

## Research on Research: Learning about Phase 1 Trials

Phases of clinical trial investigation are described in some detail in the Code of Federal Regulations. Phase 1 is described as follows:<sup>1</sup>

**21 CFR Ch. I § 312.21 - Phases of an investigation.**

(a) **Phase 1.** (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

Unlike Phase 3 and 4 trials that can include several thousand subjects, and last years, Phase I research protocols include a small number of volunteers and are relatively short in duration, because they are designed to study a new drug's pharmacological effects, toxicity and dose range. Trial participants are typically healthy individuals, although for some medicines, the first trials in human participants are patients with the disease that the experimental medicine is intended to treat.

Phase 1 trials are distinct then for several reasons:

- Few number of participants
- Short duration of trial
- Participants are usually healthy volunteers
- Results are used to determine whether to progress the drug further

Phase 1 trials are also unique because they are unlikely to improve the health of the subjects who enroll in the trial.

Researchers from Erasmus University Medical Center in Belgium described Phase 1 studies as follows:

*"Phase I studies are the core of drug development. Among many other aims, they are essential for the identification of safety risks and for the selection of a drug dose that can be used for further development. Drug development is a highly competitive field, and*

<sup>1</sup> <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.21>

*therefore, time is of the essence. This means that every phase I study should provide information as quickly as possible; with the highest possible certainty; and, preferably, with the fewest possible patients, given the limited chance for actual patient benefit."*<sup>2</sup>

## Risks and Benefits of Phase 1 Trials

Ezekiel Emanuel, M.D., Ph.D. has been the Chair of the Department of Clinical Bioethics at the Clinical Center at NIH since 1998. He is widely published on topics related to ethics in clinical research including a book entitled *Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary*, and numerous journal articles. Dr. Emanuel is an oncologist by training and has a keen interest in the ethics of Phase 1 trials.

Phase 1 research is often the subject of a great deal of mystery and criticism. Critics of Phase 1 trials argue the studies are unethical because patients have poor prospects of improving from the treatment and are at the same time exposed to medicines being tested for toxicity. Critics sometimes refer to the participants as human guinea pigs. An essay from *The New Yorker* early in 2008 described this viewpoint.

*"The relationship between testers and test subjects has become, more nakedly than ever, a business transaction. Guinea pigs are the first to admit this. "Nobody's doing this out of the goodness of their heart," Miller says. Unlike subjects in later-stage clinical trials, who are usually sick and might enroll in a study to gain access to a new drug, people in healthy-volunteer studies cannot expect any therapeutic benefit to balance the risks they take. As guinea pigs see it, their reason for taking the drugs is no different from that of the clinical investigators who administer them, and who are compensated handsomely for their efforts. This raises an ethical question: what happens when both parties involved in a trial see the enterprise primarily as a way of making money?"*<sup>3</sup>

In March 2005, Dr. Emanuel was one of the authors of a paper published in the *New England Journal of Medicine* examining such claims in Phase 1 trials.<sup>4</sup> The study looked at 460 trials with 11,935 participants in non-pediatric cancer studies conducted by the National Cancer Institute between 1991 and 2005 to determine risk and response rates (i.e., whether or not a patient with disease responded positively to the drug tested).

---

<sup>2</sup> Verweij, J et al., "The Multi-Institutional Phase I Study: Disadvantages Without Advantages?," *Journal of Clinical Oncology*, 2008 26:1915-1916.

<sup>3</sup> Elliott, C., "Guinea-Pigging," *The New Yorker*, January 7, 2008.

[http://www.newyorker.com/reporting/2008/01/07/080107fa\\_fact\\_elliott](http://www.newyorker.com/reporting/2008/01/07/080107fa_fact_elliott)

<sup>4</sup> Horstmann, E et al., "Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002," *N Engl J Med* 2005 352: 895-904.

Dr. Emanuel and the other researchers found a wide variation of negative safety events and response rates across the trials considered. They wrote, "As compared with other reviews, these data suggest that participants may benefit more from current phase 1 oncology trials than previously believed." The study's primary conclusions were:

"Overall response rates among phase 1 oncology trials are higher than previously reported, although they have not changed for classic phase 1 trials, and toxicity-related death rates have remained stable. Rates of response and toxicity vary, however, among the various types of phase 1 oncology trials."

