

Methods in Clinical Cancer Research Workshop Format for Protocol Concept Synopsis Sheet (blank)

Below is the format to follow for the concept sheet for protocols. It is based on the International Committee for Harmonization’s (ICH) synopsis worksheet, which has been adopted by most regulatory agencies in the world. We have taken some license with the format but it is essentially the same. This format and wording works best for a treatment study and to some degree an imaging study. If your study is observational, cohort, or another type of study, you may need to change some of the headings to conform to that type of study. It is difficult to make the synopsis a “one size fits all,” so you may need to adapt it for your particular study. Importantly, however, the elements and their sequence should be retained as they appear in this format. The point of a synopsis is that the critical elements of the protocol are summarized in a succinct manner. In fact, the ICH has asked that the final synopsis including results be no longer than five pages! Bulleted or numbered lists should be used wherever possible.

Please limit your protocol concept sheet synopsis to four-to-five (4 - 5) pages (using 11-point Arial or 12-point Calibri typeface with one-inch margins), including the statistical section. Material beyond the fifth page will not be read.

SYNOPSIS

Title of Study:
Investigators:
Study Center(s):
Concept and Rationale:
Primary Objective(s):
Secondary Objective(s):
Primary Endpoint(s):
Secondary Endpoint(s):
Study Design:
Schema:

Number of Patients:
Main Criteria for Inclusion/Exclusion:
Intervention and Mode of Delivery:
Duration of Intervention and Evaluation:
Statistical Methods: (due Monday evening) (a) Definition of primary outcome/endpoint: (b) Definition of secondary outcomes/endpoints: (c) Analytic plan for primary objective: (d) Analytic plan for secondary objectives: (e) Sample size justification:
Funding, Regulatory, and Feasibility Issues:
Patient Acceptability/Ethics and Consent Issues:

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SYNOPSIS

Title of Study:
Investigators: Name of the investigator(s) who is (are) responsible for conducting the trial.
Study Center(s): Name(s) of institutions involved in the trial.
Concept and Rationale: Brief justification of concept and rationale, including name and description of the investigational product(s); abbreviated summary of background findings that are relevant to the trial; brief justification for the route of administration, dosage regimen, and treatment period(s); brief rationale for biomarker, imaging, or other correlative studies. [This section is limited to one page in length.]
Primary Objective(s): The primary objective(s) of the trial (i.e., what I want to accomplish.). For example, for a standard phase I trial of a new targeted therapy agent, the primary objective might be: define the maximum tolerated dose.
Secondary Objective(s): A list of the secondary objectives of the trial. These can include objectives concerning additional clinical outcomes (e.g., overall survival), correlative outcomes (e.g., biomarkers and PK), and imaging outcomes (e.g., PET-CT). For example, for a standard phase I trial of a new targeted therapy agent, secondary objectives might be: define toxicities; determine effects of treatment on drug target activity.
Primary Endpoint(s): A list of the primary endpoints to be measured and how they will be

