3.14 Phase I and First-in-Human Studies

1.0 Purpose

The purpose of this policy and procedure is to describe the Organization’s requirements for IRB review and approval of Phase I and First in Human Studies.

2.0 Policy

- **2.1.** It is the policy of the Organization that, except in limited circumstances, phase I studies are assumed to represent no direct benefit to subjects/
- **2.2.** It is the policy of the Organization that review of phase I studies requires a careful assessment of the risk-benefit relations, subject selection, study design, monitoring and the process and content of informed consent.

3.0 Definitions

- **3.1.** ***Phase I studies*** represents the initial administration of an investigational new drug into humans, or into a specific population of humans (for example, elderly subjects, or children). The primary aim of a phase I study is determination of safety and tolerability, and assessment of maximum tolerated dose (MTD). Phase I studies may also assess pharmacokinetics, pharmacodynamics, drug metabolism, structure-activity relationships, and mechanism of action of the investigational agent. Participants in phase I trials may suffer from a disease or condition which could be the eventual target of the investigational agent (for example, an anti-neoplastic drug in patients with advanced cancer), or they may be healthy volunteers. In the former instance, early measurement of drug activity may be a secondary objective. Participants in phase I drug tests may receive a completely novel agent, an agent belonging to a class of drugs already studied in humans or a combination of new and approved drugs
- **3.2.** ***First-in-Human (FIH)*** trials represent the subset of phase I studies where the investigational agent has not been previously used in humans. The starting dose for a FIH phase I trial is typically based on the No Observed Adverse Effect Level (NOAEL), the highest dose at which no statistically significant and/or biologically relevant adverse effect is observed in the most relevant animal species.
- **3.3.** ***Phase 0 studies*** (also referred to as pre-phase I studies) are conducted prior to phase I trials to determine whether further human trials are worth pursuing. Objectives

and endpoints of phase 0 studies conducted under an exploratory IND may include evaluating modulation of a presumed drug target in humans; optimizing target assay methodology using human samples; providing pharmacokinetic (PK) data; assessing PK/pharmacodynamics (PD) relationships; and selecting the most promising agent from several chemical entities or formulations. Study participants, who can be either patients or healthy volunteers, are administered sub-therapeutic but pharmacologically active doses of drug. Participant exposure to the agent is limited. Phase 0 studies have no therapeutic intent.

4.0 General Principles

- **4.1.** Phase 0 studies have no potential for direct benefit.
- **4.2.** Phase I studies of new agents alone generally are considered to have no potential for direct benefit. Assertions of potential benefit must be based on clear pre-clinical data, or preliminary clinical data in a different population of subjects, at the dose levels proposed in the research.
- **4.3.** Phase I studies of a new agent in combination with an agent with known effectiveness, administered to subjects with a disease or condition, may be considered to have potential for direct benefit.
- **4.4.** Phase I studies of approved agents administered to new specific population of subjects (for example, elderly subjects, or children) with a disease or condition, may be considered to have potential for direct benefit.

5.0 IRB Review

- **5.1.** As a part of the analysis of the ethical basis for the research and the regulatory criteria for approval, the IRB should consider the following points
  - **5.1.1.** ***Assessment of risk***
    - **5.1.1.1.** In most cases, risk assessment is based on pre-clinical data, and can be difficult. Pre-clinical data may fail to predict human risks, leading to adverse effects in human trials (for example, consider the TGN1412 trial). It may predict clinical benefits that then fail to materialize for human subjects. And it may predict nonexistent risks in humans with the result that a potentially useful agent is discarded (Dresser J. J Law Med Ethics 37:38, 2009)
    - **5.1.1.2.** When phase I 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.
  - **5.1.2.** ***Assessment of potential benefit***
    - **5.1.2.1.** Potential direct subject benefit should be considered as noted above (section 4.0)
    - **5.1.2.2.** Potential benefit to an individual subject is usually conceptualized in the form of an improvement in health status derived from the agent being tested; however this is not always the sole potential therapeutic benefit. For example an improvement in the quality of life may qualify as a clinically relevant benefit (Chapman AR. J Clinic Res Bioeth 2:113, 2011).

