SCRS Global Oncology Program
A Guide to Conducting Phase 1 Oncology Trials

A site may want to participate in phase 1 studies for a variety of reasons including creating additional options for treatment for patients in their community, a scientific interest from physicians, early access to new compounds and treatments, and to better understand safety profiles. Typically, the goals of phase 1 studies are to understand the maximum tolerated dose of the investigational compound, the recommended dose for subsequent phase 2 studies, and a better understanding of the compound's safety profile.

The goal of this document is to serve as a guide for sites looking to begin or refine their participation in oncology phase 1 clinical research trials. This publication will provide a strong foundation by providing several components and decision trees to help advise how best to approach oncology phase 1 trials from their specific perspective. Sites can use the information herein to differentiate themselves and advance their practices beyond current abilities.

The deliverables and tangible outcomes are divided into four categories of general consideration – logistics and infrastructure, personnel, feasibility and start-up, and regulation and global landscape. Generally, each section includes a checklist of various necessary components of successful oncology phase 1 trial participation. Applicable benchmarks will be provided as a method of goal setting for the site, as well as advising the standards that should be met for the greatest chance of success and long-term sustainability.

Several important differences exist surrounding site logistics and necessary infrastructure that are critical to the execution of oncology phase 1 trials. The document covers the various types of oncology phase 1 trials, future possible decentralization of study visits, and the benchmarks that exist in this space. Also, part of this category, accessing the right patients will be touched upon, as well as financial considerations. Facilities and equipment needs are another large and unique requirement for oncology phase 1 trials and will be addressed.

The personnel portion of this document pertains specifically to how staffing might be structured for an oncology phase 1 trial center. There are several unique administrative needs, qualifications, and requirements for site personnel that will be addressed to enable success. Time commitments and special practices and procedures require inherently unique circumstances around staffing and personnel that necessitates its inclusion.

Unique and important regulatory requirements also exist for oncology phase 1 trials that necessitate a specific understanding to guide success. Their design and execution are inherently different than that of Phase 2, 3, and 4. This document is designed to help

highlight those differences as well as considerations when making the transition. Along the way, this specific guidance will be highlighted as to tie them to specific situations, trials, and environments. While a baseline understanding of the reader's specific regulatory requirements is expected, examples are provided to solidify regulatory nuances.

This publication should also be utilized as a general guidance. These recommendations will also not be applicable in every trial opportunity, and flexibility along with other possible resources should be employed to ensure a holistic approach. Specific solutions, technologies, or vendors are not endorsed or mentioned. Sites from other countries may find specific nuance guidance that will help their development for their region.

Logistical/Operational Considerations

1. Understand differences that exist
    a. Communications – communicate with urgency and frequency
        i. There is an expectation that the urgency of communication during Phase I trials is maintained at centers. Physician and site staff should have direct communication lines with the sponsor's study team.
        ii. During dose escalation, information flow about the patient status is critical. Routine and ad hoc discussions are encouraged.
        iii. Dose escalation meetings are typically required and hosted by the sponsor's study team. Site staff are expected and encouraged to fully participate in these meetings to understand the tolerance and safety of the compound being studied. These meetings are typically held at the end of each dose observation period and prior to the next dose escalation. It is critical that the investigators are engaged in these meetings and that all safety information is collected and shared prior to the next dose level.
        iv. These meetings are generally conducted via teleconference.
    b. Patient participation
        i. Additional procedures are typically requested or required for patients participating in Phase I trials beyond what is seen in standard of care treatment including, but not limited to:
            1. Safety tests (i.e. eye, dermatological, cardiac, neurological, etc.)
            2. Pharmacokinetic and pharmacodynamic samples: Multiple blood draws will be required at multiple timepoints in order to gain understanding of how the compound is being metabolized and the longevity of this drug once delivered
            3. Tumor biopsies
        ii. More frequent visits to the center for safety evaluation and/or treatment
    c. Time – plan accordingly for the management of additional procedures
        i. Time needed to complete additional procedures will be greater than routine standard of care. Procedures may have specific processes and requirements that will impact the amount of time required to complete those tasks.
        ii. Post-treatment observation periods may be required which entail

