P8140 Randomized Clinical Trials 1
Spring 2019
Final Proposal Requirements

Final Phase III RCT Proposal

Submit electronically as a WORD DOCUMENT on CourseWorks by 1pm Wednesday May 1 2019

The final assignment is to produce a protocol outline for an **NIH phase III two-parallel-group Randomized Clinical Trial (RCT)** assessing the efficacy of a clinical intervention, while taking account of associated risks and safety concerns. Length is 15-25 double-spaced pages, excluding Cover Page, Table of Contents, and References. Suggested target length is ~20 pages.

The proposal should:
1) Show how the trial will achieve the 7 key elements of the course definition of a phase III RCT to the maximum extent possible, given the particular problem and intervention
2) Address the other key issues highlighted in class: safety, outcome variables, hypothesis formulation, power, stopping rules, etc.

The proposal may address **any unanswered real clinical question about an intervention of any type (drug, device, surgical, dietary) in any medical or relevant discipline of your choice.** For non-clinicians, or clinicians working outside their field, accuracy of all clinical details is not crucial for the grade. However, the proposal must show and document evidence of a substantial search to identify a potential topic, and familiarity with key elements in published literature (possible outcome variables, key safety issues, etc.)

The requirement is for **a Phase III trial with a straightforward, two-group structure (with no lead-in)**, a classic and powerful tool. Focus on identifying a clinical problem that can be investigated by a trial of this type, and an appropriate control group, either placebo or active.

Structure for the FINAL PROPOSAL

Title Page (include study name with acronym, if possible), Table of Contents, Proposal Sections, References

1.0 *Introduction and Background:*

Briefly identify the **clinical disease or topic of interest**, the **rationale** for the trial, the **intervention and control group** (the latter either placebo or a standard-of-care intervention), and the **clinical question. You MUST provide at least one reference** for your choice of Standard of Care within this section.

Specify the key features of trial population: diagnosis (shortest wording), age range, sex, race, geographic location, etc.

2.0 Objectives

i) Primary

Present precisely the **primary null and alternate hypotheses** and indicate the direction of clinical interest.

More detailed information about the primary outcome, its instrument, and its measure should be listed in in Section 4.0.

ii) Secondary

Identify **THREE OR MORE key secondary outcomes** that support or elaborate the primary objective. (Some trials include more general non-experimental or "ancillary" objectives, e.g., to develop a registry, to collect natural history data, but this is not the concern in this protocol.)

For each secondary outcome, present precisely the **secondary null and alternate hypothesis.**

More detailed information about the secondary outcomes, their instruments, and their measures should be listed in in Section 4.0.

iii) Safety

Identify **THREE OR MORE key safety outcomes of interest** important to your intervention/disease area. **Specify the outcome, its data type, the instrument used, and when responses will be collected.**

More detailed information about safety outcomes will be provided in Section 6.0.

3.0 *Trial Design*

i) RCT Features

Outline the **type of trial** (phase, key design features, etc.). Describe **if and how your proposal will incorporate and achieve each of the seven features of an ideal RCT**.

Additional detailed information about **double blinding** will be provided in Section 3.0 ii).

Additional detailed information about **randomization** will be provided in Section 3.0 iii).

ii) Blinding

State **who will or will not be blinded in your trial.** If not double-blind, strong justification is required for why you decide this is impossible for your clinical question. State and discuss what steps will be taken to compensate for this as much as possible. **Describe the steps taken to insure that interventions are blinded.**

If blinding of the actual interventions is not possible, many trial operations can still be blinded (measurement of outcome variable, patient visits, etc.) Specify what these are in your trial, and how blinding of these operations will be achieved.

iii) Randomization

Specify the **randomization scheme.** Indicate and explain the use of any stratification variables. Describe the specific blocking scheme that will be used. Discuss how treatment assignments will be generated. Give reasons for the design choices, particularly the use or absence of stratification variables.

iv) Inclusion and Exclusion Criteria

Provide numbered lists of 1) the major **inclusion criteria** and 2) the major **exclusion criteria** (at least 5 items in each list: there can easily be 10). Indicate why key criteria were selected (for example: a medication cannot be given to children).

v) Enrolling Centers

Identify the **type of enrolling center** the trial will include (major medical centers, hospital clinics, private practices, yoga classes, etc.)

vi) Data Coordination and Trial Management

Indicate that there will be a **Data Coordinating Center (DCC) and Clinical Trial Management (CTM)** resources at a level appropriate for the proposed trial (A multicenter trial must have a DCC with appropriate experience, appropriate budget, experienced trial coordinators, experienced data managers, etc.). **Briefly discuss the DCC and CTM's role in the trial process – see the UCSF link from lecture 1 for more details…**

http://hub.ucsf.edu/clinical-study-management

vii) Sidedness of Test
State whether and discuss why your primary outcome utilizes **a two sided test**.

