Designing and Conducting Clinical Trials of Drugs in Children

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Has documented that she has no financial relationships to disclose or Conflicts of Interest (COIs) to resolve.

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Presenter: Dr. Dianne Murphy has documented that her presentation will not involve discussion of unapproved or off-label, experimental or investigational use except to describe experimental studies.

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Goals of Drug Development

- **Protect the public health by assuring that drugs to be marketed are safe and effective.**
- **Bring new drugs that are safe and effective to market in a timely manner.**
- **Speed therapeutic innovations to advance public health.**

Drug Development

- **A complex, lengthy, multidisciplinary, stepwise process involving evaluation of animal and human safety and efficacy data.**

Pediatrics is another layer of complexity

- One must deal with all the “usual” steps but also address the following questions for pediatrics:

  - What adult or animal data applies

  - What is the “benefit” or minor increase over a minimal risk to justify the trial

  - What level of text and how many assent and consent forms need to be addressed

  - What facilities can do these studies

  - What calculations are necessary for blood sampling and non-invasive vs invasive testing

Drug Development Stepwise Process

- **Laboratory, animal, then human studies**
- **Small studies before large ones**
- **Short studies before long ones**
- **Low dose before high dose**
- **Single dose before multiple dose**
- **Each step builds on preceding experience.**

Product Applications

- **IND: Investigational New Drug Application**
  - **Allows initiation of clinical studies in humans.**
- **NDA: New Drug Application**
  - **Submission of information needed for marketing approval.**
- **sNDA: supplemental NDA**
  - **Application to change manufacturing, patient population or formulation of the product.**
- **ANDA: abbreviated new drug application**
  - **Application for marketing approval of a generic drug.**

Stages of New Drug Development

- **Pre-IND**
- **IND**
  - **Phases 1, 2 and 3 clinical development**
- **NDA**
- **Post-marketing**
  - **Phase 4 clinical development**

Pre-IND
(for Pediatrics may already have this data in adults)

- **Objective: Determine drug's toxic and pharmacologic effects before first time use in humans through *in vitro* and *in vivo* animal testing.**
- **Discuss chemistry and pharmacology/toxicology**
- **Discuss clinical development plan (including statistics)**
- **Prior to human exposure**
  - **Chemical identification, characterization and purification**
  - **Animal studies**
    - **Drug must be reasonably safe for use in initial Phase 1 clinical trials**

Getting a Starting Dose

- Determine the NOAEL
  - Highest dose level that does not produce adverse effects
- Convert NOAEL to HED (Human equivalent)
- Safety factor applied to the HED.
  - In general, safety factor of 10 is recommended.
- MaxRecommendedStartingDose: obtained by dividing the HED by the safety factor.

IND Submission

- **Allows initiation of clinical studies in humans.**
- **Phase 1, 2 and 3 clinical studies**
- **30-day clock for initial submission to determine if clinical study is reasonably safe to proceed.**
- **No review clock for subsequent submissions.**

Clinical Hold

- **An order to delay or suspend an investigation.**
  - **No new patients may be enrolled**
  - **Patients already in study should be taken off drug (unless discontinuation not in interest of patient safety).**
- **May be imposed anytime during review cycle**
- **Criteria: examples**
  - **Unreasonable risk to human subjects**
  - **Insufficient information to assess risk to human subjects**

General Interactions During Review Process

- **Meetings**
  - **EOP2 with sponsor**
    - **Lowest effective or maximum tolerated dose known; preliminary evidence of efficacy and reasonable evidence of safety**
    - **Potential claims**
    - **Discussion of Phase 3 trials**
  - **pre-NDA with sponsor**
    - **Phase 3 trials almost complete or completed**
    - **Format and content of to be submitted NDA**
    - **Adequacy of components**
      - **Clinical: Will trial data support filing of the NDA?**
    - **Reviewer needs**
      - **Clinical: Data tabulations and Case Report Forms**

NDA Submission

- **74-day letter**
  - **states if application will be filed and any requests for additional information**
- **Site inspections**
- **Advisory Committee meeting if needed**
- **Labeling review**
- **Written reviews by all disciplines**
- **Regulatory decision**
  - **Risk/benefit analysis based on totality of information**
  - **includes any Phase 4 commitments**

Supplemental NDA (sNDA)

- **A supplement is an application to allow a company to make changes in a product that already has an approved new drug application (NDA)**
- **Most preclinical, clinical work performed in initial NDA**
- **Most pediatric studies are submitted as supplements**

ANDA (Generic Drug)

- **“Copy” of approved drug**
- **Safety and efficacy already established for the approved reference drug.**
- **Must contain same active drug in the same amount and acceptable inactive ingredients.**
- **Must be bioequivalent to reference drug.**
- **Must have the same labeling as the reference drug.**
- **Even if studying a “generic”, changes must go into the originator label. This means negotiations with the originator.**

Review Disciplines in Division:

(within the Center for Drugs there are 18 product development divisions)

- **Chemistry**
- **Pharmacology/Toxicology**
- **Clinical Pharmacology/ Biopharmaceutics**
- **Clinical**
- **Statistics**
- **Microbiology**
- **Project Manager**

References

- **Code of Federal Regulations**
  - **50 Human Subject Protection**
  - **54 Financial Disclosure**
  - **56 Institutional Review Boards**
  - **201 Labeling**
  - **312 IND**
  - **314 NDA**
- **Legislation (for example, FD&C Act, PDUFA, FOIA, FDAAA, BPCA,PREA, FDASIA).**