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Ethical Criteria for Improved Human Subject Protections in Phase I Healthy Volunteer Trials

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Abstract

Phase I healthy volunteer trials test the safety and tolerability of investigational pharmaceuticals. In them, participants are exposed to study-drug risks without the possibility of direct medical benefit and typically must spend days or weeks in a residential research facility. Monetary payments are used to incentivize enrollment and compensate participants for their time. Together, these features of phase I healthy volunteer trials create a research context that differs markedly from most other clinical research, including by enrolling disproportionate numbers of economically disadvantaged people of color as participants. Due to these unique trial features and participation patterns, traditional biomedical research oversight offers inadequate ethical and policy guidance for phase I healthy volunteer research. This article details five ethical criteria crafted to be responsive to the particularities of this type of research: translational science value, fair opportunity and burden sharing, fair compensation for service, experiential welfare, and enhanced voice and recourse.

Keywords

human subjects research; healthy volunteers; phase I trials; *Belmont Report* ; compensation for research

SUPPORTING INFORMATION

The appendix is available in the “Supporting Information” section for the online version of this article and via *Ethics & Human Research*’s “Supporting Information” page: https://www.thehastingscenter.org/supporting-information-ehr/.

The core ethical principles of *The Belmont Report*—respect for persons, beneficence, and justice—guide human subject research without differentiating among types of investigations that researchers might conduct.[1] This is appropriate in so far as these ethical principles generalize over a wide swath of issues that emerge when humans are the needed material for knowledge production. However, the principles' translation as regulatory requirements can prove insufficient when important differences among research protocols are overlooked. Potential limitations in oversight have generated ethical frameworks for specific research domains, such as in HIV cure-related research or placebo-controlled trials of surgical interventions.[2] Until now, phase I healthy volunteer clinical trials have not received this attention. However, we argue that there is an urgent yet long neglected need to offer improved research protections for healthy volunteers by attending to the existing ethical and policy gaps in conventional biomedical research oversight of phase I trials. To that end, we propose an ethical framework that addresses the particularities of this type of research through five criteria: translational science value, fair opportunity and burden sharing, fair compensation for service, experiential welfare, and enhanced voice and recourse.

For a new drug to receive approval by the U.S. Food and Drug Administration (FDA), pharmaceutical companies must provide evidence of that drug's safety and efficacy in humans, and research in this domain is typically regulated by the FDA and overseen by institutional review boards (IRBs).[3] Phase I trials include the initial introduction of an investigational drug in humans and primarily test the drug's safety and tolerability (i.e., "side-effects associated with increasing doses").[4] In the current drug development paradigm, healthy individuals are usually the preferred phase I participants.[5] Along with commonly enrolling healthy people, phase I trials are unique from most other clinical research in that participants typically must spend a confinement period of days or weeks in a residential research clinic. To recruit individuals who are healthy and who will consent to such confinement, phase I trials frequently offer thousands of dollars to incentivize participation.[6]

These phase I trial features have meant that achieving sufficient enrollment for a study often depends on healthy people who lack regular employment and have schedules that can accommodate confinement in a clinic and for whom the monetary incentive may offer acceptable compensation for the trial risks and burdens.[7] Many healthy volunteers are even serial participants and treat phase I enrollment as a job.[8] Phase I trials can be particularly appealing when other employment is difficult to secure due to immigration status, lower educational attainment, or incarceration history.[9] These barriers to stable employment unjustly and disproportionately impact people of color, and racist hiring practices additionally engender persistent financial precarity, especially for Black men.[10]

As a result of these social inequities, trial design decisions, and enrollment incentives, among other factors, disproportionate numbers of economically disadvantaged people of color enroll as healthy volunteers in phase I trials conducted in the United States.[11] While these demographic patterns in phase I participation should have always triggered ethical concern, the Covid-19 pandemic and the Black Lives Matter movement jointly open space for renewed attention to the urgent need for improved research protections for healthy volunteers. The important emphasis on increased demographic diversity in clinical trials for vaccines and other therapeutics must also attend to the structural racisms that magnify

vulnerabilities for people of color in research. Given the *over*representation of racial and ethnic minorities in phase I trials with healthy volunteers, enhancing the protection of healthy volunteers is an important component in the pursuit of racial justice in biomedical research, a priority that has been emphasized by an increasing number of U.S. federal advisory groups and professional organizations.[12]

From a research oversight perspective, healthy volunteers are already protected through U.S. regulations that include "economically or educationally disadvantaged persons" within a "special category of subjects who are vulnerable to coercion or undue influence."[13] However, the ethical and regulatory focus in oversight documents is largely on the type of participant, not the type of research.[14] The importance of attending specifically to the type of research has received global attention with calls for controlled human infection studies for the SARS-CoV-2 virus, wherein the ethics of such research has been a central concern.[15] Phase I healthy volunteer trials have similarities to controlled human infection studies—notably, the use of healthy volunteers and confinement designs. Yet phase I trials, which largely fall under the regulatory authority of the FDA and are far more commonplace than controlled human infection studies, also require special ethical attention. Moreover, focus on phase I trials as a study type offers an opportunity to simultaneously create added protections for the participant demographic, including enhancing respect for persons, beneficence, and justice for groups that have historically been exploited by research.[16]

Drawing on our extensive empirical research on the perspectives of relevant stakeholders (i.e., healthy volunteers, phase I investigators and study personnel, and IRB members), ethics and policy experts in the field, and a comparative analysis with oversight regimes for nonhuman animal research protections,[17] we propose an ethical framework for phase I healthy volunteer trials. This framework is responsive to the ethical challenges we have catalogued as routine occurrences in phase I research, including ethical and regulatory gaps in how clinical trials are designed, how participants are recruited and selected for trials, and how they are treated during trials. To address these gaps, the framework provides guidance to help ameliorate how participant inclusion-exclusion criteria negatively affect drug safety and tolerability data (which relates to the criterion of translational science value); how incentives for research participation exploit existing social inequalities, including those caused by institutional racism (fair opportunity and burden sharing; fair compensation for service); how the confinement structure of phase I trials may harm healthy volunteers (experiential welfare); and how participants can be left powerless by the research system (enhanced voice and recourse). The ethical criteria developed here use as their starting point the *Belmont* principles of respect for persons, beneficence, and justice. Further, the adoption of our proposed framework would supplement, not replace, the protections offered by the current oversight system, for example, fundamental requirements for informed consent and favorable risk-benefit ratios in approved study protocols.

