UBC BCCA REB Guidelines for Combined Phase I/II Clinical Trials

The Tri-Council Policy Statement - Chapter 7, Article 7.2 states the following**:**

> "*Combined Phase I/II clinical trials raise particular ethical concerns because they are often conducted with desperate populations whose therapeutic options have been exhausted. Patients afflicted with terminal cancer and HIV AIDS are examples. Such situations may distort the perceptions by patients and their families, as well as by researchers, of the balances between the harms and benefits of the research. Such factors not only relate to the process of free and informed consent, they also influence the clarity and strength of stopping and withdrawal procedures. Because of these considerations, it is essential that researchers and REBs collaborate and consult with each other throughout the course of Phase I/II clinical trials*."

Clinical trials may be designed to combine phases to minimize the risks to participants and/or to allow faster development of a new intervention (e.g., Phase I/II or Phase II/III trials). In a combined Phase I/II clinical trial ethical issues arise when the results from Phase I are not yet known. Essentially, it is not acceptable for a REB to approve the Phase II portion of a combined Phase I/II study without having sufficient information from Phase I; in particular, information related to side effects and a maximum tolerated dose. This is for two reasons: 1) the REB needs to evaluate the magnitude of and types of harms related to the experimental product or procedure in light of the clinical circumstances of potential participants; and, 2) research participants themselves need to be fully informed of the available data before agreeing to the Phase II portion.

Section 2.2, of the ICT Topic E8: Guidance for Industry: General Considerations for Clinical Trials states the following:

> "The cardinal logic behind serially conducted studies of a medicinal product is that the results of prior studies should influence the plan of later studies. Emerging data will frequently prompt a modification of the development strategy. For example, results of a therapeutic confirmatory study may suggest a need for additional human pharmacology studies…"

The UBC BCCA REB will evaluate a combined Phase I/II clinical trial on a case by case basis using the following considerations as a guide. Researchers may also use this guide to determine in advance how to frame their submission to avoid delays.

Scenario 1: Site conducting Phase II only - Phase I completed.

The submission should clearly state that the application is to proceed with the Phase II portion of the study. The protocol, application, and consent document(s) should provide background information about Phase I (e.g., where it was conducted, etc.) and must incorporate the results from Phase I; in particular, side effects and the rationale for the dose to be used in Phase II. Consent documents must emphasize the Phase II issues uncluttered by details relating to Phase I procedures.

Scenario 2: Site conducting Phase II only - **Phase I not yet completed.**

If the site is only participating in Phase II of the study (i.e., Phase I is being conducted elsewhere, or at BCCA under a separate application) and is not yet completed, the application should not be submitted until the Phase I results and related risks are available, and the Phase II dose has been determined. Once these have been incorporated into the protocol, the study may be submitted. The UBC BCCA REB will not

review the study in advance. Again, the consent document should be relevant mainly to the Phase II procedures.

Scenario 3: Site conducting both phases.

In most circumstances, each study phase must be submitted in a separate submission, and the Phase II submission will only be accepted for review by the REB until the results from the Phase I are known.

However, a single study submission for a combined Phase I/II clinical trial will be accepted in the following circumstances:

- Where there is available basic safety, tolerability, and adverse effects information from other Phase I studies;
- When the Phase I study is also evaluating therapeutic efficacy of the drug, and Phase II would be a continuation of Phase I and has the same objectives;
- The study drug is approved for use for other indications.

The UBC BCCA REB will require that the single study submission is done in two parts in order to address each phase separately and sequentially (i.e., an initial application is submitted for Phase I, and an amendment is submitted for Phase II.) The *initial* submission should focus only on the Phase I portion of the study. The REB is prepared to review and approve the Phase I portion and provide a preliminary review of Phase II (without approval) in order to advise applicants of what they ought to be considering when they submit the amendment for Phase II. The Phase II amendment submission should include the results from the Phase I portion. Under this scenario the UBC BCCA REB recommends preparing the submission documentation as set out in the table below.

Combined Phase I/II clinical trials where the site will conduct both phases.	
Application Form	The application form should initially focus only on the Phase I portion of the study. While reference may be made to the Phase II portion, there should be a clear statement to confirm the applicant's acknowledgment that the application is to proceed only with Phase I and that upon completion of Phase I, the Phase II portion will be submitted as an amendment for review/approval by the UBC BCCA REB prior to proceeding with Phase II.
Protocol	The protocol document submitted with the initial submission may be for the combined Phase I/II study with the understanding that once Phase I has been completed, a revised protocol must be submitted that incorporates the results from Phase I including any additional risks and the dose determined to be used in Phase II.
Main Consent	The main consent document should be separated into two documents: one for each phase. The Phase I consent document may include references to optional components (if applicable – see below) and the potential availability and eligibility of the Phase II portion, and that Phase II participants will be provided with a separate consent document to sign. A statement should also be included in the Phase I consent document to inform participants that although there is a plan to conduct a Phase II, there is no guarantee that the Phase II portion will proceed. The Phase II consent document should not be submitted with the initial application; it should be submitted with the amendment.
Optional	Optional consent documents may be submitted with the initial submission, *unless* the

Consent(s)	option is dependent upon a particular aspect of Phase II, then it should be withheld and submitted with the Phase II portion.
Mandatory Tissue Collection	If applicable, this does raise ethical concerns that the applicant should ensure are appropriately addressed and justification for mandatory tissue collection must be provided in the submission for evaluation by the UBC BCCA REB. Please refer to the UBC Policy on Mandatory Tissue Banking.