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First-in-Human Trial Participants: Not a Vulnerable Population, but Vulnerable Nonetheless

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Translational science is a 21st century mission. Government officials and industry leaders are making huge investments in an attempt to transform more basic science discoveries into therapeutic applications. Scientists and policymakers express great excitement about the medical advances that could come with the current "bench-to-bedside" campaign.[1]

A key step in translational science is the move from animal and other preclinical studies to initial human testing. Researchers' ability to predict human effects is limited, and "first-in-human" (FIH) tests present significant uncertainty. Participants in this form of research face risks and can experience serious, even lethal, harm. Well-known incidents involving Jolee Mohr[2] and Jesse Gelsinger,[3] as well as subjects in the 2006 study of the investigational agent TGN1412,[4] show the dangers that can arise in early human research.

The bench-to-bedside campaign will need many volunteers to participate in early human testing. Investigators and regulators must not allow the policy enthusiasm for translational science to overshadow the commitment to protect human subjects. Participants in exploratory research are diverse and as a group lack characteristics usually associated with vulnerable populations, such as impaired decisional ability or economic or educational disadvantage.[5] Yet as I discuss below, different types of FIH research have features that can diminish prospective participants' ability to exercise free and informed choice. Moreover, the level of uncertainty characterizing this form of inquiry makes subjects vulnerable to harm. As one investigator put it, researchers conducting FIH studies have "the awesome responsibility of protecting the subject in what very well may be the most dangerous period of this particular drug's development."[6] To achieve adequate subject protection, research planners and reviewers must develop standards sensitive to the particular ethical concerns FIH research raises.

In this article, I describe various forms of FIH research and the specific ethical issues they raise. After reviewing different types of FIH studies, I examine three considerations relevant to all FIH trials: (1) the requirement for adequate preclinical research; (2) study design safeguards; and (3) choice of subject population. Next, I analyze in detail specific ethical considerations relevant to the three subject populations involved in FIH research: healthy volunteers, patients with untreatable life-threatening conditions, and medically stable patients. Each part of the article offers recommendations for enhancing subject protection in FIH trials.[7]

I. First-in-Human Studies: Definitions

First-in-human studies are not all alike. Readers are probably familiar with the U.S. Food and Drug Administration (FDA) phase I trial, which includes the initial human exposure to an investigational drug (IND). Phase I trials are relatively small, typically involving from 20-80 subjects. The objectives in a classic phase I study are to ascertain "the metabolism and pharmacologic action of [a single] drug in humans, the side effects associated with increasing doses and, if possible, to gain early evidence on effectiveness."[8] Initial phase I studies supply baseline human safety data and can also give an early indication of an agent's mechanisms of action in humans.[9]

Phase I trials may deviate from the classic model in several ways, however. For example, participants in phase I drug tests may receive a completely novel agent, an agent belonging to a class of drugs already studied in humans,[10] a combination of new and approved drugs, a new combination of approved drugs, or a new dose of an approved drug.[11] Another type of phase I trial involves the first exposure of a specific population, such as elderly people, to an already approved drug.[12] The classic phase I trial design is often modified in studies evaluating the initial human response to gene transfer and other biological agents.[13]

In 2005, the FDA recognized a new category of phase I studies called the "exploratory IND study." This type of study is conducted at the beginning of phase I to determine whether further human trials are worth pursuing. Therapeutic effects are not possible at this stage; instead, investigators try to ascertain baseline information, such as the biodistribution of an extremely low dose of the new agent. Exploratory IND studies are smaller and shorter than the usual phase I study, typically involving no more than 10 people and lasting a week or less.[14] The European Medicines Agency (EMEA), the European counterpart to the FDA, also has guidelines on exploratory human studies.[15]

In 2007, the EMEA addressed another special category of phase I trials. After subjects experienced serious harm in the TGN1412 study, the agency issued a draft guideline for FIH tests involving "potentially high-risk products."[16] According to the EMEA, for these products "particular knowledge or uncertainties on (1) the mode of action, and/or (2) the nature of the target, and/or (3) the relevance of animal models" create the possibility that FIH participants will experience serious harm. The contemporary focus on biological product development could produce more such high-risk FIH studies.[17]

Because the objectives, uncertainties, and risks vary among different FIH trials, each FIH proposal must be evaluated individually. In all FIH trials, however, there must be an evaluation of the preclinical evidence, trial design, and choice of study population.