a patient spending more time in the clinic, including overnight observations.
   iii. Account for general time required for communications with the sponsor.
   iv. Resource time for data entry will be significant as there are multiple procedures, treatment timepoints, etc. that will need to be captured and included in the study case report form. Typically expected turnaround times for data entry and query resolution are shorter than later phase trials.
2. Phase 2 and/or Phase 3 trials, while potentially complex, do not typically require the same amount of communication, time/resource requirement and patient burden as Phase I trials. If experienced in later phase trials, adjustments will need to be made to accommodate this need (i.e. resources and budgeting).
3. Participating in Phase I trials provides institutions with experience working with compounds early in the drug development cycle. This experience can be shared with additional physicians within institutions and practices in order to provide a level of comfort when a later phase trial is initiated.
4. There are potential opportunities for physician investigators to publish in scientific journals and/or present posters or oral presentations at scientific congresses.
5. Selection for these trials is often quite competitive, so the information contained in this and future sections can help provide a competitive edge.

Infrastructure

1. Space / Facility
   a. Clinic
      i. Treatment and visits durations in phase I trials will often be lengthy. Dedicate appropriate space and time for clinic visits, infusions (when required), post treatment observations, and waiting room space for the comfort of patients and the efficiency of the clinic. Staffing feasibility should not be underestimated before agreeing to any phase I study.
      ii. Phase I protocols may require hospitalization during or immediately after treatment, identify a process for admitting patients to the hospital. Potential options may include dedicating beds for early phase trials with the capacity to house patients overnight or working closely with an associated hospital to contract for inpatient services. Be clear with the capabilities for any overnight/in-patient capabilities. For example, inquire if patients be simply observed overnight, if tests can be run and/or samples procured while in-patient, or if research-trained staff can support the patient while in-patient.
      iii. Robust and fully-stocked emergency supplies and medications should be in all patient areas. Establish detailed plans for quick response to infusion reactions or serious adverse events that occur during a patients visit.
   b. Laboratory
      i. For sample processing, sites will need to have experience with and capability of obtaining, appropriately processing, and shipping samples. Samples should be collected, processed and shipped in accordance with

the protocol and/or laboratory manual. Phase I trials typically include multiple sample accessioning for PK, PD, pharmacogenomics, and exploratory biomarker.

ii. Phase I studies often require very intense and frequent resources for sample management. Flexible staffing models for long day PK/PD sampling will be critical. If a site is unable to appropriately staff 10-12 hour clinic days, it will be significantly rate-limiting to the number and types of phase I studies that site can consider for its portfolio.

iii. PBMC sample processing is complex and common in phase I oncology trials. This requires specialized training and experience.

iv. Sample storage and shipping requirements for early phase trials tend to be far more intensive than phase II-III trials so detailed review of the requirements in a protocol feasibility assessment will be critical. It is common for sites to sign up for phase I trials only to discover after activation that they are not capable of staffing or completing the needs of the study.

v. Potential capital expenses
    1. -20°C freezer with daily temperature monitoring
    2. -80°C/-70°C freezer with daily temperature monitoring
    3. Refrigerated centrifuge or acceptable alternative process, documented in an SOP
    4. Ready access to dry ice and liquid nitrogen supply
    5. Pipettes for transferring small volumes (sometimes nano volumes)

vi. The tendency of phase I trials to have a large amount of sampling suggests additional space should be procured for storage for laboratory kits and supplies. This will be used to store many boxes as well as shipping supplies, etc.

c. Pharmacy

i. Access to an onsite investigational pharmacy with experienced staff in drug delivery & reconstitution in clinical trials is imperative.