<p>measured during the trial (i.e., how I will know if my objectives are achieved). Examples include response based on RECIST criteria, time to progression, change in quality of life, dose-limiting toxicities, etc. For example, for a standard phase IA trial of a new targeted therapy agent, the primary endpoint might be: maximum tolerated dose – the dose level below the one at which 1/3 or 2/6 patients experience dose limiting toxicities. For a phase IB trial, studies examining dose response relationship and measurable surrogates of drug action or toxicity in peripheral blood or biopsies might be suitable and important at this stage of design and represent primary endpoints. (MTL)</p>
<p>Secondary Endpoint(s): A list of the secondary endpoints, if any, to be measured during the trial. These can include the following:</p> <ul style="list-style-type: none"> • Clinical endpoints (e.g., overall survival) • Correlative endpoints (e.g., biomarkers, PK, etc.) • Imaging endpoints (e.g., PET-CT) <p>For relevant outcomes, briefly describe logistics of tissue procurement, specimen collection, etc. Describe how you will quantify biomarkers (i.e., define “high vs. low;” 3+ staining vs. 1+ staining; comparison of expression levels of a target on Western blot; how gene array analysis/patterns will be used, etc.). For example, for a standard phase I trial of a new targeted therapy agent, the secondary endpoints might be: toxicities – CTC v3.0 used to grade toxicities; effects of treatment – biopsies to examine expression and activity of target; measured by Western analysis; “+” result defined by an x% reduction of activity on post-treatment sample; positive outcome defined as at least 50% “+” results in an expanded cohort at the MTD.</p>
<p>Study Design: A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a simple schematic diagram of trial design, procedures and stages; measures taken to minimize/avoid bias, such as randomization or blinding.</p>
<p>Schema: Please draw a schematic flow diagram of your study.</p>
<p>Number of Patients: Number of subjects to be enrolled. A brief statement about how many patients are expected to be eligible, how many you expect to accrue of those eligible, and how long it will take to complete the study. This should be based on data obtained on the patient population at your home institution (and not an optimistic guess).</p>
<p>Main Criteria for Inclusion/Exclusion: Brief list of subject inclusion and exclusion criteria.</p>
<p>Intervention and Mode of Delivery: The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration.</p>
<p>Duration of Intervention and Evaluation: The treatment period(s), including the follow-up period(s), for subjects for each investigational product treatment/trial treatment group/arm of the trial.</p>
<p>Statistical Methods: (Due Monday evening) A brief description of the statistical methods to be employed for the primary outcome, sample size justification, and any planned interim analysis.</p> <p>(a) Definition of primary outcome/endpoint: A description of the quantitative way of</p>

measuring the outcome for each patient. For example, if disease-free survival is the primary outcome, the definition might be the time from study enrollment until the first documented date of disease progression.

- (b) Definition of secondary outcomes/endpoints:** Similar to above. For correlative outcomes, the nature of the outcome should be defined as well. For example, if change in gene expression at follow-up is a secondary outcome, it should be stated how this will be quantified. Is expression measured in a quantitative (continuous) assay, or perhaps by immunohistochemistry so that gene expression will be ordinal or binary? Will the resulting measure of change be continuous, binary or ordinal?
- (c) Analytic plan for primary objective:** A description of the primary objective will be assessed. Oftentimes, this will involve hypothesis testing (e.g., we will test that the complete response rate is greater than 20% using a Fisher's exact test). For phase I studies that use algorithmic dose finding designs, stating how the MTD is defined is sufficient (e.g., the MTD will be defined as that dose at which....).
- (d) Analytic plan for secondary objectives:** A brief description of how you will assess the secondary objectives. Some examples:
- (1)** We will use descriptive statistics and graphical displays to evaluate change in serum markers between pre- and post-treatment. A paired t-test will be used to determine if there is a statistically significant change.
 - (2)** Pharmacokinetic parameters will be graphically displayed using boxplots and summary statistics.
 - (3)** Toxicities will be tabulated by type and grade.
- (e) Sample size justification:** The sample size justification should be based on the primary objective. For phase I dose-finding studies, this will depend on the number of dose levels considered and the number of patients treated at each dose level. For most phase II studies, this will require a power calculation based on a hypothesis test and justification should include the null and alternative hypotheses, the alpha level, and the power. For a continuous outcome, an estimate of variance is also necessary. In some cases, a sample size justification is based on the width of a confidence interval (e.g., with a sample size of 40, we can estimate a 95% confidence interval for the response rate with half-width no greater than 0.16.)

Funding, Regulatory, and Feasibility Issues: A brief description of how the study will be funded; how the study drug(s) or other intervention(s) will be obtained; and (if applicable) whether the study sponsor or pharmaceutical/biotechnology company has committed to providing the study drug.

Patient Acceptability/Ethics and Consent Issues: A brief description of issues that may limit patient or advocate acceptance and suitability (competing therapies, standard of care, toxicity, etc.) and how the study drug(s) or other intervention(s) will raise issues about acceptability or compliance.(MTL)