In what follows, we define each of the five ethical criteria and detail their specific significance for the healthy volunteer research context (see table 1). While our primary focus is on phase I trials with healthy volunteers, we define each ethical criterion more broadly to indicate how it might be used, where relevant, to enhance human subject protection in other research domains. Each criterion's implications for stakeholders—policy-makers,

pharmaceutical companies, IRBs, and phase I clinics and investigators—are summarized in table 2, with associated recommendations appearing as points to consider in the appendix (available online, as explained in the "Supporting Information" section at the end of this article). While the criteria themselves explicate ethical requirements, the points to consider for stakeholders are implementation suggestions for possible concrete responses to these normative expectations for phase I healthy volunteer trials.

In proposing additional criteria for the ethical conduct of phase I healthy volunteer trials, we also recognize the profound reality that many of the problems manifest in healthy volunteer patterns of recruitment and participation can be fully addressed only by larger-scale rectification of social injustices. Nevertheless, the advanced criteria can bolster the oversight system and provide important protections for healthy volunteers that may be implemented now by policy-makers, pharmaceutical companies, IRBs, and phase I clinics and investigators.

TRANSLATIONAL SCIENCE VALUE

For human subject research to be ethical, it must be socially valuable.[18] The current oversight system mandates this through the principle of beneficence and the requirement for research to minimize participant risks and achieve a favorable risk-benefit ratio, in which benefit can be for participants themselves and/or society more generally.[19] Emanuel and colleagues have argued that clinical research has social value because of its potential to improve health or health care, provided that the research is scientifically valid.[20] A central contributor to social value is, therefore, external validity, or the extent to which studies are positioned to provide "results that will be interpretable and useful in the context of the health problem."[21]

Yet external validity is a continued source of consternation in biomedical research, and pharmaceutical industry clinical trials have received much criticism for their poor external validity regarding drug safety (and, relative to later-stage trials, effectiveness) in clinical populations.[22] When external validity is threatened by the very design of a clinical trial, the research program's social value is diminished, and the participants' exposure to trial risks may become unethical. To address this issue, we propose the ethical criterion of translational science value, according to which clinical research should be designed to ensure that results are as accurate and informative as possible for clinical populations (see table 1). In current phase I healthy volunteer trials, as we describe below, this is often not the case. To meet the ethical criterion of translational science value, phase I healthy volunteer clinical trials should be designed to include participants who can provide externally valid information about the safety and tolerability of novel therapies (see table 1). To do so, phase I healthy volunteer trials must include diverse genders and participants across the life span while limiting the enrollment of serial participants.

A key purpose of phase I trials is to establish appropriate doses of investigational drugs for future trials and their eventual clinical use.[23] Notwithstanding the inability of most clinical trials to capture or predict rare adverse reactions,[24] the current standard for phase I trial design further reduces the translational science value of the clinical trials supporting

drug approval by selecting participants who are far less likely to experience adverse events relative to the general clinical population.

Phase I healthy volunteer trials do not simply require that research participants be healthy; instead, the protocols seek fairly young (e.g., between 18 and 45 years old) individuals who can pass a battery of medical tests and procedures. Although U.S. regulations no longer prohibit females from participating in phase I trials,[25] females still face numerous barriers to enrollment.[26] Significantly, pharmaceutical companies continue to be reticent to enroll "women of childbearing potential" in phase I trials. The definition of such potential and who is excluded remain at the discretion of these companies, and out of liability concerns, most companies conservatively apply the term "childbearing potential" broadly, accounting only for the biological prospect of pregnancy and ignoring factors such as partner status and sexual orientation.[27] As a result, males are significantly overrepresented in phase I trials, with a recent report indicating that nearly 70% of participants in such trials are male.[28]

Using young and male participants in phase I healthy volunteer trials has the potential to make drugs appear safer than they actually are. Specifically, the translational science value of testing drugs on young participants is limited because older adults may clear drugs more slowly due to diminished kidney and liver function. This can lead to higher concentrations of the drug and greater likelihood or severity of adverse reactions.[29] Similarly, sex-based adverse reactions emerge due to differences in body composition and size, drug metabolism, and other genetic, environmental, and experiential factors.[30] The small numbers of female healthy volunteers in phase I trials mean that the initial—and often final—determination of "tolerable" and "safe" drug doses are based primarily on male bodies. Later trials that enroll a higher percentage of female participants rarely alter the dosing regimen, so phase I trials are pivotal in this regard and may expose future female patients to more adverse drug effects. As evidence of this possible harm, a study by the U.S. Government Accountability Office found that 8 out of 10 prescription drugs withdrawn from the market had greater safety risks for females.[31]

Beyond the important differences in age and sex between typical healthy volunteers and patient populations, serial participation by healthy volunteers in phase I trials has implications for translational science value. Some researchers have expressed concern that a self-selection bias in serial participation generates an overrepresentation of individuals who are less susceptible to adverse events and who become the basis for drugs' safety data.[32] Additionally, scholars have cited the perverse incentive that financial compensation can have on serial participants to disregard protocol requirements and/or fail to report adverse events they experience during trials, thus compromising trial results and potentially supporting higher doses of investigational drugs than should be recommended for their clinical use.[33]