ii. There may be special pharmacy requirements for reconstitution or preparation of medication based on the type of compound in use. It is recommended to be fully informed of the type of ventilation hoods that are in use in order to appropriately assess the facility for safe handling of compounds.

iii. An investigational pharmacist is highly recommended. Phase I trials most frequently include untested IP. Storage, handling, and preparation expertise is needed in the pharmacy, therefore frequent consultation on effects, mechanisms, attribution, etc. with an investigational pharmacist may be necessary.

iv. Ensure pharmacy SOPs include explicit guidance and instruction on labeling, storage, handling, destruction, etc. of IP with many unknowns (e.g. teratogenic, anti-angiogenic, specific/unique environmental sensitivities, etc.).

v. To allow for quick resolution of issues, the IP pharmacist should report directly to the Medical Director of the clinical research unit.

vi. Build in time and budget for the IP pharmacist to review potential trials before they are accepted and as early as possible in the feasibility stage. Pharmacists can be pivotal in assessment of IP procurement, storage, handling, blinding procedures, dose administration, accountability, subject training (if applicable), and more.

d. Ancillary
    i. Establish relationships with ancillary facilities in order to fill in experience or care option gaps within your site. These may be neighboring facilities, or facilities within your network.
        1. In addition to more common CT, MRI, x-ray/mammography, consider gaining access to the following capabilities:
            a. DCE-MRI, commonly used to study effects of anti-angiogenic agents
            b. PET scans often used to monitor brain mets or confirm clear
            c. US and/or CT guided biopsies
            d. US and/or CT guided intra-tumoral injection
            e. Bone scanning
            f. MUGA scanning
        2. If your facility does not have access to equipment necessary for the above example imaging, contract with neighboring facilities that can provide the imaging necessary for the study. In forming any partnerships with such third party radiology group(s), ensure they have clinical trial trained staff, or at a minimum, staff that understand the added requirements to analysis and using these techniques in a research setting.
e. Observation vs. treatment
    i. As differences in these types of trials exist, there should be consideration for appropriate infusion treatment chair space, long PK days, and or post-treatment observation periods for patients to be comfortable while waiting.
f. Capital expenses
    i. While capital expenses can vary considerably depending on site resources, location, and associations with other facilities, the primary consideration is space for participants as they participate in phase 1 trials.
        1. These include patient beds for long-term or overnight stays, infusion facilities and equipment.
    ii. Best practice is to review the type of trials your site wishes to conduct and seek information on how they will be operationalized, thus assessing your site's needs to purchase or rent additional space and equipment.

2. Policies and procedures
    a. Ensure your site and/or local IRB/EC has guidance or policies related to the collection of biopsies and/or biological samples (pre-treatment, post-treatment, # on-treatment).
    b. **For additional information on practical policies and procedures, please**

reference the ASCO resources cited here.

3. Finances, budgets and contracts
    a. Review research fees to ensure that phase I costs are considered and adapt as needed.
        i. Consider extra resourcing requirements needed for sample processing, additional meeting, patient identification, and more intense data collection.
        ii. Many of the items reviewed in this document will have associated costs that should be considered.
    b. Commonly, phase I trials require data to be entered in an expedited manner – often within 1-3 business days or as otherwise indicated by your CTA. This is particularly true in the case of ongoing or live safety monitoring studies where dose escalation or DLTs are part of the protocol. Be sure to understand and assess feasibility of staffing and costing for such needs.
    c. Charging for equipment: proper costing
        i. New equipment and research specific capital expenses may be required to participate in phase I studies. Understand these new costs and charge appropriately.
        ii. Identify the new pieces of equipment your site may need to charge for and what they may cost. Determine how that cost will be translated into the study budget.
    d. Building into source documents, patient chart review, and data entry tends to be more nuanced and requires additional time and effort that should be accounted for.

