trials, under the best of circumstances, expose healthy people with limited economic opportunities and ill people with limited health options to harm for the benefit of others [57]. Therefore it is essential to make potential participants, whether healthy volunteers or patients, fully aware of the nature of the risks and to ascertain that they comprehend the information communicated. This brings us to the topic of informed consent.

Obtaining meaningful informed consent

Another set of vexing ethical issues in all Phase 1 trials revolves

around how to communicate accurate and meaningful information about the uncertainty, risk of adverse events, and the very limited, if any, prospect of therapeutic benefit to potential trial participants in order to obtain meaningful informed consent. The informed consent process requires that potential subjects be accurately informed of the purpose, methods, risks, benefits, and alternatives to the research; that they understand this information and be able to apply it to their own situation; and also that they make a voluntary and uncoerced decision as to whether to participate in the trial [58]. Each of these components can be especially problematic for FIH trials since there is often no reliable information about benefits and risks for studies of agents never before used in humans. Directors of clinical trials and the IRBs reviewing and evaluating informed consent documents have the unenviable task of encouraging potential subjects to participate in the trial while dissuading them of the “therapeutic misconception” that confuses scientific research with therapy.

One set of problems for FIH trials is how to communicate uncertainty and risk. Three major issues are the complexity of the disclosure taking account of all sources of uncertainty, the difficulty of determining whether a patient understands the information, and assessing and responding to the patient’s expectations of benefit [59]. Volunteers entering clinical trials can also overlook discussions of risk during the informed consent process because their attention is focused on the possible benefits [60]. Studies have shown that participants in clinical trials often provide their consent to participate with “only the most modest appreciation of the risks and disadvantages of participation [61].” For example, a study of participants in 40 clinical trials found that about one-fourth of subjects reported no risks or disadvantages of participating despite being informed about them [62]. It is possible that the informed consent process did not focus sufficiently on the risks and potential harms. Alternatively it may be that potential subjects were being overwhelmed with technical data they did not understand. This lack of comprehension or discounting of the information conveyed may be a greater problem in studies using patient volunteers. A review of the literature focusing on studies that measured patient comprehension of information given during the informed consent process in Phase I cancer trials, for example, found that patients generally have a limited understanding of the trial purpose, an unrealistic expectation of the benefits and risks associated with trial participation, and a lack of appreciation of their right to abstain or withdraw [63]. Another study of adults with advanced cancer who were offered the opportunity to participate in Phase I oncology studies found that patients who chose to participate perceived the experimental therapy as more beneficial than decliners who more accurately perceived the risks related to the experimental therapy [64].

Given the problems noted with patients understanding and appropriately using the risk information imparted, some clinical trial programs take additional steps to assure meaningful informed consent. These include setting up education programs to work with potential trial volunteers, testing volunteers’ comprehension of the risks both at the point of giving consent and at later points in the trial, and appointing a patient advocate to assist and work with each of the volunteers. It would be helpful for these initiatives to be adopted more broadly.

As might be anticipated, patients with advanced disease who have no alternative therapies available appear to be especially vulnerable to the therapeutic misconception, possibly as a function of their desire to maintain hope in the face of their devastating disease. Surveys of cancer patients in Phase I trials indicate for example that their

major motivation for participating is the possibility they will receive therapeutic benefit, even though the likelihood they will do so is slight, and the chance the therapy may decrease their quality of life much greater [65]. Unrealistic optimism may bias how patients process information about potential risks and benefits. More fundamentally, this cognitive and affective distortion may compromise the capacity for autonomous decision-making necessary for informed consent [66]. The text of informed consent documents has been shown to be one of the factors encouraging the therapeutic misconception, as for example, the consent documents for early phase gene transfer trials which were inappropriately optimistic about the potential benefits of trial participation [67,68]. The media hype accompanying new treatments also plays a role in fueling unreasonable expectations on the part of patients with untreatable diseases as does the role of some patient support groups promoting early, sometimes even premature, clinical trials for the potential benefit of their members [69].

Is it ethical to recruit into Phase I clinical trials patients with advanced disease who volunteer to obtain an anticipated medical benefit? Franklin Miller and Steve Joffe take the position that because there is a slight possibility of a therapeutic benefit the decision to enroll in these studies to receive such a personal benefit does not, in itself, compromise informed consent [70]. In contrast, Nancy King argues that when benefit cannot reasonably be expected, as in early-stage investigational trials, the consent form should explicitly state “you will not benefit [71].” Given the mind set of patients, particularly those with advanced conditions, it is better to err on the side of discouraging patients. Nancy King’s position is more ethically appropriate. If patients who have been informed about the lack of benefit and the nature of the risks of participation and then evaluated to assure they have understood still volunteer, it would be ethically permissible to include them.

Reflections on going forward

FIH trials play an important role in enabling potential therapeutic breakthroughs but they also raise complex ethical and human subject protection challenges. The various sections of this article have delineated issues and suggested ways to address some of them. There is need for further study, discussion, and structured deliberation of these issues. Preferably these discussions will be held both on a societal level as well as in professional settings by ethicists and scientists working in relevant fields. The goal would be to work towards the development of a global set of standards.

Empirical research to compare ways that IRBs handle FIH trials could also illuminate the effort to develop a global set of standards and guidelines. It is likely that some IRBs at institutions with extensive clinical research portfolios have developed policies on particular issues that could provide models. A project to collect and evaluate these policies could be a valuable input into the process.

Bernard Lo and Deborah Grady propose yet another way to strengthen IRB review of highly innovative interventions in clinical trials, namely to establish centralized combined scientific and ethics review to inform local review. They specifically identify two models: the Recombinant DNA Advisory Committee (RAC) at the NIH, which as noted above conducts in-depth, public review of proposed innovative clinical gene transfer trials, and the National Cancer Institute Centralized IRB initiative, which performs in-depth review of multisite cancer clinical trials [72]. Centralized scientific and ethics review of innovative and potential risky FIH trials to inform local IRBs would bring subject expertise and experience into the assessment

process. It would also facilitate linking all sites enabling them to be immediately informed about unanticipated serious adverse events both at the time of the initial IRB review and on an ongoing basis during the trial. Preferably these centralized review bodies would also develop guidelines for various aspects of the conduct of trials, as the RAC has done. While there is no way to eliminate ethical challenges and subject risks in FIH clinical trials, centralized review under the NIH or equivalent bodies in other countries, would be able to better protect research participants.

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