Phase I healthy volunteer trials may currently succeed in checking an important regulatory box, but the recruitment of young, male, and serial participants undermines the goal of these trials to inform the safe use of pharmaceuticals by patients. Indeed, despite the regulatory requirements, ample evidence indicates that FDA-approved drugs generally convey more risks to the patients who take them than the respective clinical trials had shown.[34] The specified ethical criterion of translational science value highlights how healthy volunteer

trials must be changed to ensure real-world societal benefit (i.e., ensuring approved drugs are adequately safe) that justifies risks to participants. The criterion emphasizes that the portfolio of phase I healthy volunteer trials conducted on a single drug must include more studies involving older adults who are more representative of those who will eventually consume the drug. It is especially critical for phase I healthy volunteer trials to include more gender diversity in all tests of drugs' safety and tolerability to allow for relevant analyses of trial data.

To better address translational science value, responsible stakeholders in the clinical trial process can enact various measures depending on their role. For example, policy-makers should develop drug approval requirements to ensure safety and tolerability have been adequately assessed in appropriate participants, and pharmaceutical companies should specify clear limits on enrollment of serial participants in trials (see table 2). Specific practical steps may include sponsors raising upper age limits for trial inclusion and actively seeking the participation of healthy older adults, as well as the development of evidence-based and participant-centered contraceptive requirements to avoid the needless exclusion of people who are unlikely to become pregnant during a trial (see the appendix). Merely meeting current regulatory requirements for drug development does not equate to the ethical use of human subjects; a phase I healthy volunteer trial can be considered ethically robust only if its translational science value is augmented through the targeted attention and shared responsibility of stakeholders.

FAIR OPPORTUNITY AND BURDEN SHARING

According to *The Belmont Report*, the principle of justice dictates that research subjects be selected fairly. More broadly, fair or equitable subject selection is widely recognized as a requirement in the research ethics literature and in regulations and guidance documents.[35] Despite a focus in *Belmont* on concerns about exploitation, the concept of justice has had limited applications to individual trials or research institutions. In 2021, the U.S. Department of Health and Human Services Secretary's Advisory Committee on Human Research Protections (SACHRP) called for the research oversight system to attend to structural injustices and (in)equity issues that characterize the research enterprise.[36] The context of phase I healthy volunteer trials is highly illustrative of this urgent issue in that economically disadvantaged men of color are a sample of convenience tied to the burdensome demands of confinement trials and the offer of substantial compensation to facilitate enrollment. These facts illustrate how a focus on the structure of phase I healthy volunteer trials also brings attention to ethical problems in participation patterns.

In line with the demographic inequities in phase I healthy volunteer trials, additional oversight is needed to guide recruitment, selection, and enrollment of healthy volunteers. The ethical criterion of fair opportunity and burden sharing requires that clinical trial participants are recruited and selected through processes that grant a fair opportunity to participate and that also aim to distribute the risks and burdens of participation equitably (see table 1). For phase I healthy volunteer trials, this means that participants should be recruited and selected according to transparently communicated criteria, on the basis of wide outreach, and using relevant scientific factors. Moreover, disadvantaged minority

group members and underserved communities should not be disproportionately targeted for enrollment (see table 1).

An important dimension of fair subject selection is fair opportunity.[37] In phase I healthy volunteer trials, there are both economic and noneconomic benefits associated with enrollment. For many healthy volunteers, especially serial participants, phase I trials are an important income source. Some pursue participation as their full-time "job,"[38] and many healthy volunteers depend on study compensation to support their households.[39] Others, regardless of their financial situations, use trial participation to fund spending on nonessential consumer items or travel.[40] Participation as a healthy volunteer also conveys various noneconomic benefits, even if these benefits do not actually motivate enrollment, such as the formation of friendships, time in clinic confinement unburdened by other obligations, and health benefits due to medical screenings and the adoption of health-promoting behaviors to qualify for trials.[41]

In so far as people view phase I enrollment as individually beneficial, participant selection involves the allocation of a perceived good. Fair opportunity requires—at minimum—that prospective participants are not included or excluded on arbitrary grounds and that the offer to participate is widely advertised. Clinics should therefore adopt formal procedures to ensure that prospective participants have a fair opportunity to enroll. Fair opportunity is nevertheless constrained by the translational science value necessary for an ethically designed trial.[42] Thus, for example, limiting enrollment of serial participants does not violate fair opportunity provided these limits are transparently shared, equitably enforced, and justified by translational science goals.

Evidence suggests that fair-opportunity requirements are not being met, as healthy volunteers report being banned from enrollment at clinics for arbitrary reasons and staff favoritism affecting participant selection.[43] Achieving fair opportunity to participate in phase I healthy volunteer trials may require some clinics to significantly change practices, such as by specifying what circumstances might bar participants from returning for subsequent trials, minimizing staff discretion in participant selection, and using only well-justified physiological measures to exclude participants (see the appendix).

Fair burden sharing is another component of fair participant selection and is particularly significant in the context of phase I healthy volunteer trials.[44] While healthy volunteers may desire the opportunity to participate, phase I trial enrollment nonetheless involves both health risks and many burdens accompanying confinement periods. For the burden of research to be fairly shared, risks and burdens should be distributed equitably within the broader population and should not be borne by those without potential to benefit generally from improved health interventions.[45] Because healthy volunteers are overwhelmingly members of disadvantaged socioeconomic groups without regular access to health care, this requirement of fair burden sharing is demonstrably unmet in phase I healthy volunteer trials.[46] To better meet requirements for fair burden sharing, it is incumbent on responsible stakeholders in the phase I research enterprise to avoid targeting disadvantaged populations for recruitment. This means, for example, that pharmaceutical companies should select research clinics with wide participant pools to run their trials and IRBs should require

broad-based recruitment methods, for instance, by emphasizing the spectrum of participation benefits beyond financial compensation (see table 2 and the appendix).

