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

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APPENDIX 1.

Applying the Ethical Criteria for Key Stakeholders

This resource suggests specific applications that stakeholder groups could implement to improve the ethical conduct and oversight of phase I healthy volunteer trials. Identified stakeholders include policy-makers, pharmaceutical companies, IRBs, and phase I investigators. Applications are organized under each stakeholder group according to the ethical criteria of (a) translational science value, (b) fair opportunity and burden sharing, (c) fair compensation for service, (d) experiential welfare, and (e) enhanced voice and recourse. See table 2 in the article for a summary of these points.

Specific Points to Consider for Policy-Makers:

Translational Science Value

1. Develop drug approval requirements to ensure that trial participants adequately represent clinical populations.
   - For a drug to receive market approval, clinical trial participants should be representative of clinical populations along core demographic categories, including sex and age, particularly for pivotal dose-establishing and safety trials.
   - More evidence of safety in females and older adults should be required *prior* to the start of phase II trials.
   - Reproductive toxicity evaluated in animal studies should provide at least preliminary data in advance of human trials so people of childbearing potential are not needlessly excluded from phase I trials.
   - Contraceptive requirements for trials with potential reproductive risks should be based on the best evidence and participant-centered approaches to supporting avoidance of pregnancy to expand the eligibility of people of childbearing potential for phase I trials.
   - Approval of drugs for market should include evaluation of any demographic differences, such as sex and age, in safety and efficacy data across participants.

2. Require information sharing about clinical trials and participant demographics.
   - Phase I healthy volunteer trials should be included in the mandate for publication in clinicaltrials.gov so that issues of inclusion and translational value can be better studied.
   - Demographic information, such as sex, age, and race/ethnicity, about phase I participants should be made publicly available through National Institutes of Health (NIH), FDA, and clinicaltrials.gov reporting mechanisms.

- The FDA or Office for Human Research Protections (OHRP) should require collection and analysis of data about serial participation in clinical trials.

Fair Opportunity and Burden Sharing

1. Provide guidance on appropriate trial exclusion criteria to ensure fair opportunity.
   - To receive market approval for products, sponsors should use only scientifically valid inclusion-exclusion criteria. Criteria that function only to save money, reduce potential liability, or increase retention should be avoided.

2. Develop incentives for clinical trial participation in the general population.
   - The federal government should institute a system that encourages a broader population base in phase I trials. This could, for example, be structured as part of public service or by devising a system of benefits for current and former research participants to access medications for free or at reduced rates as recognition of their service.

Fair Compensation for Service

1. Provide guidance for timely study compensation to participants that is commensurate with protocol requirements.
   - The FDA and/or OHRP should develop clear guidance for IRBs and industry about compensation for healthy volunteers. This guidance should include
     - a policy explicitly directing that compensation for phase I trial participation should not be evaluated for undue inducement;
     - benchmark amounts for compensation (a) that would be equivalent to a fair "minimum wage" in clinical research so that there is a floor for payments and (b) that reflect the substantial requirements of participation, including variances in time, inconvenience, management of adverse events, and bodily monitoring activities required of participants; and
     - limits on completion bonuses such that study compensation is fairly distributed over the course of participation.

Experiential Welfare

1. Provide guidance on welfare standards in clinical research facilities.
   - The federal government should direct appropriate agencies to develop environmental standards to ensure the safety and welfare of participants. This would include specific guidance on, for example, capacity of clinics, required facilities and amenities, and staff training and certification.

2. Specify oversight and enforcement mechanisms for participant welfare in facilities.
   - A government agency or third party should be tasked with oversight of clinics through regular unannounced annual site inspections, and to remain operational, clinics must follow predetermined standards. This could, for example, be modeled on restaurant inspections, with clinics graded based on their adherence to safety and welfare standards.
   - Federal requirements for human subject research should make participant welfare in clinical research facilities an explicit criterion for IRB oversight.

Enhanced Voice and Recourse

1. Require stakeholders, including government agencies, to institute systems for reporting and responding to research complaints.

- The FDA and/or OHRP should create a system of anonymous reporting of complaints against clinics, sponsors, and IRBs. Complaints can be made by, and encouraged from, research participants, study personnel, IRB members, and representatives from the research sponsor's organization.
- Any agency responsible for the system of anonymous reporting should investigate complaints, including requiring or conducting clinic site visits to inspect facilities.
- Clinics, IRBs, and/or pharmaceutical companies should be fined for their failure to act on complaints.

2. Require compensation for research-related injuries.
   - Federal requirements for human subject research should require clear and fair plans to provide posttrial care and compensation to participants who are injured in research.
   - Clinics and/or pharmaceutical companies should be fined for their failure to provide in a timely manner appropriate medical care for research-related injuries or to compensate participants for lost wages or suffering resulting from such injuries.

