Asking a good early phase clinical trial question

NINDS CLINICAL TRIALS METHODOLOGY COURSE 2019
Acknowledgments

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- Funding from NINDS - PI of clinical trials methodology course
  - Funded co-investigator on NETT/SIREN-CCC and SHINE trial
- NIH-NIDCD (cluster RCT studying dizziness intervention)
- NIH-NIMHD - PI of trial of hypertension
  - Co-investigator to improve stroke care in Flint
- NIH-NHLBI (co-investigator in cardiac arrest expedited transport/ECMO trial)
- AHRQ (dizziness self treatment)
- Massey Foundation (studying pupillary response in TBI)
Objectives

► Consider purpose of clinical trials
► Consider goals of clinical trials
► Understand potential output of clinical trials
Slides / work derived from various sources

- Some slides from recent presentation about a new clinical trial called ICECAP: https://youtu.be/eU4g6upAQo0
- Prior webinars – find at webinar tab at http://neurotrials.training
- 2014 Bill Barsan – Asking a good clinical trial question https://youtu.be/9MQHmqYRaOQ
- Good to review: Pilot and Feasibility Studies – Dr. Thabane https://youtu.be/bljPT9whkQo
Questions?

- I will pause at each section header (looks like the picture at right)
- Type them in as comments and I will try to address the ones I see as I go along
Part One

SCOPE OF PROBLEM
Why Clinical Trials Stink
Why Clinical Trials Stink

ANALOGY*: Clinical Trial = Diagnostic Test

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<tr>
<th>Looking For</th>
<th>Clinical Trial</th>
<th>Diagnostic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Treatment</td>
<td>1 – Type II Error (Beta)</td>
<td>“Power”</td>
</tr>
<tr>
<td>1 - Type II Error (Beta)</td>
<td>Sensitivity OR True Positive Rate</td>
<td></td>
</tr>
<tr>
<td>Type I Error (Alpha)</td>
<td>Significance Level</td>
<td>1- Specificity OR FALSE Positive Rate</td>
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</table>

*Note: My analogy does not stink

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Clinical Trials are Models with Tons of Guesses Assumptions

Dose from animal models is close
No heterogeneity of effect
Subgroups respond equally
Some subgroups excluded
Effect size to create “reasonable” sample size
“Noise” in outcomes can be understood and overcome
Duration of treatment practical

LESSON: Make many compromises to reduce number of parameters to make model “solvable”
Therapeutic Response Surface

Clin Pharmacol Ther 1997;61:275-91
Part Two

PROGRESSION THROUGH PHASES

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Objectives

► Describe how to ask a clinical trial question
► Understand potential pitfalls
► Describe one motivational example
Development of an intervention
Part Three

PROGRESSION THROUGH PHASES
Crafting a good clinical trial question

► Generally – you should have ONE main question
  ► Is X better than Y
  ► Does X improve a patient oriented outcome compared to Y, when administered to this population, for this long, at this dose
Can the question be even better?

- In phase II: What dose, schedule, and population would hold the most promise for determining that treatment X can be proven to be better than treatment Y in a phase III trial of size N

- Either you are asking a really GOOD question or you are asking too many questions at once
What are the risks

- FDA / academia worries about
  - Falsely declaring an ineffective drug efficacious

- Academia (should) worry about
  - Falsely declaring an effective treatment neutral because something was wrong in the clinical trial
    - Population
    - Dose
    - Schedule
What is an Early Phase Trial?

- General concept: Learn versus confirm
- Learn (e.g., phase I, phase II)
  - Greater flexibility and number of questions/goals
  - Willingness to tolerate higher error rates and sources of bias
  - Not just underpowered confirmatory trials
- Confirm (e.g., phase III)
  - Rigid control of error rates (i.e., type I rate and power)
  - Prespecification and single primary question/outcome
  - Setting for the traditional 1:1 randomized RCT
Early Phase Question: 1

- Can the drug be tolerated?
  - Traditional dose-escalation question
  - Healthy versus diseased population
  - Is the maximum tolerated dose (MTD) of clinical interest
  - Pharmacokinetics versus pharmacodynamics

- **Trial Designs:**
  - 3+3 (historical interest)
  - Continual reassessment method (CRM)

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Part Three

(SOME) GOOD QUESTIONS FOR TRIALS
Early Phase Question: 2

- Can we establish “proof of concept”?
  - Addresses underlying assumptions regarding proposed mechanism of action (e.g., does the drug bind the target receptor, does the drug pass the blood-brain barrier)
  - Assumption is that treatment strategy will not work without this criterion being met (i.e., necessary but not sufficient for success)
  - Trial design: dose ranging/biomarker or assay
Early Phase Question 3:

- What dose(s)* should be investigated further?
  - Potentially useful doses may span a range of several logs
  - Dose selection often requires balance of efficacy and toxicity
  - Common mistake to narrow the dose range under consideration too early
  - **Trial design**: Dose finding trials with assessment of efficacy and toxicity (e.g., adaptive dose finding trial)
  - Could consider intensity of intervention, device settings, schedule (how often) – both for drug, device, behavioral or other non-pharmacologic interventions

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Early Phase Question 4:

- What outcome(s) should be measured?
  - Consider likelihood of effect on an outcome versus clinical importance (patient centered)
  - Consider practical issues, timing of follow up and difficulty in assessment
  - Reliability and prior validation or use of outcome measures
  - Can consider multiple outcomes, but with risk of false positive result due to “cherry picking”
  - **Trial design**: Intervention/multiple outcomes
Early Phase Question 5:

- What disease state(s) should be studied?
  - Consider availability of subjects, confounding factors and treatments, and established outcome measures
  - Common to run multiple phase II trials of the same agent in different diseases
  - **Trial design:** “Indication finding trial” with multiple diseases enrolled simultaneously to leverage investment in sites and personnel (e.g., using an integrated statistical approach)
Early Phase Question 6:

What population should be enrolled?

- Narrow population:
  - Less variability and easier to interpret results
  - Difficult to enroll required sample size and less clinical relevance

- Broad population
  - Increased variability, confounding factors
  - Concerns regarding heterogeneity of the treatment effect (HTE) and low power to detect HTE

To inform the design of a confirm phase trial, you need to enroll a “confirm-phase” population.
Early Phase Question 7:

- How should a confirmatory study be designed, implemented, and analyzed?
  - Learn-phase trials should be conducted similarly to confirm-phase trials if they are to inform confirm-phase trial design and conduct
  - Same population, treatments, and outcomes
  - Adequate sample size to answer the key questions needed to design confirmatory trial
Early Phase Question 8:

► Should a confirmatory study be conducted at all?
  ► We should only run confirmatory trials that have a substantial chance of showing benefit
  ► **Key concept**: predictive power—the probability of a positive confirmatory trial, considering all the remaining uncertainties
  ► Possible counter-example: trials of treatments to prevent Alzheimer's disease
Part Four

WRAP UP
At this time – check out CONSORT extensions!

Finding the Appropriate Extension

The table below lists the current official extensions of the CONSORT statement. You can click on each extension to learn more or to explore that extension in the checklist viewer application.

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<td>Within Person Trials</td>
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Conclusions

- Early phase clinical trials are hard
- Getting the question right is crucial
- It can be challenging to prioritize