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II. Preclinical Evidence, Design Safeguards, and Subject Populations

Animal and other forms of laboratory research provide the foundation for human studies. Before proceeding to early human testing, investigators and reviewers must determine whether the preclinical scientific foundation is adequate. This is a complex and value-laden task.

Longstanding ethical principles require that risks to human research participants be minimized and justified by the value of the knowledge the study is expected to produce.[18] There is also a general understanding that certain forms of risk are unacceptable to impose on human subjects. According to the Nuremberg Code, for example, "No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur."[19] Another of the Code's principles addresses the necessary foundation for human research: "The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment."[20]

Preclinical studies play a major role in applying these ethical judgments to FIH research. The history of medical research demonstrates that animal and other preclinical work can contribute to the development of safe and effective medical interventions. But preclinical research has limitations, too. Some of the limitations are inevitable, but others are not. Critics say that improvements in the preclinical research process could promote safer and more useful FIH trials.

To generate accurate and useful preclinical data, investigators must consider many factors. Selection of a proper animal species and animal model is essential. Species are selected based on similarities to the human biological response of interest. The most relevant animal species will vary, depending on the specific agent or other intervention being examined. Good animal models have been developed for some human conditions, but for others there is no relevant animal model.[21] Ideally, animal tests of investigational agents should mimic as closely as possible the anticipated human dose route, rate, and frequency of administration.[22] *In vitro* studies of human cells and tissue can supply additional information about an agent's potential effect in humans.[23]

Preclinical research can fall short in three ways. First, it may fail to predict human risks, leading to adverse effects in human trials. Second, it may predict clinical benefits that fail to materialize in humans. Third, it may predict nonexistent risks in humans. Although the challenge of extrapolating from laboratory data to humans makes each type of mistake unavoidable, commentators think the error rate could be reduced.

One source of inaccurate prediction is the use of an inadequate animal model. For example, human subjects in the TGN1412 trial had serious adverse reactions to 1/500 of a dose that was safe in monkeys.[24] Experts said that the reliance on monkeys may have been misplaced, given differences in the relevant monoclonal antibody receptors in human and non-human primates. [25] Inadequate animal models may also underlie disappointing human research results. Researchers commonly report beneficial effects in study animals that cannot be duplicated in humans. The literature is full of comments such as the following: "although many [experimental neuroprotective agents] appear quite effective in preclinical studies with small animal-models of ischemia (rats, mice, or gerbils), none of these have proven conclusively to be effective in humans."[26] Inappropriate models may also mistakenly predict harmful effects in humans. For example, some artificial sweeteners induce bladder cancer in rats, but epidemiological studies fail to show such effects in humans.[27] And although transgenic animals have become a staple of laboratory research, genetic similarity may not be enough to provide a good animal model for human disease.[28]

Other problems arise because animal researchers pay inadequate attention to potential human applications. Thus, for example, in gene transfer research, "[T]he vector construct or producer cells utilized in the research laboratory may not be appropriate for use in humans."[29] Bench researchers may measure endpoints that have no clinical significance in humans.[30] Some scientists also think that their peers adhere too closely to conventional ideas about biomedical discovery, for "the process of generating effective translational science is not as linear (that is, from molecules to [animal] models to humans) as is often thought."[31] They favor a more iterative process that moves back and forth between laboratory and human studies.[32] Thus, when preclinical data predict a human response that fails to materialize in FIH trials, researchers should go back to the laboratory to determine why this might have happened, rather than drop the line of inquiry altogether.[33]

Critics point to a lack of methodological rigor in animal studies, too. In a review of widely cited animal studies, Daniel Hackam and Donald Redelmeier found that only half had high methodological quality, with few incorporating "random allocation of animals, adjustment for multiple hypothesis testing, or blinded assessment of outcomes."[34] According to another review, animal studies that failed to incorporate randomization and blinding were more likely to find differences between control and experimental groups than were studies that used these methods.[35] Other commentators call for enhanced monitoring and data collection in animal studies. Victoria Hampshire and Evan DeRenzo advise animal researchers to record and report "key physiological variables such as weight, temperature fluctuations during the period of study, electrolytes, blood glucose, and serum chemistry values," as well as appetite, pain, and

distress levels.[36] By including such data in publications and IRB review materials, they say, animal researchers could supply a more informative picture of potential human responses and thus promote better decisions about FIH studies.[37]

No clear standards guide the move from bench to bedside. In an effort to address this situation, Jonathan Kimmelman proposes a principle of "modest translational distance" to determine when a FIH trial is justified.[38] According to this principle, every FIH study must satisfy a certain evidentiary threshold before going forward. That threshold can be met with different combinations of preclinical evidence, he suggests. Well-designed laboratory studies, good animal models, and promising data on disease mitigation or correction are the ideal. When such evidence is lacking, the proper action is to collect more preclinical data rather than to initiate a FIH trial.

