

Expanding a Site into Phase I Trials

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There are substantial differences in the operational requirements of an early phase research unit and a later phase research site. Expanding a later-phase site into early phase research has operational implications for staffing, physical facilities, study operations, and the subjects themselves.

Study Subjects

Later-phase (Phase II-IV) studies evaluate the effectiveness and side effects of drugs on subjects with medical conditions (i.e., patients). In contrast, most early phase (Phase I and some Phase IIa) studies enroll healthy (normal) subjects to evaluate the toxicity, pharmacokinetics (PK; absorption, distribution, metabolism and excretion) and pharmacodynamics (PD; physiological responses) of a drug. In recent years, the industry's capacity for healthy volunteer Phase I studies has expanded substantially. However, there is still a shortage of sites that can conduct studies on subjects with medical conditions. Sites that conduct later-phase studies and have suitable patient populations, particularly those in large urban centers with access to large numbers of patients, can expand into this market.

Phase I studies enroll subjects from patient populations if (a) the study drug cannot be evaluated in healthy subjects for biological reasons or (b) the study drug is too dangerous to test on healthy subjects who will not benefit from any treatment that eventually reaches the market. In either case, rigorous scientific and ethical scrutiny is required. Most Phase I oncology studies enroll patients with cancer. Other Phase I therapeutic areas that enroll subjects from patient populations include cardiovascular, dermatology, endocrinology (e.g., diabetes), infectious disease, inflammation, ophthalmology, psychiatry (e.g., schizophrenia), and pulmonary, among others.

Many of the procedures in Phase I studies are transferrable across therapeutic areas and patient populations. This article will focus on Phase I studies that enroll subjects from patient populations, but much of the discussion applies to healthy volunteer studies as well.

Most Phase I protocols require subjects to physically stay on the unit. Stays may be as short as overnight or may extend to 30 days or longer. Most Phase I subjects are students, unemployed persons, and those involved in professions that have periodic work hiatuses (e.g., seasonal workers, actors and teachers). Men are more likely to participate than women, but subjects increasingly represent diverse segments of the population independent of gender, ethnicity or other demographic characteristics. Subjects may volunteer for altruistic or medical reasons, but many have a financial motive, which raises ethical issues because remuneration can be significant, depending on study complexity, procedures and duration.

Subjects enroll in most Phase II-IV studies at random time intervals. The site's attention shifts from study to study as eligible subjects appear. Phase I studies with subjects from patient populations also usually operate this way. In contrast, healthy subject Phase I studies usually commence with a full complement (cohort) of subjects or at least a group of six or more. The subjects proceed through the protocol together and finish at the same time.

Facilities and Equipment

There are two types of Phase II-IV facilities: outpatient and inpatient. Outpatient facilities handle ambulatory subjects in a normal office and exam room setting. Inpatient facilities handle sicker subjects in a normal hospital setting, or procedure-intensive studies. Outpatient facilities may experience the rare medical emergency, but a physician, crash cart, and automated external defibrillator (AED) are adequate for most Phase II-IV studies. There should also be a plan for emergency medical transport to a hospital.

Medical emergencies also are rare in Phase I studies but are more common than in Phase II-IV studies because of drug toxicity; there is a wider range of doses and limited information on the investigational product in early phase studies, so compounds with unfavorable risk/benefit profiles are weeded out before they get to later phases. Therefore, Phase I facilities should also have resuscitation capabilities. Staff must be qualified in the use of a crash cart, AED, oxygen, code drugs, and a back board. The staff should be ACLS certified, and emergency medical technician services and rapid transportation to a local emergency room must be reliable. Location in a hospital is ideal in this respect.

Phase I facilities are unlike hospitals in important ways. First, while traditional hospital beds or specialized chairs may be used for certain patient populations or on “dosing days” in a Phase I unit, other sleeping accommodations may be arranged for healthy subjects or on non-dosing days. Such accommodations could include beds that are similar to simple hotel beds that do not need the elaborate positional controls and medical monitoring equipment of hospital beds. Many Phase I units provide dormitory rooms for young, relatively healthy participants. However, older or sick subjects may require private rooms. Suitable bathroom facilities, including showers and dressing areas, are also required. For sanitary reasons, carpeting and wallpaper are not suitable in areas used by participants.

Second, relatively healthy subjects do not spend their days in bed. They need recreation rooms for reading, watching television, surfing the Internet, playing board games, etc. Many Phase I units provide subjects with computers or wireless Internet access. Some offer personal video systems for movies. Some studies with extended stays offer activities like lectures and arts and crafts projects. For example, educational classes on diet and exercise for diabetes studies are often welcome. Some Phase I studies, especially those with long stays, offer field trips, low-impact exercise classes, haircuts, manicures and laundry service. These activities improve subjects’ comfort and build rapport between subjects and unit staff.