Broad-based recruitment strategies are required for ethical phase I healthy volunteer trials, and yet these may yield similar results to current participation patterns while the social inequities and study design factors that influence these enrollment trends remain in place. Increasing trial payments is one solution that has been suggested to incentivize participant enrollment from more diverse economic classes.[47] The question of financial incentive is discussed next regarding "fair compensation for service," but payment is not the only approach to improving fair opportunity and burden sharing in phase I trials with healthy volunteers.[48] While not positioned to solve larger social problems, clinics should additionally focus on adjunctive ways that they can help to offset participant disadvantages. This approach echoes the tenets of the Vulnerability and Equity Impact Assessment Tool developed by Yearby to guide equity in participation for medical research involving children, a framework reflecting the argument that equity in research participation is "accomplished when … [the medical research study] eliminates some social disadvantage."[49] Examples in the context of phase I healthy volunteer trials include the formal provision of non-monetary goods, such as health education and posttrial health care access[50] or even job training or employment information.[51] Such suggestions are in keeping with the broader social-justice concerns that drive the timely demand for renewed ethical attention to phase I trials.

We acknowledge that the components of the criterion of fair opportunity and burden sharing may be in some tension. For example, fewer individuals who rely upon trial income will be included in phase I healthy volunteer trials if the participant base is broadened. From the standpoint of some healthy volunteers with few alternative income sources, the benefit of financial remuneration may be valued more highly and offset the participation burden of a potential health risk from enrolling. Ultimately, these realities once again reflect that the ideal of fair subject selection for phase I trials with healthy volunteers must be navigated against background injustices and structural racism that undermine the opportunities of many people of color and produce the conditions in which clinical trial participation is an appealing—and sometimes essential—way to earn a living. Fair opportunity and burden sharing is best satisfied when remedies that incentivize broader participation in clinical trials also address social inequalities.

FAIR COMPENSATION FOR SERVICE

Despite regulatory guidance permitting or even encouraging compensation,[52] and notation that such payments should be both "just and fair,"[53] research oversight primarily rests narrowly on managing how payment might undermine decisional autonomy, not on whether the payment amount is fair. Current IRB oversight guidance in particular specifies that payment amounts should be set to avoid "coercion or undue influence."[54] Even so, SACHRP has advised that payments for research rarely create an ethical threat to the research enterprise, particularly when "people adequately consider and understand what they are being asked to do and when what they are being asked to do is acceptable."[55] Our criterion of fair compensation for service states that clinical trial compensation

should be commensurate with the requirements of participation and disbursed in a timely manner (see table 1). For phase I healthy volunteer compensation, attending to fairness is important to ensure that amounts and payment schedules adequately reflect the substantial time, inconvenience, and body-monitoring activities required of participants, as well as management of expected adverse events (see table 1).

From healthy volunteers' perspective, study income is a tangible benefit without which trial enrollment would appear nonsensical.[56] Scholars have also cautioned that low payment amounts may be unethical, as they may exploit participants.[57] The rationale for limiting payment in phase I healthy volunteer trials is therefore important to consider. Bioethicists have generally rejected the proposition that (genuine) offers of compensation can coerce involvement in clinical trials,[58] and payment is precluded from counting as a direct trial benefit for purposes of balancing overall risk and benefit. The latter policy avoids the justification of inordinately risky trials by substantial remuneration.[59]

The remaining question, then, is when do financial incentives become an *undue* inducement and thus ethically impermissible? Some bioethicists have understood undue inducement to mean that the participant's decisions are in a sense controlled by the offer of money,[60] whereas others require that the participant's reasoning about research risks and benefits become distorted by the financial aspect of the exchange.[61] Regardless of how one conceptualizes the ethical significance of undue inducement, financial factors strongly influence the clinical trial enrollment decisions of healthy individuals. These people sometimes enroll despite strong misgivings, serious concerns about risks, or prior decisions to avoid certain types of trials.[62] Unfortunately, these empirical findings do not help establish optimal payment amounts because even low payments can have these effects, depending on individuals' financial situations.

The question of how much remuneration to healthy volunteers constitutes undue inducement also routinely ignores the broader economic system in which phase I trials are embedded. Many pharmaceutical companies report revenues of billions of dollars annually, and most phase I clinics are run as for-profit enterprises. Therefore, the idea that these companies should limit the compensation offered to healthy volunteers, who are already living at the margins of financial viability, appears patronizing at best. Yet payments are set at amounts and under conditions that are favorable to industry, including the arguably punitive provision in which participants are ineligible for any compensation designated as a "completion bonus" when they miss a follow-up visit, exercise their right to leave a trial, or are withdrawn from a trial due to an adverse event or any other reason.[63] Indeed, in this context, lessening payments for clinical trial participation threatens increased exploitation rather than combatting any potential for diminished voluntariness purported to result from undue inducement.[64]

Other recent payment guidance has differentiated between compensation and incentives as study remuneration, suggesting both that undue influence is of less concern for compensation payments and that incentives are not owed as a matter of fairness.[65] However, when trial participants face economic precarity in their everyday lives, as many phase I healthy volunteers do, the line between "compensation" and "incentive" is blurred.[66] Fair

compensation for service offers a different approach by adjudicating payments on the basis of how much time participants must invest in the clinical trial and the degree of burden associated with that trial.[67] In particular, for phase I healthy volunteer studies, compensation for each trial should be directly tied to the inconvenience of clinic confinement, adherence to protocol restrictions, volume and type of bodily-monitoring procedures, and management of expected adverse events. Moreover, fair compensation for service also requires that payments are disbursed fairly, both in the sense that participants should receive their monies in a timely manner and that funds are equitably allocated when payments are divided across a clinical trial's longevity.