<u>Specific Points to Consider for Pharmaceutical Companies</u>:

Translational Science Value

1. Design trials that adequately represent clinical populations.
   - Sponsors should harmonize and minimize restrictions on the inclusion of people of childbearing potential in phase I trials.
   - Sponsors should raise age cutoffs for participation and include healthy older adults.
   - The parameters for "healthy participant" criteria for trial inclusion should be loosened to reflect patient-characteristic body mass index, blood pressure, mild comorbidities, and other physical factors.
   - Phase I trials should be appropriately powered to analyze data for pharmacokinetic and pharmacodynamic differences relevant to key demographic characteristics of the intended patient population (e.g., sex and age).

2. Specify limits on enrollment of serial participants in trials.
   - Sponsors should increase restrictions on the use of the same participants in trials of the same product or the same class of drugs. To enforce these restrictions, better tracking of clinical trial enrollment should be instituted.

3. More closely model real-world conditions in trial protocols.
   - Sponsors should include behavioral restrictions, such as those pertaining to diet and exercise, in clinical trial protocols only when they safeguard participants or are necessary for valid trial results. Otherwise, clinical trial conditions should simulate real-life conditions as much as possible.

Fair Opportunity and Burden Sharing

1. Limit trial exclusion criteria.
   - Inclusion-exclusion criteria should be relaxed to allow for a wider range of healthy individuals to participate. Beyond those pertaining to age and sex that are important for the translational science value, these should include criteria related to diet (e.g., religious or value-based food restrictions), behavioral factors (e.g., sexual activity), or medical history (e.g., childhood illnesses or broken bones).

2. Select research clinics with broad participant pools.

- Sponsors should prioritize the selection of clinic trial sites based on the demographic diversity of facilities' participant databases and/or recruitment methods.
- Sponsors should also ensure that clinical trial sites use fair selection methods to enroll eligible participants.

3. Offer a diverse array of participant incentives.
   - To encourage broader participation in clinical trials and to create greater benefits from participation, sponsors should offer higher amounts of study compensation that would motivate enrollment of people from broader economic classes.
   - Sponsors should also offer suitable nonmonetary incentives. Examples may include free or reduced-cost access to pharmaceuticals or subsidized health insurance.

Fair Compensation for Service

1. Provide for study compensation that is commensurate with protocol requirements and require its timely disbursement.
   - Sponsors should budget for fair payments to healthy volunteers that are equitable across trial sites.
   - Study pay should be calculated by accounting for substantial contributions of time, inconvenience, management of adverse events, and required bodily monitoring and interventions.
   - Participant compensation should be disbursed fairly across the trial. Prorated amounts for early withdrawal should also be fair, and substantial completion bonuses should not offset inadequate payment for the rest of the trial. Completion bonuses should generally be modest and used to encourage final outpatient study visits rather than overall retention in a clinical trial.

Experiential Welfare

1. Contract only with high-quality research clinics.
   - Sponsors should select clinics that demonstrate investment in their infrastructure for the comfort and safety of participants.
   - Sponsoring companies and their lobbying groups (e.g., PhRMA) should support a federal requirement for clinic standards and oversight by relevant regulatory bodies.

2. Design trial protocols to promote participant well-being and limit welfare risks and harms.
   - Sponsors should not include unnecessary restrictions in trial protocols, such as those pertaining to diet, that could impinge on participants' well-being.
   - Sponsors should not include low-information-yielding procedures in trial protocols.
   - The use of in-dwelling catheters when they enhance participant welfare, such as in trials that employ daily frequent blood collection, and when they are preferred by participants should be explicitly required by trial protocols.
   - Trial protocols should allow flexibility for participants to leave clinics and return without penalty for unforeseen, critical circumstances (e.g., family emergencies or job interviews) when it is safe for participants to do so.

Voice and Recourse

1. Formalize a system for reporting and responding to research complaints.
   - Sponsors should institute a call-in, email, and web-based reporting system for participants or study personnel to make formal complaints about clinical trial protocols and clinic operations. Information about this system should be included in consent forms for every study.

2. Routinize and provide compensation for participant input to the clinical trial process.

- Sponsors should invite direct feedback from participants about the design of clinical trial protocols and the clinic experience. Sponsors should be responsive to information by changing the design of future trials and instituting mechanisms to improve participants' experiences.
- Sponsors should identify experienced participants who can serve on advisory boards and be paid for their time and feedback.
- Sponsors should encourage and incentivize trial sites to have in place routine participant-engagement mechanisms (e.g., feedback surveys) drawing on healthy volunteer expertise for ongoing quality improvement.