Third, security and supervision are important on a Phase I unit. Entering subjects are likely to undergo a search of their belongings to ensure they are not bringing in contraband items. Valuable personal items like jewelry are discouraged. Participants can usually store items like laptop computers in personal lockers. Visitors usually are not allowed on Phase I units, as they may pose unknown risks. Above all, subjects are expected to follow “house rules” that mandate good behavior and compliance with study procedures. Subjects who fail to follow the rules, such as those who attempt to bring contraband food or substances onto the unit, or those who do not make themselves readily available for study procedures (e.g., dosing and blood draws), are likely to be discharged and excluded from consideration for participation in future projects. Tension between subjects in close quarters is a genuine concern, as it can pose a risk not only to persons and property, but also to data integrity. Therefore, staffing must be adequate to ensure appropriate levels of security and supervision on the unit at all times.

In hospitals, the staff usually comes to the patient’s bed; in Phase I units, the subjects often come to the staff’s work area, depending on the study design and requirements. Phase I units thus require one or more rooms for dosing, phlebotomy and data collection. Drug usually is prepared in a locked pharmacy area, where it is packaged or prepared for administration. It is then transported to the dosing area for dispensing. Phlebotomy rooms

are similar to exam rooms, except they have a phlebotomy chair instead of an exam table. There should be a nearby bathroom with a toilet, sink and pass-through for urine samples. The number of subjects dosed at any one time varies depending on the capacity of the Phase I unit, but cohort sizes of eight to 12 subjects are common and manageable by most study teams. Since the safety profiles of drugs in early development are not fully known, a full cohort may not be dosed at one time, in order to mitigate the risk of serious adverse events. This practice has become more common since 2006, when six subjects participating in a Phase I clinical trial became critically ill after being concurrently dosed with an investigational biologic.

Phase I units also include a nursing station or office for paperwork; a laboratory room for blood sample collection, processing and storage; a room for study drug storage; a storage room for other study materials; and a storage room for study records. Specialty Phase I units may have facilities that are uniquely suited to their needs, such as a surgical suite for units that do tissue biopsies, a well-ventilated room for exercise tolerance tests, or even a private bedroom where subjects can produce sperm samples. They may have affiliations with other providers of clinical services, e.g., for CT, MRI, PET and ultrasound scans. Some rooms (especially the pharmacy) should be secure. Video surveillance of all work areas and common areas is ideal. In theory, Phase I units in hospitals can utilize the hospital's investigational pharmacy and other facilities, but it does not work well in practice because of rigorous Phase I requirements.

Phase I units require the equipment typically found in Phase II-IV facilities: scales, sphygmomanometers, ECGs, centrifuges and freezers. However, Phase I units need more of these items because subjects usually move through a study in groups. The old saying is: "One is not enough." For example, it is not unusual for a Phase I unit to have several freezers, each set to a specified temperature for sample storage: -20° F, -70° F, and -85° F. Back-up freezers, dry ice production facilities, and back-up power provide sponsors with an added measure of confidence that precious biological samples will not be lost in the event of a power failure. Depending on the type of studies the unit performs, other specialized equipment is almost certainly needed. For example, a unit that conducts respiratory studies may require a full line of pulmonary function test equipment, while a unit that conducts central nervous system studies may require cognitive test equipment.

Phase I studies typically involve a total of 12 to 24 subjects in one or more facilities. As a result, Phase I units usually accommodate subjects in multiples of six. However, some bioequivalence or thorough QT studies can enroll over 100 subjects. There is a wide range of bed capacities in Phase I units. Most facilities have six to 60 beds, with an average-sized facility having 24. Some facilities have 300 or more beds. Starting small minimizes the cost of excess capacity. Ancillary rooms should be scaled accordingly. When starting out, be prepared to run one study at a time, with down time between projects. Some Phase I protocols specify periods when subjects will be seen as outpatients, which can result in periods when the unit alternates between being empty and being temporarily filled to capacity. Although there is no hard and fast rule, break-even profitability generally requires bed utilization rates of 30%-50%.

Staffing

Phase I units, like hospitals, require constant staffing. One 24/7 position requires four people, each working 42 hours per week (plus overlaps for transition). At least one nurse or physician should be present at all times when subjects are "in house," even during lunch. Staffing intensity is greatest on dosing days and when PK or other assessment schedules are tight, but less during interim days and washout periods. The success of a Phase I unit

rests heavily on staffing schedules. Inadequate staffing results in poor service and high risk. Excessive staffing reduces profitability.

Phase I data collection requirements are far more demanding than in most Phase II-IV studies. Timelines are to the minute, not the hour or day. Also, much more data are usually collected. Dosing time, PK sample time, transit time, processing time, and storage time and temperature are among the data points that must be collected to the minute, along with repeated measurements of vital signs. The high volume of data usually requires that more than one staff member be involved with each subject during data collection periods. A synchronized timekeeping system throughout the entire unit is essential. There is nothing more confounding than records that show a sample being stored before it was collected.