By instituting the ethical criterion of fair compensation for service, phase I trial payments would likely increase to account for the substantial participation burdens required of healthy volunteers. Proposals that trial participants be paid wages similar to those of essential hourly workers are inadequate to achieve fair compensation for service.[68] Indeed, our approach both implies that fair compensation may require higher payments and acknowledges that even low compensation in phase I healthy volunteer research may function as incentive payment. Some will be concerned that this approach aggravates the already serious problem of undue inducement for this type of research. We disagree. The empirical reality that any undue inducement that does occur in research payments varies based on individual circumstance, alongside the serious philosophical ambiguities with this concept, are decisive in undermining its applicability as an ethical barrier to higher payment. Instead, the approach of fair compensation for service has distinct advantages.

Most significantly, fair compensation for service addresses an ethical gap in research oversight caused by the failure of current guidance to institute a floor for payments or sufficiently address payment disbursement schedules. Even the most recent SACHRP guidance on research compensation places the responsibility of determining payment on investigators, who are asked to make the case to IRBs that the amount they have selected is appropriate[69]—a justification that might limit remuneration when research teams anticipate that IRBs are more inclined to approve lower amounts. This guidance also leaves a lacuna regarding compensation disbursement precisely where advice is needed for phase I healthy volunteers. It states both that "in circumstances in which an individual has no income … an offer of payment for research may function as an incentive" and that, in contrast to compensation payments, "incentives paid as completion bonuses can be appropriate and are not necessarily unduly influential."[70]

Importantly, while fair compensation for service may raise payment amounts, the criterion also subscribes in principle to the view that there are limits to ethically acceptable payments. In keeping with the current regulatory requirements, for example, setting very high compensation amounts based on significant risk would not be compatible with this criterion. The proposed transparent system of payment for time and burden would instead help healthy volunteers discern that compensation is not directly tied to risk, and it could clarify mixed guidance on this topic.[71]

A final advantage of this approach to research payment is that fair compensation for service limits paternalistic intrusion on participant decision-making by setting payments at a level

that is fair for *any* healthy volunteer regardless of their perspective about individually acceptable risk or their need for trial income. This may also have a desirable impact on broadening the participant base for phase I healthy volunteer trials, which would address ethical concerns associated with fair opportunity and burden sharing.[72]

We encourage key stakeholders to apply this criterion through such measures as issuing policy guidance to establish fair compensation amounts for standard clinical trial components, including confinement time and routine medical procedures; ensure the provision of fair and timely prorated daily payments; and limit the use and/or size of completion bonuses (see the appendix). One tool already developed that can be leveraged to assist with such fair compensation standards is the algorithmically based and validated "patient burden score" for clinical trial protocols.[73] As already recommended by SACHRP, IRBs should no longer examine payment amounts for clinical trials primarily through the lens of undue inducement, which encourages an overly conservative approach to approving study compensation (see the appendix).[74] Ultimately, fair compensation for service offers an alternative approach to regulating research payments when the financial exchange drives participation and the ethical problem impacting phase I healthy volunteers lies not with the hypothetical potential for undue inducement but with instances of their exploitation.

EXPERIENTIAL WELFARE

The principle of beneficence has traditionally focused on risks and benefits of research interventions[75] rather than on participant welfare within the research setting. In the context of phase I healthy volunteer trials, the ethical conduct of research must further account for effects on participants of mandatory clinic confinements and restrictions from everyday activities. In addition to the protocols dictating the dosing of investigational drugs and the medical procedures monitoring participants and collecting data, healthy volunteers are subject to strict environmental, activity, and nutritional control measures during their trial participation. All these features of phase I trials require ethical attention beyond conventional constructions of beneficence. Our proposed ethical criterion of experiential welfare thus specifies that research-related harms should be minimized and the psychological, emotional, and physical well-being of participants supported, particularly, but not only, while they are confined to an in-patient or residential clinic (see table 1).[76] To meet this criterion, phase I clinic environments should be structured and maintained in keeping with high standards of participant welfare. In addition, the frequency and invasiveness of medical procedures as well as restrictions on participant activities should be minimized and scientifically well justified (see table 1).

While the concept of welfare is familiar in terms of generally fostering or protecting human well-being, it has typically been used as an ethical principle for research only in laboratory settings where nonhuman animals are used. In that context, "welfare" is viewed as a standard to evaluate and manage the harms to which animals are subjected through their use in research. One mechanism for promoting animal welfare is the 3Rs (replacement, reduction, and refinement) ethical framework. Among other criteria, it requires animal researchers to refine their study procedures to minimize the pain and distress animals experience as consistent with the study's scientific goals. It also encourages researchers

to refine animals' quality of life in housing and husbandry practices by providing species-specific standards to reduce stress and prevent boredom (i.e., enrichment). Additionally, animal welfare is directly overseen by institutional animal care and use committees (IACUCs) that not only review research protocols but are also charged with inspecting the facilities in which research is conducted and animals are housed to ensure cleanliness, proper temperature, and compliance with other environmental standards.[77]

Human and nonhuman animal research are overseen by separate regulatory systems and sets of ethical criteria.[78] Comparative approaches to these oversight systems sometimes aim to extend human protections to animal subjects in an effort to better protect vulnerable animals.[79] Yet the concept of welfare found in the animal research context can likewise be extended to phase I trials to better protect healthy human volunteers' physical and mental well-being by refining trial protocols and emphasizing enrichment measures in clinics to minimize the myriad harms participants experience from research participation beyond serious adverse events.[80]

The very purpose of phase I trials is to induce side effects in at least some participants to better understand investigational drugs' safety profile.[81]As a result, most healthy volunteers experience adverse events during these trials.[82] Few such events are classified as serious or life-threatening,[83] but healthy volunteers' experiential welfare is nevertheless diminished by common issues, such as headache, nausea, diarrhea, and impaired digestion.[84] These symptoms can be especially negative for a variety of reasons when experienced in a research clinic. Trial protocols often disallow medications to treat symptoms, and despite feeling unwell, participants are routinely required to stay in the procedure area so staff can observe them. Bathrooms may be locked, with access to them requiring staff permission when participants' waste output is monitored. More generally, participants have little privacy in shared clinic spaces, which can be taxing regardless of how participants are otherwise feeling. Under the current research ethics rubric, harms like these—despite greatly affecting participants' experiential welfare—are generally not considered as those that must be managed and minimized for clinical trials to proceed.