3. Follow clear and fair procedures of remediating problems that develop during trials.
   - Sponsors should discontinue contracting with research clinics that have ongoing problems with participant welfare or other significant complaints.
   - Sponsors should develop transparent and accessible procedures for healthy volunteers to be compensated adequately for study injuries or other substantial harms or wrongs. Such compensation, care, or remediation should be provided in a timely manner.

<u>Specific Points to Consider for IRBs</u>:

Translational Science Value

1. Review protocols for how well trial participants represent clinical populations.
   - IRBs should not approve study protocols that have inclusion-exclusion criteria that are not scientifically justified, such as those regarding sex and age.
   - IRBs should limit the restrictions imposed on people of childbearing potential so as not to exclude unnecessarily females who are unlikely to become pregnant during a trial (e.g., females who are not sexually active, females who do not have sex with men, or females who use barrier methods of birth control).
   - IRBs should require clinics to have a plan to recruit diverse (in terms of sex, age, etc.) participants who reflect clinical populations.

2. Ensure that protocols place adequate limits on the enrollment of serial participants.
   - IRBs should require that clinics detail how they will track repeat participants' prior trials to ensure that they do not enroll in more than one trial for a single investigational drug and to place limits on their enrollment in trials for drugs within the same chemical class.

Fair Opportunity and Burden Sharing

1. Require broad-based recruitment methods.
   - IRBs should require clinics to recruit participants broadly. This means that, at a minimum, they should ensure that study recruitment is not targeted only or primarily at underserved communities.

2. Require that any obstacles to enrollment are limited.
   - IRBs should disallow arbitrary exclusion criteria that do not impact the scientific goals of the protocol (e.g., where someone lives, diet and lifestyle factors, or unrelated medical history).
   - IRBs should require clinics to follow a fair process of selecting which eligible participants will be invited to enroll and to provide information to participants about that selection process.

Fair Compensation for Service

1. Ensure that study compensation is commensurate with protocol requirements and disbursed in a timely manner.

- IRBs should no longer use concerns about "undue inducement" to assess study compensation. Instead, the dominant ethical considerations should be based on assessments of fair compensation for service.
- IRBs should require payments for phase I healthy volunteer trials based on the substantial requirements of trial participation, including time, inconvenience, management of adverse events, and required bodily monitoring and interventions.
- Completion bonuses for trials should be allowed only for trials that have the greatest risk of attrition or withdrawal. Whether or not completion bonuses are used, fair and timely prorated daily payments must be ensured.

Experiential Welfare

1. Provide or ensure oversight of research clinics, including facilities and staffing.
   - Unless another entity is tasked with this role by the federal government, IRBs should conduct regular unannounced annual inspections of phase I clinic facilities to enforce welfare standards or otherwise make such inspections a requirement for protocol approval.
   - IRBs should require verification that clinic staff are appropriately credentialed and/or trained for their role in the trial (including, but not limited to, performing venipuncture).

2. Require that protocols minimize welfare risks and harms.
   - As part of protocol applications, IRBs should require sponsors and clinics to describe how they will attend to participants' welfare during confinement.
   - IRBs should ensure that protocols minimize invasive interventions, such as blood draws, to what is strictly required for scientific validity.

Voice and Recourse

1. Ensure that protocols include a system for reporting and responding to research complaints.
   - IRBs should have their own system of anonymous reporting of complaints about clinics, including for matters of welfare, payment, and respectful treatment, as well as injuries or other harms. Detailed call-in, email, and web-based reporting mechanisms should be included in every consent form.
   - IRBs should investigate complaints made by participants and study personnel against clinics, including through site visits to inspect facilities. When the identity of the person filing the complaint is known, IRBs should report back to that individual their findings from the investigation and what remediation has or will occur.

2. Follow clear and fair procedures to remediate problems that develop during trials.
   - Clear and fair plans to provide posttrial care and compensation to participants who are injured in research should be required for IRB approval of research protocols.
   - IRBs should deny or withdraw approval for protocols conducted at clinics with serious, repeated, and unresolved complaints.

<u>Specific Points to Consider for Phase I Investigators</u>:

Translational Science Value

1. Limit reliance on serial participants.
   - Clinics should invest resources in recruitment campaigns to expand their participant pools.
   - Clinics should minimize their reliance on repeat participants by screening new participants for each study and by placing restrictions on participants enrolling in the same types of clinical trials.

- Clinics should design facility policies and spaces in ways that encourage the participation of diverse gender groups. This could include the option of single-gender dormitories as well as advocating for fewer restrictions on the participation of people of childbearing potential.

