BC Cancer Research Ethics Board Guidelines for Combined Phase I/II Clinical Trials

The design of clinical trials has shifted recently to include models that combine different phases (e.g., Phase I/II, Phase Ia/II, Phase II/III, etc.). It is proposed that combining phases may minimize risks to participants and/or allow faster development of a new intervention. Traditionally, Research Ethics Boards (REBs) have been reluctant to review subsequent phases until the preceding phase/s has/have been completed. Indeed, 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…"

Combined Phase I/II clinical trial proposals, in particular, have raised ethical concerns relating to safety considerations when ethical review of the Phase II portion is requested in the absence of Phase I results. While it is not acceptable for the REB to give full approval to the Phase II portion of a combined Phase I/II study prior to the completion of the Phase I, the BC Cancer REB (BCC REB) recognizes the need to develop pragmatic guidelines regarding the implementation of combined Phase I/II trials and is proposing guidelines that will both protect the subjects and provide timely review of protocols.

The BC Cancer REB will evaluate combined Phase I/II clinical trials 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 BC Cancer under a separate application) and is not yet completed, the application may be submitted prior to the completion of the Phase I results. However, while the Phase II may be reviewed prior to the completion of the Phase I, the Certificate of Approval cannot be issued until the recommended dose is defined, the consent form modified if necessary, and the Health Canada approval completed.

Scenario 3: Site conducting both phases.

A single study submission for a combined Phase I/II clinical trial will be accepted for review. However, prior to commencing Phase II, an amendment must be submitted requesting approval for the Phase II dose, as well as any modifications to the consent form which may be required. Results of the Phase I should be provided; specifically, updated information about toxicity and risks so the REB can ensure patient safety is adequately considered.

If the Phase II portion has substantially different testing or protocols, two separate consents may be necessary. If the study protocol is similar, a single consent may be adequate, but this will be assessed on a case by case basis. Delegated/expedited review of the amendment may be possible in some cases, but issues such as unanticipated serious toxicities or substantial modifications to the trial design may necessitate review by the Full Board. In all circumstances, the PI is encouraged to consult with the REB administration to ensure issues are addressed and the optimal submission and review processes are undertaken.

Combined Phase I/II clinical trials where the site will conduct both phases.	
Application Form	The application form should initially focus only the portions of the study that the centre is participating in. 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 reviewed as an amendment and fully approved 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, an amendment 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 if the two portions are substantially different: one for each phase. 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.
Optional Consent(s)	Optional consent documents should be submitted with the initial submission unless the 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, please refer to the UBC Policy on Mandatory Tissue Banking for information. The submission should ensure that ethical issues are appropriately addressed and justification for mandatory tissue collection is provided.