

# Clinical Trial Development and Implementation

PSG Annual Meeting  
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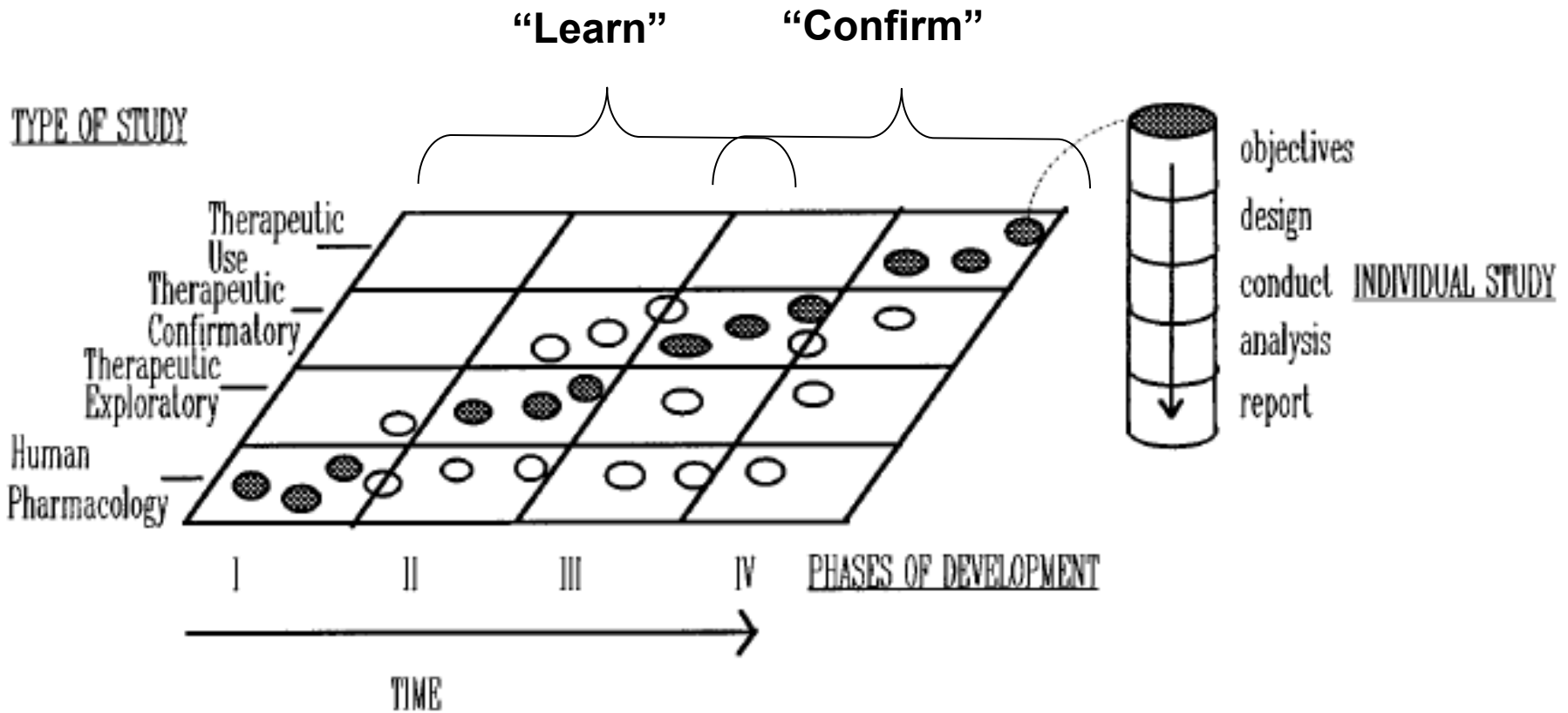
**biogen idec**

# Topics

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- Clinical Development vs. Clinical Trial
- Planning
- Implementation

# One approach to framing clinical research questions...



Federal Register / Vol. 62, No.242 / Wednesday December 17<sup>th</sup>, 1997



# Planning a Trial:

## The question is what is the question?

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- Identify an important clinical question
- Work backwards from the overall goal to identify the series of questions
- Honestly evaluate the literature
  - What is the next step in development?
  - Is this a feasible step?
- Sharpen the question: “safety and tolerability” is not a question
- Fit the question into an analysis plan
- Repeat this process and make sure it still makes sense
- Seek critical input at each step

# Issues to Address in Phase II Trials

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- Pharmacokinetics: acute/chronic
- Drug activity (pharmacodynamic)
- Safety
- Potential efficacy
- Populations and outcomes
- Agents to be studied in Phase III (Go/NoGo)
- Drug dosage(s) schedule(s) to be studied in Phase III

# Some Types of Phase II Designs

- No Fixed Design: Match Question with Design
  - Two-stage designs
  - Futility designs
  - Selection designs
  - Other randomized, parallel group designs
- More liberal error rates and use of controls

## Phase II: Safety and Activity

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- Determine dose (exposure) response related to potential clinical benefit and safety.
- Select the most promising dosage(s) among several dosages
- Determine if intervention merits further research (phase III) trial is warranted or if should be discarded
- No universal design

