APEC Preliminary Workshop: Review of Drug Development in Clinical Trials

Session 9 A– Clinical Trial Assessment – Phase III

Susan D‘Amico
Vice President and Global Head
Clinical Quality Assurance
Disclaimer

The information within this presentation is based on the presenter’s expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
Slides Adapted from Presentation by:

Richard C. Meibach, Ph.D.
Scientific Officer, Global Development

ECPM Course: “Learning and Confirming Trials”

http://www.ecpm.ch/ecpm/english/ecpmcourse/session3.html
What is a protocol?

“A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial.”

ICH GCP protocol definition
Enhancing Consistency: Regulatory Protocols

- ICH E6 Section 6 “Guideline for Good Clinical Practice”
- Intended for regulatory submissions
- Unified standard for EU, Japan and US for acceptance of clinical data
  - Developed with consideration of Australia, Canada, the Nordic countries and the WHO GCP’s
Protocol Content – ICH E6

- General information
  - Title, Contacts, ID
- Background
  - Name, Synopsis, Product
- Trial Objectives/Purpose
- Trial Design
  - Exposure, Endpoints, Subject incl/excl
- Treatment of Subjects
  - Dosage regimen
- Efficacy Assessment
  - Statistical plan
- Safety Assessment
  - Statistical plan
- Statistics
  - Sample size
- Access to source documents
- QA/QC
- Ethics
- Data Management
- Financing/Insurance
- Supplements
Traditional Phases of Clinical Trials

- Protocols differed depending on the phase of drug development:
  - **Phase I** studies – first test in humans, usually healthy normal volunteers, objectives are tolerability and pharmacokinetics
  - **Phase II** first patient studies to look at efficacy and safety
  - **Phase III** larger trials to convince regulatory agency of the efficacy and safety of the investigational drug
  - **Phase IV**: post marketing trials to support use of the drug. Less rigorous design may not even be controlled
Issues that Can Occur with Traditional Phased Approach

✓ Most compounds were safe enough to get through phase I – no real screening took place
✓ Did not have any evidence of efficacy until the end of phase II
✓ Many trials had insufficient safety and efficacy at the end of phase II and therefore went into phase III at high risk
✓ Many trials failed at the end of phase III costing hundreds of millions of dollars
✓ Several drugs made it to market only to have to be dropped for safety problems
  ✓ Tasmar – Roche drug for PD
  ✓ Posicor – Roche drug for hypertension
  ✓ Hismanal – Janssen drug for allergic rhinitis
✓ Drugs get approved but we find out we got the dose wrong
Enhanced Approach in Clinical Development with Protocols of Today

- The phased development approach of drugs is NOT a requirement but is a guidance.

- As long as there is sufficient safety data one can proceed faster and hopefully smarter.

- We are in a transition phase to improved protocol designs

- Patients can be studied in phase I and some efficacy can be obtained – often called Ib (includes experimental medicine and translational medicine, proof of concept, seamless designs)

- Phase II can be divided in half – Phase IIa and IIb

- Phase II can be skipped

- Phase II can be combined with Phase III (adaptive designs)
Protocols of the Future

- Wyeth recently announced the best model for the 21st century:
  - Phases I, 2 and 3 will be replaced with Learn and Confirm studies
  - March, 2006 issuance of update
  - Part 1- Report. What has been learned since 2004
  - Part 2 – List. What opportunities are available.
    - Biomarker Development
    - Streamlining clinical trials
    - Biinformatics
    - model based drug development
    - data pooling consortium
Protocol Design

- Due to increasing pressure on our industry, protocols are no longer considered “proprietary and confidential”

- Most regulatory authorities prefer consistency – do not change design unless the MOA dictates a change

- There are many places to go to find protocol designs as more and more clinical trial registries are posted
  - [http://ctr.gsk.co.uk/welcome.asp](http://ctr.gsk.co.uk/welcome.asp)
  - [http://www.ifpma.org/](http://www.ifpma.org/) (not yet operational)
  - [http://www.wyeth.com/ClinicalTrialListings](http://www.wyeth.com/ClinicalTrialListings)

- The FDA has a website for all NDA reviews which usually include details of the protocol [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/)
Objectives of Study

