

Research Integrity Office

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Informed Consent and
IRB Review for Combined
Phase Studies (Phase I/II,
I/Ib, etc.)

I. Introduction

Clinical trials of investigational drugs are generally classified into Phases I-IV as they move through the development process. The following points briefly describe the four phases in terms of their typical goals and design:

- **Phase I:** Primarily seeks to evaluate the safety of the new drug in a relatively small number of subjects. Usually attempts to determine the maximum safe dose of the drug through a dose-escalation design.
- **Phase II:** Evaluates the safety and effectiveness of the drug in people with a specific type of disease. Generally includes more subjects than Phase I, but usually not more than 100.
- **Phase III:** Larger, usually randomized trial to compare the effectiveness of the investigational drug with standard treatment (or placebo).
- **Phase IV:** Generally occurring after a drug has received FDA approval, these studies further evaluate the effectiveness and long-term safety of the drug.

It is becoming increasingly common to combine early-phase clinical trials to promote faster development of new drugs and/or reduce risks to subjects through adaptive trial design. In addition, some studies do not fit the traditional Phase I and Phase II models and have more nuanced titles, such as “Phase I/Ib.”

This Help Sheet provides guidance on how to present and describe combined early-phase clinical trials in consent forms and when to use separate consent forms to describe different parts of the same trial. It also provides tips on navigating the IRB approval process and suggested consent form language.

II. General Guidelines

The Phase of a study is determined by the nature and scope of the primary aim. The primary aim of a Phase I study is safety, while the primary aim of a Phase II study is effectiveness.

- A Phase I/II study seeks to evaluate the safety of the study drug while selecting the dose of the drug to use in Phase II. Once the dose is determined, Phase II begins with the primary aim of determining whether the drug is effective at the selected dose.
- Early-phase clinical trials may include an expansion cohort, sometimes described as “Phase Ib.” For example, a Phase I/Ib study might be a dose escalation study to

determine the maximum tolerated dose (MTD) of the drug, followed by continued enrollment at a determined dose (perhaps a dose below the MTD or at the MTD) to collect more safety data. While effectiveness might be a secondary endpoint in a Phase I/Ib trial, the primary aim for both parts is safety. This is what separates Phase Ib from Phase II.

Clear descriptions of the purpose of the study and the procedures involved are two important elements of the informed consent process. Phase I/II and other types of early-phase combined clinical trials can be challenging to explain in a manner that is understandable to potential subjects. The following consent form guidelines can help clarify these issues:

- **When parts of a study have different primary aims, a separate consent form should be used for each.** In general, this means that a Phase I/Ib trial may describe both portions in the same consent form. For a Phase I/II study, on the other hand, it may be more appropriate to use a separate consent form for each phase to avoid confusing the fundamental purpose of the different phases of the study. In addition, even when the primary aim is the same for both parts of the study, it may be best to use separate consent forms if the eligibility criteria or procedures are drastically different, or to eliminate the confusion of the dose escalation in the expansion portion of the study. This is especially relevant when subjects are only enrolled into one phase of the study or another and do not cross over.
- **If creating separate consent forms because OHSU subjects are participating in only one part of the study (such as Phase II of a Phase I/II study), the consent form should only contain information pertinent to that phase.** For instance, this may occur when Phase I is already complete and OHSU was not a participating site. In such cases, the consent form should describe the purpose of the study in terms of the primary aim of Phase II, and should describe only the procedures that subjects at OHSU will undergo. However, relevant information learned in Phase I, such as new risks, should be mentioned.

III. IRB Approval

When one part of a study is dependent on the findings from another part of the study, such as the dose for Phase II being dependent on the outcome of Phase I, the IRB will review the entire protocol at initial review but may limit its approval.

- If OHSU is participating in both phases of a study, the IRB may limit its approval to Phase I and require another full board review before beginning Phase II once the dose and all other pertinent information for Phase II is available.
- If OHSU is only participating in Phase II and review is sought before the completion of Phase I, the IRB may grant approval based on the Phase I description of the study but close the study to enrollment until Phase I is complete and all pertinent information regarding Phase II is available and has been reviewed and approved by the IRB via a new modification.

IV. Suggested Consent Form Language

Purpose Section

- **Phase I Consent for Phase I/II Study:** The purpose of this study is to
 - Test the safety of the study drug to see what effects (good and bad) it has on you and your cancer

and/or

 - Find the dose of the study drug that can be given safely.
- **Phase II Consent for Phase I/II Study:** The purpose of this study is to find out what effects (good and bad) the study drug has on you and your cancer.
- **Phase I/Ib Combined Consent:** The purpose of this study is to test the safety of the study drug to see what effects (good and bad) it has on you and your cancer.

Helpful Concepts

- **Dose Escalation:** We do not know the highest dose of the study drug that is safe. The dose of the study drug you receive will be based on when you enroll in the study. Up to 6 subjects will receive the starting (lowest) dose. If the side effects are not too bad, the next group of subjects will receive a higher dose. We will continue this pattern until we find the highest dose we can safely give. Your dose will be [leave blank and write in at time of consent] _____.
- **Expansion Phase after Dose Escalation (Phase I/Ib):** Once we find the highest dose of the study drug we can safely give, more subjects will be enrolled at this dose level so that we can learn more about the safety and side effects of the study drug.
- **If procedures are different for different study groups, preface procedures section with:** The exams, tests, and procedures you will have in this study depend on which study group you are in. The procedures for both groups are listed below. You will be in group [leave blank and write in at time of consent] _____.