Similarly, although the risk of medical procedures done on healthy volunteers must be both scientifically justified and considered reasonable in relation to a trial's societal benefits, the impact of these procedures on individual welfare may be less considered. For example, frequent blood collection is used in phase I trials to capture data about the pharmacokinetics of the investigational drug, but undergoing 10 to 12 blood draws in a single day can be painful and difficult for healthy volunteers. When clinic staff who lack phlebotomy training are assigned to blood collection duties, discomfort and even harm to subjects is exacerbated.[85] More rarely, phase I trials require lumbar punctures or muscle biopsies, and while these procedures are generally performed only by appropriately trained clinicians, they can cause participants considerable pain and discomfort that is, again, potentially magnified by their clinic confinement.[86] Other procedures, such as collecting urine and fecal samples, may not cause pain, but they can be inconvenient and even cause participant embarrassment depending on how the clinics manage the collection process.

Participant housing and amenities also suggest the importance of experiential welfare in healthy volunteer trials. Phase I clinics vary dramatically, with some exhibiting concerted investment in creating participant-friendly spaces and others cutting corners with subpar or dilapidated accommodations.[87] Reflecting on these latter clinics, healthy volunteers have specifically voiced critiques of facility cleanliness, temperature, and infrastructure.[88] Some healthy volunteers have even compared the experience of confinement to being in jail[89] or expressed concern about being vulnerable to harm from other participants.[90] Healthy volunteers also routinely note problems with the taste, quality, and amount of food they receive.[91] Moreover, when trials require lengthy confinement periods, healthy volunteers often become bored, complain about having limited access to outdoor spaces, and experience psychological difficulties from feeling shut in and being separated from loved ones. Social tensions also arise, particularly from over-crowded clinics or from dormitory-style bedrooms in which noise and a lack of privacy can quickly become stressors on participants. Clinic policies can also affect experiential welfare, depending on whether healthy volunteers are allowed to bring items from home, including laptops and cellular phones, or have visits from family members during confinement.

These circumstances indicate that there is an unmet need for experiential welfare standards for participants in the oversight of phase I clinics. While conducting site visits is technically within the purview of the FDA and IRBs, phase I clinics are not regularly inspected.[92] FDA visits moreover typically occur when trial data are audited, so the focus of FDA personnel is on trial documentation for long-completed studies, not current facility conditions.[93] IRBs are not mandated to perform such inspections, and many phase I trials are reviewed by central IRBs without a local presence needed to provide convenient clinic oversight. Additionally, IRBs are often understaffed,[94] further restricting their ability to inspect clinics and lowering any enthusiasm for monitoring participant welfare concerns beyond regulatory requirements.

Implementing experiential welfare as an ethical criterion for research would require policy-makers to develop welfare standards and clear oversight and enforcement mechanisms; pharmaceutical companies to use only high-quality research clinics for their trials; IRBs to ensure that protocols minimize welfare risks and harms; and phase I clinics and investigators to promote the needs and comfort of healthy volunteers through their facilities, staffing, and policies impacting participants' activities (see table 2). Participant experiential welfare would be improved if pharmaceutical companies excluded from phase I protocols any low-information-yielding procedures or unnecessary restrictions pertaining to diet or other activities and if IRBs verified that clinic staff are appropriately credentialed and/or trained for their trial roles (including, but not limited to, venipuncture) (see the appendix). Without such attention, the experiential welfare of healthy volunteers may be jeopardized in phase I trials, particularly when the harms of participation not directly tied to the clinical trial protocols are neglected.

ENHANCED VOICE AND RECOURSE

The ethical principle of respect for persons in research is primarily emphasized through requirements for informed consent and participants' right to withdraw from a study.[95] This focus reflects core concerns about ensuring that research participation is voluntary.[96]

However, in addition to having information adequate to determine whether to enroll and remain in research, participants' clinical trial experiences must also be considered. Respect for persons necessitates that any wrongs or harms sustained by participants during trials should be satisfactorily addressed. Our criterion of enhanced voice and recourse fills an ethical gap between informed consent and respect for persons in phase I research by requiring that participants should have meaningful opportunities to express concerns regarding their experiences in clinical trials and have direct recourse for wrongful treatment or harms incurred through trial participation (see table 1). Healthy volunteers specifically should be invited and incentivized to join efforts to improve phase I trials through community engagement or other mechanisms. Provision of recourse for wrongs or harms experienced during trial participation should be mandated and accessible, and procedures for reporting and responding to research complaints should be formalized, as should protection from reprisal (see table 1).

As research participants, healthy volunteers are not typically recipients of compassion, whereas participants with a health condition often are. To some degree, healthy individuals' trial participation is even a stigmatized activity because it is equated with financial desperation and/or body commodification.[97] Perhaps for these reasons, most attention to healthy volunteers' experiences has focused on when they deceive researchers or otherwise break the rules of participation.[98] Consequently, their voices have been relatively unheard even in an era when researchers are thought to have an obligation to increase and sustain community engagement in the design and conduct of clinical trials.[99] Ground-up efforts by healthy volunteers, such as the "jobzine" Guinea Pig Zero and the website Just Another Lab Rat, gather information and provide reviews of clinics.[100] These efforts have attracted the attention of phase I investigators and bioethicists, but there is no evidence that they have resulted in better recourse for healthy volunteers' concerns. Thus, formalized mechanisms to attend to these participants' experiences and perspectives remain an unmet need.