First-in-human studies that lack solid scientific grounding not only waste time and resources, they expose participants to risk without good justification. High-quality preclinical research that is tailored to human investigational and therapeutic goals could reduce risks for FIH subjects and increase the value of the knowledge generated in human trials.[39]

Some human risks cannot be predicted by preclinical research, however. As Alastair Wood and Janet Darbyshire note, "[O]ur incomplete understanding of the mechanisms underlying [a novel compound's] toxicity and the limitations of animal models inevitably means that some potentially serious toxic effects go undetected in preclinical screening."[40] And when a novel agent is aimed at a new biological target, researchers cannot know what the initial human reaction will be.[41] In this situation, strict safeguards are needed to limit the initial human exposure to unexpectedly toxic novel agents.

In FIH trials, an important safety factor is the selection of an appropriate starting dose. The general approach in phase I trials is to administer a dose based on the No Observed Adverse Effect Level, which is "the highest dose at which no statistically significant and/or biologically relevant adverse effect is observed"[42] in the most relevant animal species. This dose is then modified to take into account size differences as well as safety concerns and uncertainties left by the preclinical knowledge base. There is growing agreement, however, that lower doses should be selected in some circumstances. The TGN1412 trial revealed that for biologics and other compounds meeting the European Medicine Agency's "high-risk medicinal product" definition, a different approach to dose setting is needed. The EMEA recommends using an approach that evaluates the available data to produce "the anticipated dose level leading to a minimal biological effect in humans."[43] Other approaches are to administer a "microdose," which the FDA defines as "less than 1/100th of the dose of a test substance calculated (based on animal data) to yield a pharmacologic effect,"[44] or the "no observed effect level," which is based on "the highest dose associated with no significant alteration in any form in exposed animals compared with controls."[45]

Other safety measures can be built into FIH trial design. The method of administering an investigational agent can affect risks to subjects; for example, a slow infusion allows researchers to halt drug delivery if problems arise.[45] To minimize the number of people exposed to risk, experts recommend an observation period between each subject's drug exposure. (A major problem with the TGN1412 study was the decision to administer the agent to six subjects all at once, rather than the recommended sequential dosing.[47]) Researchers should also evaluate the data produced by each cohort of subjects before proceeding with the next group and should consider revising the dose escalation plan if any unexpected responses occur.[48] Proposals for FIH research should include criteria for halting administration of the agent to individual subjects and subject cohorts, as well as for stopping the trial altogether.[49]

Data monitoring plans and committees should also be required for FIH research protocols. Protocols should include long-term monitoring of FIH subjects, for "[t]oxic exposure to a chemical, even for a relatively short time … could produce genetic, molecular, chromosomal or cellular changes that lead to disease, disability, or death."[50] Adil Shamoo and David Resnik propose a special FIH data safety and monitoring board of toxicologists and clinicians to evaluate data relatively early in the trial.[51] Studies should also be conducted by people with the proper training and skills to address potential adverse reactions and in facilities with the equipment necessary to provide participants with adequate care.[52]

In the wake of the TGN1412 trial, some experts called for systemic changes to increase FIH trial safety. To prevent unnecessary harm to subjects, Wood and Darbyshire want a regulatory mandate for research sponsors to submit information on all phase I trials to a central database.[53] This would allow officials to determine whether a proposed FIH trial involves an agent previously shown to be harmful to humans. To protect sponsors' proprietary information, access could be limited to regulatory officials. An even better strategy, Wood and Darbyshire say, would be to mandate a publicly accessible phase I database, for this would enable FIH investigators around the world to discover any existing safety information about the agents they plan to study. Other experts recommend more specialized training for investigators conducting high-risk FIH trials, as well as heightened scrutiny of such trials by ethics and regulatory review committees.[54]

Three different study populations are recruited for FIH research. Investigational agents are usually tested on healthy volunteers. However, when investigational interventions present serious risks, such as in trials of potential chemotherapy drugs, seriously ill patients unable to benefit from standard therapies are recruited for FIH trials. Patients with stable disease may also participate in FIH trials.