Because of the blood draws, dispensing of drugs, and need for awareness of the subjects' medical status, most Phase I study coordinators are nurses, usually registered nurses. Foreign medical graduates can be a good fit. Depending on the studies, a physician may be required 24/7. A credentialed laboratory manager (certified in clinical laboratory science, preferably with Phase I experience) and pharmacist (who may be part-time, depending on study demands) are required. Competence, but not professional credentials, is required for documentation, subject recruiting, quality assurance, catering, housekeeping and other functions. A core staff of salaried personnel supported by per-diem staff provides flexibility. Paramedic training can be very useful from time to time. Advanced cardiac life support training for clinical staff is important, along with mock emergency response drills.

A typical six-bed Phase I unit employs about eight full-time-equivalent staff. A busy 40–60 bed unit employs about 30–40 full-time-equivalent staff. These numbers are much higher than in most Phase II-IV studies. The good news is that scheduling is much easier because subjects participate in groups and stay onsite for the entire study.

Operating Procedures

Most Phase II-IV sites conduct diverse protocols. Every protocol is a new adventure. In contrast, healthy subject Phase I units have core competencies, such as doing the same “feed ‘em and bleed ‘em” protocol to perfection, but also can get involved in some very diverse projects. Some Phase I units may specialize by conducting studies with specific patient populations or working in limited therapeutic areas. These sites often run protocols that are complex but involve procedures that are similar from study to study.

With regard to standard operating procedures, the recommendations of industry consultants vary. Some recommend that a healthy subject Phase I unit typically should have only a few SOPs, including:

- Subject recruitment
- Informed consent
- Investigational product management, dispensing and administering
- Data collection
- Sample collection and management
- Document management
- Emergency response
- Meals and nutrition
- [others]

Some industry experts believe that an efficient Phase I unit should have as many as 60–90 SOPs. Phase I units that conduct specialty studies, such as those that require special

medical equipment or expertise, or studies that employ seriously ill patient populations, may have even more SOPs to cover the complexity of the procedures or patient care.

Whereas many Phase II-IV sites treat SOPs as shelfware, most Phase I units are meticulous in following SOPs to ensure consistent, high-quality performance. As a result, site monitors assess source and case report form (CRF) data against the SOPs that govern their collection. Further, while Phase II-IV studies have many study-specific case report forms that sites may not want to convert into their own source document format, Phase I units almost always use their own standardized source documents and other forms.

In most outpatient Phase II-IV studies, the sponsor supplies the investigational product (IP) in a bottle, card or other package, ready for dispensing or administering to the subjects. In contrast, many Phase I sponsors deliver the IP in bulk. The Phase I pharmacist then prepares individual doses of the IP.

Phase I studies utilize a local laboratory or sometimes a centralized commercial lab. Unlike later-phase studies, sponsors expect Phase I units to have their own independent relationships with laboratory service providers, and at least one local provider is required for “stat” (same day) processing. Sponsor requirements for Phase I labs are relatively stringent, with audits common. Accurate tracking of samples from the point of collection to receipt by the laboratory is essential. Tracking usually employs labeling conventions (uniformly prepared sample labels), electronic data entry (e.g., the entry of the times a sample was collected, transported to the laboratory, centrifuged and stored), and procedural controls (SOPs that govern how a laboratory worker will handle the sample).

Business Development

Business development for a Phase I unit is decidedly different from that required for a Phase II-IV site. The biggest difference is that the client is the pharmaceutical company’s clinical pharmacology department, rather than the clinical operations department. Drug sales reps are unlikely to know people in clinical pharmacology, but clinical operations people may be able to make introductions. Additionally, clients expect to interact with an organization that has a formal structure, solid SOPs, quality controls, and a subject database, rather than a physician with a clinical practice. Clinical pharmacology people attend the conferences of organizations like the Association of Clinical Pharmacology Units (ACPU), the American Society for Clinical Pharmacology and Therapeutics (ASCPT), American College of Clinical Pharmacology (ACCP), and the Drug Information Association (DIA). Potential sponsors will want to know about your personnel, facilities and experience. If you have not yet conducted any trials in your Phase I unit, describe the high quality of your Phase II-IV trials. At least one person with Phase I experience is very helpful both for business development and ramping up operations. Sponsors are unlikely to contract with Phase I units before a successful inspection, so request one.

Phase I units that run at capacity can be very profitable, but the high fixed costs are challenging. Even when the unit is booked to capacity, a sponsor can cancel a study on short notice, leaving unused capacity and no cancellation fee. The Phase I market has become more competitive in recent years as industry capacity has expanded and demand has decreased. Low-cost facilities have emerged in developing countries. Currently, they are mostly limited to simple studies, but that is likely to change over time. Any new Phase I unit needs to offer potential clients a compelling reason to risk their development programs in a new facility.

Conclusion

Phase I studies have much in common with Phase II-IV studies, but there are significant differences. The most important point is that, while Phase II-IV sponsors may be forgiving of under-enrollment, protocol deviations, data entry errors, and other problems, Phase I sponsors insist on almost perfect performance — and they have long memories for failure. While Phase II-IV studies can be conducted as a sideline, Phase I studies require concentrated attention.

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