Clinical Trials: From Inception to Implementation

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Inception

- Someone has a thought
  - Principal Investigator
    - Investigator Initiated
- Discussed among their peers
  - This leads to identifying potential sites/personnel that the PI wish to collaborate.
- If it is a drug study, how to obtain the drug
  - Drug company

Inception (cont)

- Once a concept is formed – 2 things should occur
  - ☐ Writing of the protocol (the beginning)
  - ☐ Determination for funding
    - Based on:
      - ☐ Disease (how common)
      - ☐ Time of year
        - FDA Orphan Products Division has a yearly submission
        - NIH has a 3 times a year submission
        - MDA has a biyearly submission
        - How much money can you apply for

Inception (cont)

☐ Determination for funding (cont)
  ■ Based on:
    ☐ How will drug be supplied
      ▪ Drug company supply drug/placebo or just drug
      ▪ Any additional funding from drug company for the study
      ▪ Have to purchase drug/placebo
    ☐ Your resources
      ▪ GCRC
      ▪ Discretionary funds
    ☐ Resources available at other sites
☐ Compare first draft of protocol with the amount of money you will need

Next Step

- Take a good hard look at the protocol and the finances
  - Modify the protocol to match the funds
  - Find ancillary funding to match the protocol
  - Inquire into each sites indirect costs
    - Can vary per funding source (8% to 75%)

Concept of funding

- Once you identify the funding source you are going after – what do you need for that application
  - Do you need an IND (investigational new drug application process)
    - The IND is the means through which the sponsor seek an exemption to ship and distribute drug across state lines
      - 3 IND types: (investigator, emergency use, treatment IND)
        - Investigator IND
        - (21CFR Part 312)

IND

- You may have to submit 30 days prior to funding deadline
  - Example: FDA Orphan Products Division requires an IND.
- What do you need
  - Opening letter that contains: (limits)
    - Project Title
    - Introductory Statement
    - General Investigational Plan
  - Table of Contents
  - Form FDA 1571
  - Form FDA 1572 from all sites involved
  - Investigational Brochure
  - CV's from all Principal Investigators
  - Protocol

Investigational Brochure

- For new drugs
    - Brief description of drug
    - Summary of pharmacological and toxicological effects in animals and humans
    - Summary of the pharmacological and toxicological disposition in animals and humans
    - Summary safety and effectiveness in humans (prior studies)
    - Description of possible risks and side effects
- For drugs already marketed
    - Drug insert/monograph

Funding applications

- PI determines the funding they are seeking.
  - Start gathering information needed – funding source specific – NIH is different than FDA Orphan Products Division
    - Letter of support
      - Simple PI letter
      - Institutional Letter of Support (amount of money to be awarded to that site)
    - Biosketches
      - http://grants1.nih.gov/grants/funding/phs398/phs398

It is never this simple

http://grants1.nih.gov/grants/funding/phs398/phs398.html

- Follow font and format specifications. Otherwise, application processing may be delayed, or the application may be returned to the applicant without review.
- **Font**
- Use an *Arial, Helvetica, Palatino Linotype or Georgia typeface, a black font color, and a font size of 11 points or larger*. A symbol font may be used to insert Greek letters or special characters; the font size requirement still applies.
- Type density, including characters and spaces, must be no more than 15 characters per inch.
- Type may be no more than six lines per inch.
- Use black ink that can be clearly copied.
- Print must be clear and legible.
- **Paper Size and Page Margins**
- Use *standard size (8 ½" x 11")* sheets of paper.
- Use at least one-half inch margins (top, bottom, left, and right) for all pages, including continuation pages. No information should appear in the margins, including the PD/PI's name and page numbers.

Page Formatting

Since a number of reviewers will be reviewing applications as an electronic document and not a paper version, applicants are strongly encouraged to use only a standard, single-column format for the text. Avoid using a two-column format since it can cause difficulties when reviewing the document electronically.

The application must be single-sided and single-spaced.

Consecutively number pages throughout the application. Do not use suffixes (e.g., 5a, 5b).

Do not include additional pages between the face page and page 2.

Do not include unnumbered pages.

Figures, Graphs, Diagrams, Charts, Tables, Figure Legends, and Footnotes

A smaller type size is acceptable, but it must be in black ink, readily legible, and follow the font typeface requirement.

Grantsmanship

Use English and avoid jargon.

If terms are not universally known, spell out the term the first time it is used and note the appropriate abbreviation in parentheses. The abbreviation may be used thereafter.

Photographs and Images

Do not include photographs or other materials that are not printed directly on an application page in the body of the application. Pictures or other materials that are glued or taped onto application pages are incompatible with the current duplication/scanning process.

You may include black-and-white or color images in the six (6) submitted copies provided such images are printed directly on the application page and are critical to the content of the application.

Copies

Send the original application (signed by an authorized organizational official) and five identical, legible, single-sided photocopies.

Do not use photo reduction.

The application must contain only material that reproduces well when photocopied in black and white. Glossy photographs or other materials that cannot be photocopied must be submitted in the appendix (see Section 5.7).

Note: Photographs may be included in the appendix; however, a photo copy of each must also be included within the page limitations of the Research Plan.
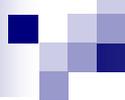
Page Limitations and Content Requirements

All applications and proposals for NIH funding must be self-contained within specified page limitations.

Observe the page number limitations given in Table 1. Only in cases involving interdependent multiple subprojects (e.g., Program Projects and Multi-Center Clinical Trials) will the PHS accept applications that exceed the page number limitations. However, specific page number limits may apply to each subproject. For information pertaining to page number limits for such projects, contact the awarding component to which the application may be assigned. (See Agency Contact Table.) The page number limitations may also be different for other specialized grant applications; consult and follow the additional instructions for those applications.

Funding applications (cont)

- How is it submitted
  - □ Online
    - Time zone restriction
    - PDF?
  - □ Hard copy
    - Can be the most difficult
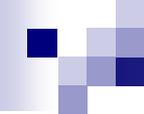
It is never this simple

- IND may come back within the 30 day window to ask for further clarification
- Those darn PI's are constantly changing the protocol
  - Which means your funding application is constantly changing

What's next

- Primary site of the PI has to approve application before submission
  - Before this happens, the other sites must approve their budget portion
    - Some sites need 2 weeks to approve
    - Therefore, need to factor in the amount of time the other sites need to approve + the time your site need to approve the application

It is never this simple

- Those darn PI's are still changing the protocol
- While you are attempting to gather the information needed – common problems
  - Biosketches
    - Not on the current biosketch form
    - Out of date
    - Not using the proper font or size of font
      - You either retype them yourself or ask the PI's to modify it
    - Too many pages (4 page maximum)
  - Not every site is on your timetable
  - The dollar amount changes; therefore, the institutional letter of support changes.

Deadline

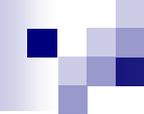Submit electronically and hope it goes through

OR

Submit paperwork and hope it gets there on time

It is never that simple

- Should send the IND folks an updated protocol
    - They need to be kept abreast of any changes
    - Answer questions that they may need to have answered
- And wait
- Answer any questions from the funding source
- And wait

While you wait

- **Those darn PI's are still modifying the protocol**
- **You get ready for the next step**
  - ☐ Implementation strategies