The choice of subject population depends partly on a trial's scientific objectives. In many cases, healthy people provide the "cleanest" data, for it can be difficult to separate the effects of a study intervention from those caused by a patient's disease or medications.[55] In some circumstances, however, patients are preferred because the target of the investigational intervention exists only in people with a particular health problem. In such cases, data from patients will be more informative than data from healthy individuals.[56] Research objectives can also affect the category of the patient group asked to serve as subjects. For example, a trial evaluating long-term effects must enroll patients expected to survive for a sufficient length of time.[57] The "best data" criterion for selecting the FIH study population has both scientific and ethical dimensions, for studies must provide useful knowledge to justify exposing participants to harm.[58]

Besides data quality, the balance of risks and potential benefits determines which population is asked to enroll in FIH trials. Sometimes investigators can minimize risks to subjects by selecting a particular study population. Healthy people can ordinarily tolerate adverse effects from experimental interventions more easily than patients can.[59] Because drug toxicity could exacerbate patients' existing medical problems, most FIH drug trials enroll healthy individuals.[60] But some FIH studies would be more risky for healthy people than for patients. For example, trials involving monoclonal antibodies and other agents that can provoke an exaggerated immune response present lower risks for patients with compromised immune systems than for healthy individuals.[61]

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A more controversial ethical judgment is that higher risks are acceptable in FIH trials involving people who already face lethal and other serious risks from a pre-existing disease. According to this view, when "there is any reasonable doubt about the prediction of safety based on preclinical data, such as when man might react differently to any of the preclinical species studied, then healthy subjects should not be studied."[62] Thus, when FIH trials involve healthy people, there should be stronger preclinical evidence that risks are low than there need be when trials involve people with an underlying serious disease.[63]

This position in part reflects the difference in relative risk faced by healthy and seriously ill patients. In this sense, healthy individuals who die or have serious health problems as a result of research participation experience a greater loss than those facing the same kinds of harm from an untreatable condition.[64] Accordingly, safety evaluations may be made in light of an individual's alternatives for life and health.[65] The FIH risk-benefit ratio can also be more favorable for seriously ill patients than for other people, for participation at times offers patients direct and indirect benefits not available to healthy volunteers.[66]

Lines are also drawn between patients whose life-threatening disease can be managed with available therapies and those whose disease is terminal. Stable patients face higher relative risks; thus, the view is that there should be stronger evidentiary justification for FIH trials involving this patient population than there need be for trials involving patients with treatment-refractory disease.[67]

At the same time, however, even patients with an untreatable life-threatening disease can experience serious losses and receive no personal benefit in FIH research. To protect patient-subjects, there should be a baseline evidentiary prerequisite for any FIH study: "If all persons are entitled to be valued equally, any subject should be able to have confidence that a translational trial meets a common threshold of justification."[68] Accordingly, in every case, there should be a "high standard of consensus in the scientific community" that the FIH study is justified.[69]

Although longstanding conventions govern most FIH study population choices, such choices are not always clear cut. For example, controversy surrounded the choice of stable patients for the gene transfer trial involving Jesse Gelsinger. Critics argued it would have been better to enroll infants with a terminal form of the genetic condition under study.[70] Besides scientific and risk-benefit judgments, considerations related to subject decision-making can influence the choice of study population. Participation by members of any study population should be conditioned on their informed and voluntary choices to enroll in FIH research. Below I discuss specific concerns about risk-benefit judgments and prospective subjects' decision-making in the three FIH study populations.

III. Respected Volunteers or Exploited Underclass?

Today, healthy young and middle-aged adults are the participant population of choice for most FIH trials. At one time in the U.S., drug safety studies relied primarily on prisoner-subjects. By the 1980s, however, ethical concerns and regulatory restrictions largely eliminated this practice.[71] Since then, researchers have relied primarily on paid volunteers to serve in FIH trials. Volunteers tend to be "people who need money and have a lot of time to spare: the unemployed, college students, contract workers, ex-cons, or young people living on the margins who have decided that testing drugs is better than punching a clock with the wage slaves."[72] Although this shift may be an improvement over the former reliance on prisoners, current FIH recruitment practices raise questions about data quality, risks to participants, and exploitation.