# Implementation

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- Conducting a trial is a team effort
- Members of the PSG and CTCC can guide you and help with logistics
- You will need to provide the energy
- Expect it to be difficult
- Things that you have never heard of will go wrong and cost \$\$\$

# Life Cycle of a Clinical Trial

**Grant Award  
and/or Parent  
contract  
established**

**Orientation or  
Initiation  
Meeting**

**Database Locked  
Analysis**

- Protocol Synopsis finalized
- Schedule of Activities finalized

- Protocol finalized
- Model ICF finalized
- Sites selected
- Operations Manual/MOP completed
- CRFs finalized
- IRB approvals obtained
- Site subcontracts/ payment schedule in place
- Finalize Contracts with third party vendors (labs, ECGs etc.)
- Build database
- Finalize Study drug packaging/labeling\*

- Enroll subjects\*
- Distribution of study drug to sites
- Answer Protocol/CRF questions
- Take incident calls
  - SAEs
  - Dosage Adjustments
  - Premature Withdrawals
  - Drug Disclosure
- Data query process
- Clean/Close database
- Transfer database to Biostatistics

- Perform primary/ secondary analysis
- Submit abstract
- Submit manuscript
- Submit CTR
- Post-hoc analysis

**CONCEPTUAL  
PHASE**

**PLANNING  
PHASE**

**IMPLEMENTATION  
PHASE**

**ANALYSIS/  
PUBLICATION  
PHASE**



# Project Management: You Need This

- Definition:

- Is the discipline of organizing and managing resources in such a way that the project is completed within defined scope, quality, time and cost constraints.

- A project uses carefully defined sets of activities that utilizes resources (money, people, materials, energy, space, provisions, communication, quality , risk, etc.) to meet the pre-defined objectives.

# Project Manager (PM)

- A good PM is one who:
  - Is highly organized
  - Is remarkably flexible
  - Has planned and executed a large birthday party (Ira Shoulson, MD), Bar-mitzah/Bat-mitzah or a large wedding
  - Has Anal Retentive tendencies (OCD)..a good thing in this industry
  - Can still see the forest through the trees
  - Has excellent oral and written communication skills
  - Can build strong relationships with all kinds of staff both internal and external to the institution
  - Is not afraid to raise issues early on and work on finding solutions
  - Willing to put in long hours

# Project Manager: multi-center vs. single center study

- The site coordinator may function as the PM for a small study (~1-3 sites), however, for larger multi-center studies typically >5 sites the PM is someone other than a site coordinator
- Be cognizant of potential rater bias when a site coordinator who sees/evaluates subjects also functions as the PM
  - Based on interaction with other site coordinators/investigators (e.g. may change how they rate subjects mid study, may identify AEs based on what other sites are seeing etc.)



# Key Planning Milestones (Timeline)

- Funding
- Drug Supply
- Final Protocol/model ICF
- IND submission/approval – (must wait 30 days before starting the study)
- IRB approvals/subcontracts – (4-6 months to get approvals)
- Orientation mtg – (more than  $\frac{1}{2}$  the sites should have IRB approvals/subcontracts)

# Key Implementation Milestones (Timeline)

- Drug Supply available at the site – (within days of the orientation mtg)
- FPI = First Patient In - (within days of the orientation mtg)
- FPO = First Patient Out - (determined by duration of treatment)
- LPI = Last Patient In – (based on planned enrollment period)
- LPO = Last Patient Out
- Database Lock – (eDC: 2 weeks following LPO; paper: 6- 8 weeks following LPO)
- Analysis Completed – ( 4 weeks post DBL)
- Abstract/Full Manuscript ( abstract 2 weeks following completed analysis; manuscript 3 months post analysis)
- Submission of Regulatory Report (CTR etc.)

# Drug Supply

## ■ Items for consideration:

- Purchase active and matching placebo or have donated?
- How will drug be delivered (e.g. Bulk shipment in drums, unit packaged, all at once, quarterly shipments)
- Secondary packaging/labeling and distribution requirements?
- Blindedness testing: Are active and placebo identical in: color, taste, smell, appearance, shape, size?
- Stability testing: ambient and accelerated: how many lots of each or is it even required?
- Expiry/retest issues?
- Storage requirements: ambient, refrigerated, light sensitive, moisture sensitive?
- Drug Accountability centrally and at site level
- Site SOPs to address all aspects of study drug receipt, dispensing, return etc. (overall accountability)

# Topics

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- Clinical Development vs. Clinical Trial
- Planning
- Implementation
- Find a mentor who has done this
- Find a PM part or full time
- Be active in a network that supports trials
- Seek formal training

# Clinical Trial Methods

August 15-21, 2011  
Vail, Colorado

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- >> Focusing on phase I and phase II clinical trials
- >> Designed for fellows and faculty who are clinical researchers in the neurosciences
- >> Supported by the National Institute of Neurological Disorders and Stroke

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# Coming in 2012

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## Clinical Trials in Neurology: Design, Conduct, and Analysis

Bernard Ravina  
Jeffrey Cummings  
Michael Poole  
Michael McDermott

Cambridge University Press