- **5.1.2.3.** Extraneous benefits such as payment or adjunctive medical services that might benefit individual participants should not be considered when conducting a risk-benefit analysis (Emanuel EJ, et al. JAMA 283: 2705, 2000)

- **5.1.3.** ***Subject Selection***
  - **5.1.3.1.** Choice of subject population (healthy volunteers vs patients with a disease or condition) should depend on the scientific objectives of the trial, as well as the risks associated with the intervention and the consequences of those harms should they occur.
  - **5.1.3.2.** If patients with a disease or condition are considered the appropriate subjects, careful consideration should be given to the choice of "stable well-managed patients" vs those with poor managed, debilitating or end-stage disease. The former group may be more likely to benefit, may provide better data, and may be likely to make a free and deliberate choice. However the consequences of harm arising from participation may be greater than for those for whom there are limited other choices, or for whom death or disability is inevitable.
  - **5.1.3.3.** When healthy volunteers are considered as appropriate subjects, care must be taken to assure payment (if offered) does not constitute undue inducement and is not exploitative, and that potential subjects do not conceal personal information that could disqualify them from trial enrollment in order to receive payment.
- **5.1.4.** ***Study design and toxicity monitoring***
  - **5.1.4.1.** Trials should be designed with sequential, rather than concurrent, enrollment. There must be an adequate interval for monitoring effect of the agent on a subject before the next subject is enrolled, and before a dose escalation is made.
  - **5.1.4.2.** The data and safety monitoring plan should be sufficiently robust to assure that subjects are not exposed unnecessarily to harm. The plan should include frequent and clear safety evaluations, well defined dose limiting toxicities, and adequate oversight.
- **5.1.5.** ***Informed consent***
  - **5.1.5.1.** Extreme care must be taken to avoid therapeutic misconception and unrealistic optimism.
    - **5.1.5.1.1.** "Therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial." (Henderson GE. PLoS Med 4(11):e324, 2007). Two core concepts are (1) subjects need to understand that the main purpose of the research protocol is to produce generalizable knowledge; and (2) conducting a research protocol differs from providing individualized care (Pentz RD. Cancer 118(18):4571, 2012).
    - **5.1.5.1.2.** Unrealistic optimism "occurs when people perceive their own personal outcomes as being more positive than those of other people in similar circumstances when, in fact, there is no good reason to do so." Unrealistic optimism may compromise autonomous decision making when it interferes with the appreciation and processing of information related to risks and benefits (Crites JS. J Med Ethics 39(6):403, 2013)
  - **5.1.5.2.** General concepts and specific language for ICFs are described in section 6.0 below

