ORI Guide for IRB Review of Phase I Drug Trials

Phase I trials are often conducted with healthy individuals to assess safety and tolerability of a new drug or biologic. Trials involve a small group of participants in a controlled environment under tight timelines. Phase I trials may also be conducted in a patient population. Phase I oncology trials typically include cancer patients with no further treatment options.

Sponsors provide preclinical animal and toxicology data, previous clinical data if available, along with manufacturing information and proposed protocols to the FDA in an Investigational New Drug (IND) application. FDA's approval of the IND is based on the assessment that the product is reasonably safe for use in initial, small-scale clinical studies.

Phase I trials assess the effects of the drug on the body (pharmacodynamics) and the effects of the body on the drug (pharmacokinetics) in terms of absorption, distribution, metabolism, and excretion (ADME). In addition, they may assess dose escalation, pharmacogenomics, food-drug or drug-drug interactions.

1. **Adequate Preclinical Data**
    a. Ask for and consider preclinical results, including in vitro and animal studies. These have limited ability to indicate risk or predict effects in humans. Data from any prior use in humans should be presented to the IRB
2. **Investigational New Drug (IND)**
    a. Confirm Phase 1 trials of drugs or biologics are being conducted under an FDA approved Investigational New Drug (IND) submission
3. **Study Design**
    a. If includes patient population consider if placebo-controlled; justification for lack of crossover design
    b. Consideration of current standard care
4. **Assess Personnel Qualifications & Facility Emergency Care Provisions**
    a. Emergency Readiness & Contingency Plans
5. **Subject Selection**
    a. Exclusion of subjects thought to be "at-risk" for particular adverse event (AE)
    b. Therapeutic misconception for patients with no other treatment options
6. **Dosing schedule**
    a. Use of Investigational Drug Service (IDS)
    b. Max safe starting dose, dose increments, dose escalation – small dose increases between cohorts
    c. Slow infusion vs. bolus dose
    d. Use Sentinel Dosing Schedules – consider amount of time between dosing to assess potential adverse events in one subject, before dosing a second subject

7. **Safety Monitoring:**

    a. Assess plan for identification of AE or unanticipated problems
    b. Predictable and unpredictable toxicities
    c. Lab data adequate to assess all organ systems and organs likely to be affected by drug
    d. Stopping Rules and thresholds for lab abnormalities
    e. When AE delayed, repeated administration can lead to accumulated toxicity
    f. Report per sponsor and IRB Policy on Unanticipated Problem and Safety Reporting
    g. Monitoring should extend at least 30 days after study or through half-life of study drug

8. **Compensation:**

    a. Remuneration amount based on time/effort/number of procedures; not on risks
    b. Schedule prorated – should be no financial penalty for withdrawal due to adverse event
    c. Consider economic status of population being recruited relative to potential for undue influence

9. Consent Process Considerations:

    a. Effective use of Key Information
    b. Identifies purpose (safety, proof of concept); clear that first trial in man
    c. Therapeutic Misconception for Phase I oncology trials
    d. Explanation of standard of care alternatives
    e. Clear description of treatment assignment, dosing ranges, multiple arms, etc.
    f. Potential risks associated with drug, research procedures, and quality of life
    g. Unforeseeable risks
    h. Financial cost if oncology trial
    i. Clear that compensation prorated and not tied to withdrawal
    j. FDA typically will retain data collected to the point of subject withdrawal
    k. Not typically considered to be an “applicable trial” for registration on Clnicaltrials.gov

10. **Institutional Biosafety Committee (IBC)**

    a. Review may be required for experimental Immunotherapy

References

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- Kurzrock, R., & Stewart, D. J. (2013). Compliance in Early-Phase Cancer Clinical Trials Research. *The Oncologist*, *18*(3), 308–313. http://doi.org/10.1634/theoncologist.2012-0260
- Protecting Phase I Subjects: IRB Considerations June 2013, Advarra IRB http://www.sairb.com/PDF/Protecting-Phase-I-Subjects-webinar-slides-Schulman-IRB-6-5-13.pdf
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