## **Pfizer's Phase I Research**

Pfizer is one of the world's largest sponsors of clinical trials and is one of the few biopharmaceutical companies in the world to run its own Phase 1 Clinical Research Units in the U.S., Belgium and Singapore.

Pfizer's database of Phase 1 study data is believed to be unique in that it contains data on over 8,000 volunteers going back several years. Dr. Ezekiel Emanuel and the Department of Clinical Bioethics at the Clinical Center at NIH thus proposed to partner with Pfizer to answer some important questions about phase I research including:

1. What is the impact on comprehension of using shorter informed consent documents?
2. What are Phase 1 participants' attitudes toward research and their role in this research?
3. What is the safety across Phase 1 trials?

### ***1. Analysis of shorter informed consent documents***

The NIH is working with Pfizer to conduct a "study within a study" whereby some potential trial subjects are asked to review an informed consent document that is four to five pages long, instead of the typical document that is about 20 pages long, depending on the study. The ultimate goal is to generate evidence determining whether the shorter informed consent documents is at least as effective in educating study volunteers as the traditional, longer version.

### ***2. Survey of Phase 1 participants examining attitudes***

Some research has been conducted analyzing patients' attitudes toward participating in clinical studies. One of the most cited studies is conducted by CenterWatch, a well-respected information services company focused on

clinical trials. The CenterWatch 2007 National Survey of Study Volunteer Experiences found 91% of participants reported they would participate in a future study, and 85% would recommend participation to a family member or friend.

Studies about attitudes of participants in Phase 1 trials, however, especially Phase 1 trials utilizing healthy volunteers are extremely limited. The NIH-Pfizer survey would include questions about participant's motivations and impressions of participating in Phase 1 studies. The collaborative effort would generate new insights into this area.

### ***3. Analysis of safety endpoints across trial types***

Hopefully it is clear by now that Phase 1 trials, by their very nature, are small and vary tremendously in their scope. As such, comparing safety endpoints across types of trials, whether by therapeutic area, by dosage, or intervention is difficult. The data is reported in a standardized way, but is not necessarily compiled in a way that enables analysis.

In order to conduct its own analyses across its broad portfolio of therapeutic agents, Pfizer created an integrated database query tool called Silhouette. Data can be viewed across a number of elements including:

- Study phase
- Study parameters
- Pharmacologic type
- Mechanism of action
- Adverse event rate
- Therapeutic area
- Demographics (including gender, race, age, weight, geographical region, etc.)

A fellow from the NIH Clinical Bioethics Center will work closely with Pfizer to create a panoramic view of the data available in Silhouette. Currently, there are data points on 8,000 volunteers (de-identified, of course so the researchers cannot determine the person's name, address or other personally identifiable information) and there will soon be 10,000 volunteers in the database. For instance, Silhouette could be utilized to look at adverse events by demography, health status, targeted disease, medical history, physical findings, lab results, etc. The user interface in Silhouette is very intuitive and it allows one to query hypotheses "on the fly". As an example, one could look at adverse events in Asian females who have clinically significant abnormalities on their electrocardiograms – a query which could be run in a matter of seconds.

Furthermore, sliced and diced data could be exported to Excel or other tools for other analyses.

Dr. Emanuel is particularly interested in this collaborative effort as a way to build on the earlier published research on safety and response that was conducted on non-pediatric oncology Phase 1 trials.

The convergence of health information technology advancements, more sophisticated computer environments and an intense interest in gathering information on safety and risk of biomedical interventions such as pharmaceuticals and medical technologies is driving trial sponsors and the government to work more closely than ever before to assure the public of the safety of innovative treatments. The Silhouette database will be the only set of data in the world being updated real-time, worldwide in a standardized format. Pfizer's collaborative efforts with NIH will garner new information scientists, researchers, ethicists, physicians and patients can act on.

## Discussion Questions

1. What are the unique aspects of Phase 1 trials?
2. How are ethical considerations different in Phase 1 trials than for other stages of clinical research?
3. Why is information on participants' attitudes about Phase 1 studies limited and how should it be rectified?
4. Would you be willing to participate in a Phase 1 clinical trial? Why or why not?
5. What criteria should be used by sponsors to determine the amount to be paid to patients to participate in clinical trials?
6. If you were on an ethics committee, would you be more concerned a sponsor was paying too much or too little for subjects to participate in a two-week research study where the patient is expected to stay on-site and undergo procedures, such as blood samples, EKGs and completing questionnaires each day?