Because of the often-unknown risks of investigational drugs, the highly controlled clinic environment, and the intensive protocol requirements, there are potentially more opportunities for healthy volunteers to feel wronged or experience redressable harm as a result of their participation than might occur in later-phase trials. While phase I participation rarely causes disability or death, a range of less severe bodily harms may require medical follow up or compensation for lost wages or suffering. When phase I participants are healthy individuals, the ethical requirement for compensation for study-related harms[101] becomes particularly significant. In the U.S., however, such ethical injunctions do not translate into specific regulatory mandates for compensation beyond a prohibition on exculpatory language in consent forms.[102] The burden is instead placed on the shoulders of research participants, primarily through the tort system, which rarely favors participants' claims.[103] For healthy volunteers who have few financial resources and often lack health insurance, being powerless to negotiate successfully with phase I clinics, contract research organizations, and/or pharmaceutical companies means risking being left on their own to pursue and manage claims of harm. In these instances, they pay for their own follow-up health care and might even be disqualified from enrolling as healthy volunteers in future studies as well.[104] Adequately protecting healthy volunteers, therefore, requires instituting formal procedures that are straightforward and accessible to allow participants to seek

recourse for research-related injuries.[105] Given the increased importance placed on this ethical issue by some academic medical centers, phase I healthy volunteer trials—that largely occur in the private sector—are an essential type of research for which to create a federal mandate for compensation for study-related injuries.[106]

In addition to physical harms, healthy volunteers may experience other instances in which recourse may be needed. Healthy volunteers have been known to receive unfair treatment by clinics and their staff. For example, participants report instances of clinics inadequately informing them of trial exclusion criteria, thereby causing them to waste their time (and sometimes money) to screen for a study for which they are not actually qualified.[107] Clinics have also cancelled trials and failed to notify participants in a timely manner, possibly to channel them into other, less desirable studies.[108]

Despite the fact that healthy volunteers have the right to withdraw from clinical trials, some participants voice concern that doing so means that a phase I clinic will not select them for subsequent trials.[109] Clinics can and do ban healthy volunteers from future enrollment, and participants have argued that there is a lack of transparency about this process, with clinics sometimes offering no explanation for what prompted that action and no mechanism to dispute the decision.[110]

As a final example, healthy volunteers report dehumanizing and antagonistic interactions with staff, and they may feel compelled to tolerate abusive treatment.[111] To ensure that healthy volunteers are treated fairly throughout the clinical trial process, they require formal mechanisms to register complaints against clinics and their staff and have those instances investigated and, when appropriate, rectified.[112] These procedures are necessary to address practices that devalue the service and contribution that healthy volunteers make to the research enterprise.

Ensuring that phase I healthy volunteers are treated with respect, then, involves much more than adequate informed consent.[113] Specifically, robust respect in this context requires provision of open and accessible feedback mechanisms to learn from participants about their study involvement and encourage engagement in improving research design and clinic practices. At minimum, such respect requires not repressing, ignoring, or otherwise shutting down participant perspectives or requests for information.[114]

Implementing the ethical criterion of enhanced voice and recourse requires action on the part of multiple stakeholders to ensure research oversight can adequately account for a diverse array of issues that potentially need to be addressed. We suggest that federal requirements for phase I healthy volunteer trials should require clear and fair plans to provide posttrial medical care and appropriate compensation to participants who are injured in research; IRBs should institute well-advertised anonymous reporting systems (and subsequent investigation procedures) for complaints against clinics, with respect to matters of welfare, payment, and respectful treatment, as well as injuries or other harms; and clinics should create participant engagement mechanisms using healthy volunteer expertise for ongoing quality improvement for clinic policies and practices (see the appendix). Enhanced voice and recourse are

fundamental to an ethics oversight system that protects participants from possible research abuses.

THE PROMISE AND LIMITATION OF IMPROVED ETHICAL CRITERIA

Phase I healthy volunteer trials are unique among biomedical research studies. The current oversight system is characterized by ethical and policy gaps pertaining to phase I trial protocol design, healthy volunteer recruitment and selection, and treatment of participants during confinement. To address some of the ethical complexities of these trials, the five criteria proposed here—translational science value, fair opportunity and burden sharing, fair compensation for service, experiential welfare, and enhanced voice and recourse—offer needed focal points for the oversight system to protect healthy volunteers as research participants. These criteria chart a way forward that complements and expands upon the current regulatory protections for human subjects yet can directly ameliorate key ethical problems arising in the phase I industry.

The five ethical criteria developed here may apply to other clinical research settings as well and are broadly defined to invite such use. For example, controlled human infection studies also use healthy volunteers and employ a confinement design, so there are clear overlapping ethical concerns between these study types. Even with concerted, recent attention to the ethics of controlled human infection studies, our proposed framework offers ethical criteria that warrant consideration and have not yet been applied to those trials.[115] Additionally, depending on the specific elements of a trial's design and context, the ethical criteria developed here may be relevant to clinical research in which the participants are patients rather than healthy volunteers. Nevertheless, our focus has been trained specifically on phase I healthy volunteer trials based on extensive empirical research and prolonged engagement with the ethical issues that arise in these studies.