Personnel

1. Baseline needs
    a. Principal Investigator
        i. Phase I investigators are typically experienced oncology research physicians who have participated in phase 2/3 research and/or have participated as a sub-investigator on phase I studies and have experience in phase I/IIa dose escalation studies to determine the maximum tolerated dose (MTD).
        ii. Investigators should have dedicated research time allotted to performing research related review and activities.
    b. Roles required
        i. Research coordinator: this role assists the PI with patient recruitment, study logistics and sponsor contact for communications and monitoring visits. Generally, the coordinator will be the main point of contact for both the institution and the sponsor during the course of the trial.
        ii. Data entry: dedicated data entry resources need to be available to enter data into the trial specific case report form.
        iii. Infusion nurse: trained and qualified infusion professionals for administration of the investigational product as well as experience in PK sampling (staff available after working hours/weekend).
        iv. Nursing / Medical Assistant: trained and qualified individuals to capture

applicable study specific data and adverse events during the course of the trial.

v. Laboratory technologist: trained and qualified individuals to collect, process, ship and report out results on required laboratory test.
vi. Schedulers – staff needed to schedule the patient for all applicable study visits.
vii. Pharmacist / pharmacy technician: trained and qualified individuals that are knowledgeable in clinical research and study-level details in the preparation of the investigational product.
viii. Administrative / Management: support and management staff for the clinical research program.
ix. Regulatory associates: staff trained in clinical research regulatory requirements to complete required ethics committee and sponsor submissions and/or notifications during the course of the study.
x. Quality assurance associates: role or staff dedicated to review of the sites processes and audit program to ensure a high-quality program.
xi. Budget associate: individuals trained in budget preparation and negotiation for clinical research trials.
xii. Contracting associates – individuals trained and supported by legal for negotiation of research related contracts.
xiii. Patient financial services to explain costs to patients as outlined in the Informed Consent.
xiv. Tasks should only be delegated in accordance with sufficient licensure and any local regulations.

2. How to gain necessary experience
    a. Sponsors and CROs are more likely to place a trial if staff within that site have the experience necessary. Acting as a sub-investigator on trials under the guidance of an investigator who has experience within the applicable therapeutic area and trial design is the most efficient way to obtain phase 1 trial experience.
    b. Keep documentation related to staff experience including number of trials in the given indication as well as trials in other related indications. This can be managed through the coordinator, sub-investigators, site director, etc.
3. Baseline trainings or knowledge needs
    a. All staff should be GCP and Human Subjects Protections trained.
    b. For solid tumor trials, RECIST and iRECIST experience are required. Other indications will require specialized tumor burden assessment and response criteria. Investigators should be familiar with the training required. SCRS provides this training to its community at this link.
    c. If your site wishes to participate in specialized phase 1 trials, your facility or a facility you have access to needs experience with checkpoint inhibitor trials, oncology vaccine trials, cell and gene therapy, CART-T, immune-related response criteria.

Regulations (Country, State and Local) and Quality Considerations

1. Fit-for-purpose SOPs and operations for phase 1

a. Consider what SOPs need to be created
    i. Examples: Detailed IMP SOPs including internal transport of IMP to other locations if applicable (if your site has multiple locations); new USP guidelines require the use of CSTDs for IV administration, however the phase 1 compound may have had limited CMC testing so it is important to know local requirements and brands used for IV equipment.
b. IND submission timing: It is important to ask about the status of this during feasibility/SSU. Working at regulatory risk, as noted in other sections, feasibility and study start up often begin prior to FDA approval/clearance and more often than later phases, may receive comments back from the agency that require an amendment. Being willing and able to work at regulatory risk can be an advantage, but it is important to understand the impact on time and resources for all of the potential re-work. Consider inclusion of an additional fee in the budget or potentially a separate contract.
c. OUS submission: requirements may vary OUS for submissions that are different from the US-based IND submission to the FDA. Check local country guidelines for submission.
d. Crossing state lines
    i. Understand your site's local and regional regulations related to drug shipment or patient insurance coverage, particularly in the case of referred patients that are from other states or locations. There may be nuances that exist as they pertain to tasks associated with phase 1 studies.