> To improve data quality and participant protection, researchers should "objectively evaluate [paid FIH volunteers] whenever feasible to assess their ability to enroll and continue enrollment." A national or multi-site registry of phase I participants would give researchers access to information about subjects' health and past research exposures that could compromise data quality or subject safety.

Healthy research participants cannot personally benefit from FIH trial interventions. Thus, the production of valuable information is the sole ethical justification for this form of FIH trial. Yet critics worry about the value of the data generated in FIH trials involving paid volunteers. Monetary incentives and economic need may combine to yield a test population that supplies biased or confusing data.

One concern is that people will conceal personal information that could disqualify them from trial enrollment. A person's health status and use of alcohol, cigarettes, and drugs affect the quality of safety and other data collected in FIH trials. But someone who sees research as a means to generate income has an incentive to lie about these matters.[73] Although researchers can use objective examinations and tests to secure information about disqualifying health and lifestyle conditions, eligibility screening also depends on accurate self-reporting.[74]

Repeat volunteers raise additional data quality concerns. As Carl Tishler and Suzanne Bartholomae observe, "[R]esearch subjects with unrepresentative personality or psychological characteristics tend to be physiologically or metabolically different from normal subjects and may exhibit different responses to drugs."[75] They say that repeat volunteers could have medical, psychological, and neurological abnormalities that affect data interpretation and reduce the generalizability of research findings. They also report that repeat volunteers claim they are able to tell whether they are in an experimental or control group, which could affect research results. Trials producing invalid data lead to erroneous judgments about investigational interventions, waste resources, and fail to produce useful knowledge.[76]

Payment also complicates the effort to protect participants from excessive research risks. Besides promoting data quality, eligibility criteria exclude from research individuals whose physical conditions, habits, and prior study exposures make them unusually vulnerable to harm from research interventions. When people conceal information to avoid being excluded, they jeopardize their safety. Also at risk are enrolled participants who fail to report symptoms for fear of being removed from a trial.[77]

Dishonest subjects may be unaware of the personal risks of concealment, or they may value financial gain over personal safety.[78] If payment promotes concealment, and concealment endangers subjects, then reliance on paid volunteers may be inconsistent with the mandate to minimize risks to subjects.

Payment to FIH volunteers raises concerns about exploitation, too.[79] Exploitation occurs when someone takes unfair advantage of another. The question is whether the FIH research enterprise imposes a disproportionate share of exploratory research burdens on low-income people through the use of financial incentives.

The debate over exploitation portrays the research payment system in two very different ways. Defenders characterize trial payment as consistent with payment practices outside the research setting. They say that FIH trial participation is comparable to other paid tasks that are tedious and unpleasant, and that expose workers to risk. They see no good reason to deny individuals the option of earning money through research participation rather than through other available work options.[80] Some volunteers reportedly take this view: "As guinea pigs see it, their reason for taking the drugs is no different from that of the clinical investigators who administer them, and who are compensated handsomely for their efforts."[81] On this view, payments are

equivalent to wages for participants' time and effort and are a fair and reasonable means to advance society's interest in developing new treatments.

But critics say that the payment system exploits low-income people. In the current situation, they say, poor people assume risks so that higher-income people can get better health care. Paid volunteers commonly lack health insurance and thus cannot obtain many of the treatments developed through clinical research.[82] Some also question whether individuals joining studies for financial reasons make sufficiently voluntary choices. The problem is that substantial financial inducements "could cause individuals to expose themselves to risks or potential harms that they would ordinarily view as unacceptable."[83]

Revisions could make the FIH payment system less vulnerable to exploitation charges. Reformers propose three major changes. First, they say, officials and researchers should develop a standardized compensation model. Neal Dickert and Christine Grady recommend a formula incorporating a standard sum for the hours spent in research, using the pay scale for unskilled labor as a baseline. They also suggest that supplementary payments could be made for particularly unpleasant procedures.[84] Second, fair treatment of research "workers" includes a workers' compensation program. Accordingly, industry and other study sponsors should provide health care and no-fault compensation to healthy participants harmed in the research process.[85] Third, there should be programs to increase volunteers' access to health care. On this view, society owes participants in burdensome and risky FIH research an opportunity to benefit from the therapies they help to produce.