4.0 *Data Collection and Patient Follow-up*

i) Outcome Details
For each efficacy outcome listed in Section 2.0, **detail the specifics of the outcome variable: and its type – continuous, dichotomous, or time to event; the instrument used, and the measure(s) used to construct the variable.**

Include how the instrument **accurately reflects the outcome of interest** and if/why it is a validated instrument.

Discuss how, where, and when each variable will be measured. Describe this process in the clinical setting. What information is **collected and recorded, and by whom (for example a Data Coordinator, Clinical Coordinator, or clinician administering a test)?**

Remember: You may not use a repeated measures design for the primary outcome.

ii) Data Collection Mechanism
Specify the mechanism for **data collection** (e.g. web-based data management system with Electronic Case Report Forms (eCRFs), which is preferred; or data entry by hand with faxed-based management system.)

iii) Schedule of Visits
Include a table showing the detailed **Schedule of Events** that will be followed for every patient enrolled. **This table must be consistent with all other sections of your proposal**.

iv) Trial Timeline
Include a Figure showing the trial timeline, including length of time needed for startup before randomization, randomization and total follow-up (not individual) follow-up time; data cleaning after follow-up ends; and statistical analysis. Adapt the Figure in Lecture 2 slide 28 so that it is appropriate for your trial.

5.0 *Statistical Considerations*

i) Type of Outcome
Specify the **primary outcome data type (continuous, dichotomous, or time to event),** and the appropriate **statistical test** for the null and alternative hypotheses. Specify that the **statistical design is superiority, the appropriate experiment wide type I error rate, and the sidedness of the test.**

ii) Power Calculation: Unadjusted and Adjusted Effect Size
You MUST provide at least one reference for the unadjusted effect size value for the control group. Describe the reasoning for determining the **least clinically meaningful effect**

size in your trial proposal. Present the **calculations you use to find the Adjusted Effect Size in an Appendix.** Specify all needed parameter values. Discuss in the Proposal text why this adjusted effect size is used in the sample size calculation in place of the unadjusted effect size.

NOTE: You cannot assume 0% Crossover or 0% non-compliance for the proposal.

iii) Sample Size
Specify the **Sample Size** needed for your trial for your desired level of Power. The sample size should reflect an Interim Analysis Design and should reflect the adjusted effect size. Include the relevant PASS output. Make sure to indicate the software used to calculate the sample size. List all data utilized in the calculation and summarize succinctly in a sentence.

For all sample size calculations in PASS, use the Group Sequential procedures.

iv) Sensitivity Analysis
Using the procedures presented in class, provide a table showing how changes in key parameters affect the needed sample size. Discuss the table. Make sure to **title the table, describe its contents, and discuss** its results in relation to your proposal.

v) Interim Analysis Plan
Include a pre-specified **Interim Analysis Plan**. In a separate paragraph, explain the process of taking interim looks, how the Type I error rate will be controlled appropriately, and mention the methodology used (remember: for a placebo control, specify a different lower stopping boundary than for an active control).

Include the number of planned interim analyses, the interim boundaries for each point, and the terminal criteria (with appropriate z-score and associated p-value).

Include a figure that combines all stopping boundaries. Make sure to **title the figure, describe its contents, and discuss** its results in relation to your proposal. Make sure to indicate the software used to calculate this value. Explain any symmetry or asymmetry of the stopping bounds in the figure.

NOTE: **You MUST use information, not time,** for the spacing between "looks".

6.0 *Safety Considerations*
i) **Detail how** each safety outcome of interest from Section 2 iii) is measured.
ii) Provide clear reasons **why these specific key safety outcomes are important in regards to your intervention/disease area**.
iii) What **other, more general, safety outcomes** will your trial monitor?

7.0 *Limitations and late-breaking problems*
Discuss the **limitations** of your proposed project. If your thinking develops and you become

aware of limitations that would ideally be addressed in future revisions, note these with brief indications of a strategy for improvement.

8.0 References

A **complete list of references, NEJM style**, is required. See previous writing guides.

Additional requirements

Maximum length, excluding Cover Page, Table of Contents, and References is 25 pages
Double-Spaced (not 1.5 or 1.75 spacing)
Smallest font size permitted is 12
Margins at least 1 inch all around.

Points will be deducted for not following the listed structure, formatting, and styling.