Feasibility

1. Scientific interest
    a. Phase I oncology specialists often accept protocol designs of many types, but infrequently would decline a study based on the type/design. Early engagement with productivity leading oncology ECD specialists is key. Incorporating SME feedback into the protocol, plan, and operations is key.
    b. Feasibility is often driven by experience, rather than historical data predictions.
    c. Recruitment rates for a dose-finding study are quite different than fixed-dose expansion cohorts (ph IIa-b). Examples include single patient cohorts, step dosing, 3/3 designs.
    d. Slot assignments are often driven by the safety profile of the treatment(s), making dose-finding (ph I) enrollment predictions difficult and highly specific to the proposed treatment at hand. Assure the trial is utilizing slot assignments during feasibility.
    e. Consider patient burden, especially required time for PK schedule, patient and caregiver travel time, and observation time, when reviewing protocol design and provide feedback to sponsor.
    f. Consider resources and equipment needs such as special pumps (e.g. syringe pumps), inpatient beds or observation room, private infusion bays, freezers, laboratory hoods, crash carts, etc.
2. Patient access and unmet patient needs

a. What do patient needs mean as it varies in density?
    i. Phase I trial enrollment is often driven by standard of care failure, referral channels that the phase I investigator(s) and staff have set up, and available treatment options – not typically due to volumes of patients with a specific tumor type. It is critical for sites doing this research to know their referral channels well and always prune, protect, and grow them.
b. Networks, referrals, & pre-screening: how this work is accomplished
    i. Leverage networks your organization is part of or ancillary to.
    ii. Establish a referral network with other institutions and community oncologists, especially those that do not offer clinical trials as a treatment option. It is critical this is done prior to study initiation or acceptance.
    iii. Know and understand referral channels relevant to phase I trials and be able to articulate this to CROs/sponsors for increased confidence that your site has the right access to patients for the trial(s).
    iv. Enable pre-screening work and what this looks like
        1. Every CRO/sponsor will ask you for ongoing "potential". This refers to pre-screening i.e. how many patients you've looked at and considered or pre-screen failed over each week/month. Note this is not the same as screen failed.
        2. Request pre-screening work be reimbursed in budgets.

3. Additionally, operationalization and the ability of the site to perform the trial should be considered when assessing a protocol.

Start up

Phase I clinical trial start up timelines are critical to the successful enrollment and subsequent completion of the trial. Below are areas of consideration for study start up:

1. Institution requirements
    a. Governance committees: determine if there are any phase I specific needs from your institution.
    b. Operational committees: understand the complexity of the protocol and consider operational and training needs to ensure timely study start up.
2. Sponsor process and expectations: phase I nuances may put pressure on "start up" timelines and place an increased burden on processes. This should be managed to reduce process inefficiencies.
    a. At times, sponsors engage oncologists/sites pre-IND (or pre-country health authority [HA] submission) for interest in participation and/or feedback regarding protocol design and inclusion/exclusion criteria.
        i. For centers who are selected to participate in dose-escalation phases of a clinical trial and are targeted for first patient in, the site may be asked to begin protocol start up activities prior to health authority approval (HA).
        ii. If applicable, sites need to understand their institutional requirements and understand the risks of a protocol amendment due to HA feedback

resulting in:

1. Potential start up delays
2. Changes to study procedures
3. Updates needed to the study budget
4. Updates needed for ICFs and other protocol documentation

b. Many processes run in parallel internally at the sponsor and therefore documents may be completed and shared with sites as they become available in lieu of sending a full and complete regulatory packet to the site. Efficiency in this area is critical as sponsors are eager to plan for phase 2 trials.
c. Regulatory packets for sites often need to be put together and worked on in pieces, versus full 'reg pack' sent to site(s) (i.e., protocol versions are still being finalized, ICF templates being completed or translated, and BGT/CTA templates being built).