In sum, there is a division of opinion about the state of the healthy volunteer trial system. According to the critics, reliance on paid volunteers makes drug-safety and other FIH trials an unnecessarily unreliable and risky endeavor. If monetary incentives were eliminated, then FIH trials would be safer and produce higher-quality data. But those defending the current system contend that abandoning monetary incentives would have a disastrous impact on FIH trial recruitment. Defenders also challenge the claim that low-income volunteers would be better off if this income source were eliminated.[86]

Intermediate reforms could address some problems with the current system. To improve data quality and participant protection, researchers should "objectively evaluate [paid FIH volunteers] whenever feasible to assess their ability to enroll and continue enrollment."[87] A national or multi-site registry of phase I participants would give researchers access to information about subjects' health and past research exposures that could compromise data quality or subject safety.[88] Explicit discussions with prospective participants about the risks of failing to report health problems and past study experiences could decrease the incidence of such omissions.[89] Adopting a wage-based payment system would fairly compensate participants for their contributions, keep payment at a level that avoids undue inducement, and supply an adequate number of volunteers for FIH trials.[90] Last, treating FIH participants more like military or police recruits would make the testing system more defensible. On this view, if society counts on volunteers to take risks for the benefits of others, then it should provide them with adequate medical and other support in return for their contributions.[91]

IV. Patients with Treatment-Refractory Disease

When healthy volunteers are deemed unsuitable for scientific or ethical reasons, patients with untreatable life-threatening conditions may be recruited for FIH trials. A well-known example is the phase I investigational chemotherapy trial. Patients have also been subjects in FIH trials evaluating gene transfer agents, organ transplantation innovations, and potential stroke therapies.[92] The first trials involving human embryonic stem cells are expected to recruit patient-subjects.[93] Debate over the ethics of conducting FIH trials in patients lacking standard

treatment options focuses on risk-benefit ratios, information disclosure, and subject decision-making.

Like other FIH trials, those enrolling seriously ill patients are designed to determine whether investigational interventions are safe in humans. In the traditional phase I oncology trial, the first subject cohort receives a very low dose of the investigational agent. If that amount appears safe, then the next cohort receives a higher dose, and the doses are subsequently increased until investigators determine the maximum tolerated dose.[94]

The traditional dose-escalation regimen is a cautious approach, designed to minimize risks to FIH trial participants. Risks are inevitable, however. A good assessment of the risks comes from a review of National Cancer Institute (NCI) phase I trials conducted from 1991-2002. Reviewers found that 15 percent of subjects in phase I trials of single chemotherapy agents experienced serious but nonfatal toxic events.[95] Reviewers also found a toxicity-related death rate of .49 percent for FIH trials involving a single chemotherapy agent.[96]

Potential health benefits to subjects are a major justification for the practice of recruiting seriously ill patients for FIH trials deemed too risky for healthy people. But the traditional dose-escalation regimen decreases the possibility that subjects will receive such benefits. As Manish Agrawal and Ezekiel Emanuel observe, "[I]ronically, [the classic phase I oncology trial design] ensures that the majority of patients are treated at doses that cannot produce responses in human tumors."[97] The review of NCI-sponsored FIH chemotherapy trials found an overall response rate of 5 percent. Reviewers defined response as full or partial tumor disappearance or absence of disease progression.[98] Cancer trials use these endpoints as surrogates for clinical improvements, such as longer life and increased comfort, but not everyone with a tumor response will experience a clinical benefit.[99]

Researchers are attempting to develop FIH trial designs that present a more favorable risk-benefit ratio for subjects. With the aim of increasing response rates among subjects, modified trial designs allow more subjects to receive higher doses of investigational chemotherapies than is possible in the traditional dose-escalation approach.[100] Because molecular-targeted and other agents do not exert effects through toxicity, FIH trials involving these agents incorporate alternative endpoints that are less risky and burdensome for subjects.[101]

Although their chance of clinical benefit is low, seriously ill patients may obtain other kinds of personal benefits from FIH trial participation. Patients enrolled in FIH trials may benefit psychologically from knowing that they are contributing to improved care for future patients and from gaining some control over their illness situations. They may also appreciate the added contact with researchers and clinicians that often accompanies study enrollment.[102] At the same time, investigational interventions and research-related procedures may impose burdens on FIH trial participants in the form of extra costs, clinic visits, and evaluation procedures.[103]