2. Ensure trial protocols are closely followed.
   - Clinics should minimize opportunities for participants to engage in rule-breaking behavior that threatens study validity (e.g., ignoring washout periods or failing to follow necessary restrictions).
   - Clinic staff should enforce necessary restrictions by reporting all protocol deviations to sponsors and withdrawing participants from studies when their continued involvement threatens study validity. Should this occur, participants must be informed of the reasons for their withdrawal.

Fair Opportunity and Burden Sharing

1. Use broad-based recruitment methods.
   - Clinics should avoid narrowly recruiting from disadvantaged communities.
   - Clinics should mobilize recruiting strategies that reach members of groups underrepresented within clinical trials (e.g., females, older adults, and more affluent populations) *and* explicitly invite people in that pool to screen and enroll.

2. Limit obstacles to enrollment.
   - Clinics should offer compensation for screening.
   - Clinics should provide transportation to/from the clinic or reimburse people for those expenses.
   - Participation in clinical trials may additionally be facilitated by provision of child-care vouchers, increased allowances for leaving the clinic for emergent situations, and flexible family visiting policies.

3. Use transparent and unbiased selection processes.
   - Clinics should not use arbitrary exclusion criteria that do not impact the science (e.g., where someone lives, diet and lifestyle factors, and unrelated medical history).
   - When clinics determine that a specific individual should be banned from participation either for a period of time or indefinitely, the individual should be given information about that decision as well as its rationale and recourse for rectifying the situation when possible.
   - Clinics should minimize staff discretion in the selection of participants. Selection of participants on the basis of being a "known quantity" (i.e., having repeat-volunteer status) should be discouraged.
   - Transparent criteria for selecting eligible individuals for each trial should be developed, and clinic staff should communicate clearly with potential participants about whether they will be used (or are slated to be an alternate) in a specific trial.
   - Clinics should avoid competitive call-in or other selection processes that disadvantage some prospective participants.

Fair Compensation for Service

1. Provide timely study compensation that is commensurate with protocol requirements.
   - Clinics should ensure that study payments compensate participants adequately by accounting for substantial contributions of time, inconvenience, management of adverse events, and required bodily monitoring and interventions.
   - Clinics should find alternatives to completion bonuses to retain participants. Completion bonuses should be used only for trials that have the greatest risk of attrition or withdrawal, but prorated daily payments should still be fair.

Experiential Welfare

1. Make participant welfare—as manifested in facilities, staffing, and participants' activity restrictions—a top priority.

Clinic environment and provisions:

- The clinic space should be clean and safe.
- Participants should be housed with sensitivity to their gender and/or sexual identities, including provision of single-occupancy all-gender bathroom facilities.
- Clinics should provide suitable sleeping quarters, including adequate space for each participant, provision of comfortable mattresses and bedding, and enforcement of light and sound restrictions.
- The clinic should be kept at a comfortable temperature, and participants should be allowed to have layers of clothing for warmth as needed.
- Clinics should provide high-quality and palatable foods that are served at the proper temperatures.
- Clinics should provide regular opportunities for time outdoors.
- Clinics should provide diverse amenities and activities for participants to use during confinement.
- When space allows, clinics should allow participants to check in the evening before a study as a courtesy for those traveling farther distances.

Restrictions:

- Where restrictions on activities, food, drink, and/or use of specific products are necessary, clinic staff should explain clearly to participants why they should adhere to restrictions in order to ensure the validity of the clinical trial data and/or participant safety.
- Participants should be permitted to drink coffee or tea if there is no caffeine restriction in the protocol.
- Clinics should provide opportunities for participants to have visitors during lengthy confinement periods.

Staff care:

- Clinics should discipline or fire staff who do not treat participants with respect.
- Clinics should ensure that all staff performing venipuncture are highly proficient.
- Clinics should create a staff position in which one of their primary responsibilities is to promote participant welfare (e.g., an activities coordinator or participant advocate).

Voice and Recourse

1. Implement a system for reporting and responding to research complaints.
   - Clinics should institute a system of anonymous reporting for any study-related complaints. Information about reporting should be in each consent form, and signage in the clinic should describe how reporting can be done.
   - Clinics should ensure that participants have adequate information about recourse for being wronged or harmed during a trial.

2. Enhance participant input to the clinical trial process.
   - Clinics should create participant engagement mechanisms using healthy volunteer expertise for ongoing quality improvement for clinic policies and practices.
   - Mechanisms could include a compensated advisory board with significant healthy volunteer membership, anonymous quality-improvement polls, a suggestions box or online suggestions

platform used during studies, and compensated quality-improvement focus group discussions moderated by third parties.

3. Follow clear and fair procedures to remediate problems that develop during trials.
   - Clinics should retrain staff based on minor complaints and reassign or fire staff who have many, ongoing, or grievous complaints against them.
   - The clinic should designate a staff member to serve as a participant advocate for securing aftercare or compensation when someone has been injured in a trial.