Importantly, the criteria promoted here are insufficient on their own to fully address the social inequities that have become the basis for the successful recruitment and retention of many healthy volunteers. While outside of the limited scope of the ethical oversight of research, changes to the broader social and economic system are necessary to have the most impact on who enrolls as healthy volunteers in research. Without more employment opportunities, higher wages, immigration reform, and a robust social safety net, economically vulnerable people of color will continue to be overrepresented in phase I healthy volunteer trials and to shoulder a disproportionate burden of moving pharmaceuticals forward in the regulatory pipeline.

In the past, it has been too easy for bioethicists and policy-makers to overlook the social realities and deep injustices that create the motivations for healthy individuals to join clinical trials. Yet other ethical problems with phase I healthy volunteer trials have also been overlooked even when addressing those issues does fall within the purview of the oversight system. With increased recognition of the need for racial-justice reforms to all institutions and unprecedented global attention to drug development due to the coronavirus pandemic, now is the time to commit to protecting healthy volunteers through the research oversight system for phase I trials. An appendix for policy-makers, pharmaceutical companies, IRBs,

and phase I clinics provides concrete recommendations (summarized in table 2) to translate the five proffered ethical criteria for phase I healthy volunteer trials into practice. These ethical criteria and implementation suggestions are an initial yet critical step in a broader push for a more just approach to research ethics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Targeted Ethical Criteria for Phase I Healthy Volunteer Trials

Criteria	Definition	Significance for phase I healthy volunteer trials
Translational science value	Clinical research should be designed to ensure that results are as accurate and informative as possible for clinical populations.	Phase I healthy volunteer clinical trials should be designed, particularly regarding key demographic factors such as age and sex, to include participants who can provide externally valid information about the safety and tolerability of novel therapies.
Fair opportunity and burden sharing	Participants for clinical trials should be recruited and selected through processes that grant people a fair opportunity to participate and that aim to distribute the risks and burdens of participation equitably.	Participants for phase I healthy volunteer trials should be recruited and selected according to transparently communicated criteria, on the basis of wide outreach, and using relevant scientific bases. Disadvantaged minority group members and underserved communities should not be disproportionately targeted for enrollment.
Fair compensation for service	When offered, clinical trial compensation should be commensurate with the requirements of participation and disbursed in a timely manner.	Phase I healthy volunteer compensation amounts and payment schedules should adequately reflect the substantial time, inconvenience, and body-monitoring activities required of participants, as well as the management of expected adverse events.
Experiential welfare	Research-related harms should be minimized and the psychological, emotional, and physical well-being of participants supported, particularly, but not only, while they are confined to an in-patient or residential clinic.	Phase I clinic environments should be structured and maintained in keeping with high participant welfare standards. The frequency and invasiveness of medical procedures as well as restrictions on participant activities should be minimized and scientifically well justified.
Enhanced voice and recourse	Study participants should have meaningful opportunities to express concerns regarding their experiences in clinical trials and have direct recourse for wrongful treatment or harms incurred through trial participation.	Healthy volunteers should be invited and incentivized to participate in efforts to improve phase I trials through community engagement or other mechanisms. Provision of recourse for wrongs or harms experienced during trial participation should be mandated and accessible for participants. Procedures for reporting and responding to research complaints should be formalized, as should protection from reprisal.

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Table 2.

Implications of Ethical Criteria for Phase I Trial Stakeholders

Criteria	Policy-makers	Pharmaceutical companies	Institutional review boards	Phase I clinics and investigators
Translational science value	• Develop drug approval requirements to ensure that trial participants adequately represent likely clinical populations. • Require information sharing about clinical trials (e.g., in clinicaltrials.gov) and participant demographics.	• Design trials that adequately represent likely clinical populations. • Specify limits on enrollment of serial participants in trials. • More closely model real-world conditions in trial protocols.	• Review protocols for how well trial participants represent likely clinical populations. • Ensure that protocols place adequate limits on enrollment of serial participants.	• Limit reliance on serial participants. • Ensure that trial protocols are closely followed.
Fair opportunity and burden sharing	• Provide guidance on appropriate trial exclusion criteria to ensure fair opportunity. • Develop incentives for clinical trial participation in the general population.	• Limit trial exclusion criteria. • Select research clinics with broad participant pools. • Offer a diverse array of participation incentives	• Require broad-based recruitment methods. • Require that any obstacles to enrollment are limited.	• Use broad-based recruitment methods. • Limit obstacles to enrollment. • Use transparent and unbiased selection processes.
Fair compensation for service	• Provide guidance for timely study compensation to participants that is commensurate with protocol requirements.	• Provide for study compensation to participants that is commensurate with protocol requirements and require its timely disbursement.	• Ensure that study compensation to participants is commensurate with protocol requirements and disbursed in a timely manner.	• Provide timely study compensation to participants that is commensurate with protocol requirements.
Experiential welfare	• Provide guidance on welfare standards in clinical research facilities. • Specify oversight and enforcement mechanisms for participant welfare in facilities.	• Contract only with high-quality research clinics. • Design trial protocols to promote participant well-being and limit welfare risks and harms	• Provide or ensure oversight of research clinics, including facilities and staffing. • Require that protocols minimize welfare risks. and harms.	• Make participant welfare —as manifested in facilities, staffing, and participants' activity restrictions—a top priority.
Enhanced voice and recourse	• Require stakeholders, including government agencies, to institute systems for reporting and responding to research complaints. • Require compensation for research-related injuries.	• Formalize a system for reporting and responding to research complaints. • Routinize and provide compensation for participant input about the clinical trial process.	• Ensure that protocols include a system for reporting and responding to research complaints. • Follow clear and fair procedures to remediate problems that develop during trials.	• Implement a system for reporting and responding to research complaints. • Enhance participant input about the clinical trial process. • Follow clear and fair procedures to remediate

Criteria	Policy-makers	Pharmaceutical companies	Institutional review boards	Phase I clinics and investigators
		• Follow clear and fair procedures to remediati problems that develop during trials.		problems that develop during trials.