Medical and psychosocial benefits are possible for seriously ill participants in FIH trials, and modified trial designs could improve the risk-benefit ratio. Even FIH trials that offer no prospect of personal benefit may be ethically justified if they are expected to produce information relevant to the development of improved therapies.[104] To be ethical, however, a FIH trial must enroll patients who understand the trial's objectives and potential consequences. There is ongoing concern about the quality of seriously ill patients' choices to join early-phase studies. Commentary focuses on two features of the decision-making process: (1) the disclosure and discussion that precedes enrollment; and (2) the prospective subject's state of mind.

> Imprecise consent forms, optimistic investigators, and media hype about laboratory discoveries can foster the therapeutic misconception and promote patients' unrealistic hopes for clinical benefit in FIH trials.

Empirical studies reveal several problems with consent forms in phase I trials. One problem is that forms fail to convey meaningful information about the low chance that subjects will experience clinical improvement. Although forms rarely promise clinical benefit,[105] they often use vague and ambiguous language that could mislead patients about their research prospects. For example, a classic phase I oncology trial form might say: "No benefit can be guaranteed by taking part in this study, and the chance of benefit from this experimental treatment cannot be accurately predicted."[106] Patients could reasonably interpret this to mean that their chance of improvement is less than 100 percent, but much more than the objective estimate of less than five percent. At times, different sections of the same form convey inconsistent ideas about the probability of benefit, such as when a form clearly labels a trial intervention as investigational, but also refers to that intervention as a treatment (rather than an unproven intervention).[107] Another problem is that forms fail to highlight differences between the study definition of positive response and the way that patients would define it. Few phase I oncology trial forms, for example, alert patients to the fact that tumor response is not equivalent to clinical improvement.[108] Forms that fail to distinguish clearly between knowledge benefits to society and direct benefits to subjects could lead prospective participants to overestimate the chance of personal benefit.[109]

The discussions prospective subjects have with FIH investigators can reinforce consent form inaccuracies.[110] Besides harboring optimism about the new interventions they are studying, [111] clinician-researchers may downplay the low odds of clinical benefit, on grounds that a candid appraisal would "take away [patients'] hope."[112] Thus, while the choice to participate in FIH trials is a reasonable response for patients who cannot be helped by standard therapies, FIH trial forms and discussions do not do as much as they should to give patients a true picture of the nature of that choice.

A second feature affecting the FIH decision process is the seriously ill patient's pre-existing mental state. Their lack of treatment options can put patients in a desperate frame of mind. This leads some writers to question whether patients are capable of making voluntary choices to enroll in early-phase trials.[113] Others wonder about the seriously ill person's susceptibility to misleading messages about investigational interventions.[114] Unduly positive messages can come from researchers or from breathless media accounts of cutting-edge research.[115] Imprecise consent forms, optimistic investigators, and media hype about laboratory discoveries can foster the therapeutic misconception and promote patients' unrealistic hopes for clinical benefit in FIH trials.[116]

> Much could be done to make FIH trials a more ethical activity. We should not lose sight of an uncomfortable reality: FIH trials expose healthy people with limited economic opportunities and ill people with limited health options to harm for the benefit of others.

The ethical concerns are significant enough to generate a few calls for an end to enrolling seriously ill patients in FIH trials. Writers taking this position say that current practices take advantage of patients' anguish to advance the research endeavor. Patients' chances of benefiting from FIH trial participation are too small to justify exposing them to risks considered too serious for healthy people; indeed, healthy people are more likely than seriously ill patients to benefit from any therapies developed through early-phase research.[117] Critics say that recruiting seriously ill patients for risky FIH trials is an unjust practice, for it rests on "the explicit assumption that the lives of the dying are less valuable and therefore more expendable than those of the healthy."[118] To protect their rights and interests, terminally ill patients should thus be recruited for research only if there is a "reasonable probability (based on scientific data) of improving the health or well-being of the subject, or of significantly increasing the subject's length of life without significantly decreasing its quality."[119]

Supporters of a ban on involving severely ill patients in FIH trials are in the minority, however. Writers defending the inclusion of such patients point to a lack of evidence that seriously ill trial participants lack the ability to make informed and voluntary decisions about enrollment.[120] They also contend that there is a reasonable balance of risks and benefits available to patient-participants in FIH trials.[121] Moreover, enrolling alternative populations in early-phase chemotherapy trials and other risky FIH research would present ethical problems, too, for this would expose volunteers to high levels of relative risk. If society wants to promote treatment advances, they say, the most defensible approach is to allow seriously ill patients to participate in FIH research.