6.0 Informed Consent Model Language

- **6.1.** Methods
  - **6.1.1.** For Phase I studies conducted in classic 3 + 3 design, or similar dose escalation design, CF language should reflect the escalation of dose (between cohorts) to toxicity. For example: “The purpose of the study is to find the highest dose of X that can be given safely. To do this a small number of subjects are given a low dose of X, and side effects are noted. If the side effects are tolerable, then the next group will get a higher dose, and this will be repeated with successive groups until some patients get certain side effects. The particular dose you get will depend on when you enter the study. The dose you get will not increase.”
- **6.2.** Risks
  - **6.2.1.** For Phase I studies conducted in classic 3 + 3 design, or similar dose escalation design, CF language should reflect the escalation of dose, with development of worse or new adverse effects in higher dose cohorts For example: “The dose of X will be increased with each successive group of subjects in order to see what dose causes side effects. Therefore, depending on when you enter the study (which group you are in) you may get more side effects, or new side effects, not seen with lower doses.”
- **6.3.** Potential Benefits to the Subject:
  - **6.3.1.** CF language should reflect General Principles above (section 4.0).
  - **6.3.2.** When there is potential for direct benefit, it should reflect the disease stage of the target population. For example, while use of a new agent in combination with an agent with an approved chemotherapy regimen may have potential for direct benefit, such benefit is unlikely to be significant or long-lasting in a patient with late stage cancer.
  - **6.3.3.** When potential benefits are suggested, the CF language should highlight differences between the study definition of positive response and the way that patients would define it.
    For example, a phase I oncology trial CF should alert subjects to the fact that tumor response is not equivalent to clinical improvement.
    For example: “It is possible that X [the investigational agent] would make your tumor shrink. However, it is important to understand that the tumor shrinking might not mean you will live longer, or even that your symptoms will improve”
  - **6.3.4.** When potential benefits arise from combination of an effective therapy with the investigational agent, CF language should clearly state that the benefit arises from the approved effective agent (which may be available outside the study) unless there is pre-clinical data to suggest the investigational agent augments the efficacy of the approved drug.
    For example: “It is possible that the combination of [standard therapy] with X [the investigational agent] would make your tumor shrink. However, it is important to understand that the [standard therapy] might cause your tumor to shrink even if you didn’t get X.”
  - **6.3.5.** CF language should minimize description of collateral benefit (for example, avoid phrases like “satisfaction associated with helping find a cure for X”)
  - **6.3.6.** CF language can include such benefits as improvement in quality of life, or relief of pain, if such benefits are realistic at the lowest dose levels to be administered.

- **6.4.** Potential Benefits to Others
  - **6.4.1.** CF language should describe realistic potential scientific benefits associated with the research, and should avoid framing benefits in terms of FDA approval.
    For example "The research may help us determine the safest dose of investigational drug X" is acceptable, as opposed to "This research will help develop a new treatment for disease" or "… provide information to allow FDA approval of drug X"

7.0 Phase I Studies in Children

- **7.1.** Use of early phase investigational agents in children may pose ethical challenges. Investigators need to be especially alert to the risks of unreasonable optimism and therapeutic misconception on behalf of the parents who are asked to provide consent (permission). When older children are involved, investigators must pay close attention to eliciting assent and respecting dissent.
- **7.2.** In general, phase I studies in children hold out greater potential for direct benefit, since there is usually already data from adults suggesting efficacy, and starting dose in pediatric trials is usually close to the adult MTD, thereby suggesting less likelihood of a sub-therapeutic dose (Berg SL. Oncologist 12:1336, 2007). Therefore, pediatric phase I trials may potentially be approvable under 21 CFR 50.52 (Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects) and 45 CFR 46.405.

8.0 Phase I Studies in Decisionally Impaired Persons

- **8.1.** Use of early phase investigational agents in decisionally impaired persons may pose ethical challenges, to the extent that these potential subjects may not be able to provide consent for themselves. Investigators must actively assess capacity to provide consent and assent, especially when capacity may wax and wane. Investigators must structure the consent/assent process in a fashion that maximizes the ability of the prospective subject to provide his/her voluntary, informed agreement to participate.
- **8.2.** Phase I studies in decisionally impaired persons may be more problematic than those conducted in children (section 7.2 above), since there may not be preliminary efficacy data and starting doses may be at the NOAEL (see section 3.2 above). Therefore, there may be no or limited potential direct benefit.
- **8.3.** Criteria for inclusion of decisionally impaired persons, based on risk-benefit relationship, are described in HRPP policy 4.6 (IRB Review of Research Involving Subjects with Impaired Decision-Making Capacity), sections 7.2 (Category 2 – Greater than minimal risk with the prospect of direct benefit) and 7.3 (Category 3 - Greater than minimal risk with no prospect of direct benefit).
  Note that the latter category requires that the research represent only a minor increase over minimal risk, which is unlikely to be true when conducting research with a novel agent.

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