- Avoid general statements (e.g. to study the safety and efficacy of drug x in the treatment of Y)

- Insure that every procedure can be linked back to an objective (e.g. Do not collect blood samples for population pK unless that is one of the objectives)
Objectives (con’t)

- Avoid having too many objectives in a trial
  - Pharmacokinetics
  - Genetics and genomics testing
  - Quality of life
  - Cost effectiveness
  - Testing new rating scales

- Should break down objectives to Primary, Secondary and Exploratory
Study Design

- Most often studies are blinded
  - Single-Blind
  - Double-blind
  - Open label with blinded rater

- If blinded, protocols must state conditions under which blind may be broken
Study Design (con’t)

- In order to prevent selection bias, patients must be randomized to their treatment.

- Comparison of two treatments can be done in parallel or crossover.
  - Preferred design is parallel – uses more patients.
  - If crossover need to insure there is total washout of effect.
In Inclusion and Exclusion Criteria

- In general the amount of inc/exc should decrease as you learn more about the drug and the development has proceeded closer to approval.

- If you have too many restrictions, regulatory agencies may put those restrictions in the label.

- They may also require you to perform a labeling study prior to approval.
Protocol Requirements

- When scheduling tests, should not pose a burden to a patient (ie keeping them in the doctors office for five hours)

- The number of tests should decrease as the drug moves to the next phase (e.g. the drug has already been submitted to health authorities for approval. The drug has no CV and liver toxicities. You start a 6 month phase IIIb trial and have monthly ECG’s and weekly laboratory tests. Why?
Choosing a Dose

How do we choose the initial dose in human?

- Used to be rather arbitrary
  - Some picked 1/10 the expected efficacious dose
  - Some picked 1/3 the dose of animal tox
  - Some picked 1/10 the mouse LD_{10} dose
- Today we use a formula developed by the FDA
  - Take the highest dose in which there was no AE’s in an animal tox study = NOAEL
  - Convert this to the Human Equivalent Dose (HED) using a standard formula based on body surface area
  - Start at 1/10^{th} the HED
Protocol Amendments

- True or False?
  - Any change to a protocol is called an amendment
Protocol Amendments

- False

  - An amendment is any change to a protocol once it has been submitted to an IRB/Ethics Committee or Health Authority for approval
Amendments

- Amending a protocol is necessary at times *however*
  - It can delay timelines
  - It increases workload
  - It increases development costs
  - It decreases investigator satisfaction
**Amendments**

When does a protocol get amended?

- A protocol can be changed at any time
- When a change is made BEFORE it has been reviewed by a regulatory authority or an IRB/Ethics Committee for approval purposes it is considered a revision and not an amendment
- Revisions are not tracked – no histories need to be kept
Amendments

- When an amendment is necessary – there needs to be an audit trail. We need to know what the original version looked like.

- Therefore one can change the body of the protocol as long as there is a log attached of the actual changes.

- Although a protocol can be changed for any reason, it should never be changed to turn a negative trial into a positive trial (e.g. increasing sample size is dangerous without appropriate pre defined guidance).
Summary

- Clinical trial protocols vary depending on the phase of development of the new medicine.

- There are ICH guidelines on the structure of protocols.

- One should use protocol designs already approved by regulatory authorities modified for your specific drug.

- All of the safety information on the drug must be in a separate Investigator Brochure.

- After IRB/EC/HA approval any changes need to be documented and tracked.
References

- Fundamentals of Clinical Trials, Friedman, Furberg and DeMets 1998, Springer-Verlag, New York
- Understanding, Evaluating and Implementing Clinical Protocols 1999 Barnett International Clinical Training Group, Media PA
- New Drug Development: A regulatory overview, Mark Mathieu, 2005 Parexel, Waltham, MA
- Clinical Trial Registries
  http://www.campbellalliance.com/articles/Final_Clinical_Trial_Registries_3-23-05.pdf#search='clinical%20trial%20registries'
References (con’t)

- Critical path initiative
  - //www.fda.gov/oc/initiatives/criticalpath

- ICH E6 Good Clinical Practice Guidance, April, 1996
Thank You
for your attention!

Questions?