Many commentators accept the practice of allowing patients lacking standard therapies to enroll in FIH trials, but call for reforms that could promote informed and voluntary choice. Reformers say researchers should give patients clear, straightforward information about a trial's objectives and the low likelihood that the investigational intervention will improve or lengthen participants' lives. Investigators and review committees should eliminate from consent forms language that could lead patients to overestimate the chance of personal benefit.[122] Patients should also receive information about alternatives to trial participation, and clinical caregivers should be available to discuss other options with patients who claim to have "no choice" other than to enter an FIH trial.[123] Another reform option is to recruit less seriously ill patients for FIH trial participation, but this approach presents its own ethical problems.

V. "Healthy" Patients

People with serious but manageable diseases are the third population recruited for FIH trials. Investigators seek members of this group for three reasons. The first is to maximize data quality. Advanced illness and medication exposure can complicate efforts to determine the effects of investigational interventions in patients with treatment-refractory disease. In some situations, data from less seriously ill patients can supply a better picture of a study intervention.[124] Worries about the quality of severely ill patients' decisions are a second reason to recruit stable patients. Because they have other treatment options, patients whose disease can be controlled are more equipped to make free and deliberate enrollment choices than are patients who cannot benefit from standard therapies.[125] Their greater opportunity to benefit from future therapies is a third reason to study stable patients. Because they have longer life expectancies than severely ill patients, they are more likely to benefit from any treatment improvements that FIH trials make possible.

But the ethical preference for stable patients is not obvious. Increased opportunities for free and informed choice and personal health benefits come at the price of greater risk to trial participants. Treatable patients ordinarily have longer and higher-quality lives than patients with treatment-refractory disease. Thus, the relative research risks for stable patients are higher than they are for patients with an inevitably fatal and debilitating illness.[126] Subjects with stable disease may also face higher risks than healthy FIH trial subjects. Patients' underlying conditions and maintenance therapies can elevate the risks of exposure to investigational interventions or trial-related tests and procedures. These factors may have contributed to the deaths of FIH trial participants Jesse Gelsinger and Jolee Mohr.[127]

In light of the possibilities for increased risk, careful ethical review should accompany any move to rely more heavily on stable patients for FIH trials. In this form of trial, it is essential to prevent inflated promises of personal benefit and to ensure that researchers and prospective participants appreciate any distinct health risks created by underlying illness or medication exposure.

Kimmelman proposes three additional guidelines for this form of research. First, he contends that the preclinical evidence supporting an FIH trial in stable patients should be stronger than that required for trials involving patients with untreatable illness. Before proceeding with a stable-patient trial, investigators should present evidence of both safety and efficacy in good animal models. Moreover, the animal and other preclinical evidence should be published so that others can make independent judgments about its quality.[128] Second, when an FIH trial in stable patients is proposed, patients should be involved in deciding whether the trial presents an acceptable balance of risks and benefits. Patients may have values, perspectives, and knowledge that conflict with or supplement the views of investigators and IRB members evaluating FIH trials.[129] Third, like healthy volunteers, subjects with stable disease should be compensated for any injuries that result from their research participation.[130]

Conclusion

The bench-to-bedside campaign is likely to generate an increased demand for FIH trial subjects. This development offers an opportunity to revisit longstanding ethical concerns about FIH trials. First-in-human trial participants may not qualify as a vulnerable group, but they can be harmed or wronged in distinct ways. Investigators and oversight bodies should take measures to safeguard the FIH participants whose contributions are needed to make translational science aims a reality.

Current FIH practices may be free of clear moral violations, but this is no reason for complacency. Much could be done to make FIH trials a more ethical activity. We should not lose sight of an uncomfortable reality: FIH trials expose healthy people with limited economic opportunities and ill people with limited health options to harm for the benefit of others. Frank recognition of this fact could spur the effort to make FIH trials safer, more transparent, and more fair to participants.

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Biography

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