What We Learned Running Investigator Initiated Trials

James D. Lewis, MD, MSCE
Division of Gastroenterology
Center for Clinical Epidemiology & Biostatistics
University of Pennsylvania

Hans Herfarth, MD, PhD
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina
Your Own Trial vs. Other’s
Investigator Initiated Trials

- Get formal training in research methods
- Understand the science behind the hypothesis
- Familiarize yourself with traditional trial designs
- Create an advisory group
- Start small
  - Participate in other’s trials first
  - Single center pilot studies
# Pitfalls of Clinical Research Grants

**Observational**
- Study question
- Residual confounding
- Selection bias
- Misclassification bias (particularly if retrospective)

**Clinical trials**
- Study question
- Choice of outcomes
- Feasibility
  - sample size
  - blinding
- Investigator’s resources and experience
# What is a Good Clinical Research Question

## FINER Criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feasible</strong></td>
<td>Adequate number of subjects, Adequate technical expertise, Affordable in time and money, Manageable in scope</td>
</tr>
<tr>
<td><strong>Interesting</strong></td>
<td>Investigators, peers and community are interested in the outcome of the study</td>
</tr>
<tr>
<td><strong>Novel</strong></td>
<td>New finding or confirms, refutes or extends previous findings</td>
</tr>
<tr>
<td><strong>Ethical</strong></td>
<td>Will be approved by institutional review boards and FDA (if IND is needed)</td>
</tr>
<tr>
<td><strong>Relevant</strong></td>
<td>To scientific knowledge, To clinical and health policy, To future research</td>
</tr>
</tbody>
</table>
## Planning the Outline of a Trial

### PICOT criteria

<table>
<thead>
<tr>
<th>Specification</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>What specific patient population is targeted?</td>
</tr>
<tr>
<td>Intervention</td>
<td>What is the investigational intervention?</td>
</tr>
<tr>
<td>Comparison group</td>
<td>What is the correct comparison group for the intervention?</td>
</tr>
<tr>
<td>Outcome</td>
<td>What is the intended aim/outcome of the study?</td>
</tr>
<tr>
<td>Time</td>
<td>What is the appropriate time to assess the outcome?</td>
</tr>
</tbody>
</table>

*Important: Keep it simple! Focus on 1 question and 1 answer! “Wouldn’t it be nice to also know” .... adds complexity and raises the risk that the trial looses its focus.*
Who Is Going To Pay for This?

- NIH
  - Large trials – U01
  - Small to medium – R01 ($500K/yr cap)
- PCORI
  - If in their focus areas
  - If they still exist
- Foundations – pilot studies
- Industry – If it meets their goals
Why to Seek Co-Sponsorship

- NIH budget may not be enough
- NIH does not like to buy medications
  - Negotiate for drug and placebo
- If using placebo without co-sponsorship, increases work and expenses for investigator to establish the placebo and blinded medication
  - Manufacturing
  - Smell, taste, etc.
  - Most manufacturers have this
- Manufacturer co-sponsor may do FDA reporting for you
“Wow! We got the grant!”
Steering Committee

Make up of Steering Committee

• Include participants with experiences conducting investigator initiated trials
• Include PI from 3-4 sites

Tasks:

• Constructive critique of trial protocol
• Help in establishing essential trial infrastructure
• Needed for discussions of exemptions in inclusion and exclusion criteria during the trial
• Problem solving (e.g. the QT-elongation with ondansentron in MERIT-UC)
Need for Publication rules

- Establish the rules before you start the trial and make it accessible for all participants
- Reward high enrollers into the trial with Co-authorships
- Define the roles for authorship for essential participants e.g. databank
- Example authorship rules at www.CCFACRA.org
Resources

Pharma Sponsored

• Space
  – Clinical
  – Administrative
  – Storage

• Personnel
  – Regulatory
  – Coordinator

Investigator Sponsored

• Space
  – Clinical
  – Administrative
  – Storage

• Personnel
  – Project management
  – Regulatory (IND)
  – Monitoring
  – Statistical
  – Data management
Special Resources

• Investigational pharmacy
  – Create placebo or blinding
  – Packaging and distribution of drug
  – Medication destruction

• Data management
  – Substantially greater requirements for
    • Multicenter study
    • IND studies
Clinical Trials with Investigational Drugs

- Be sure you find the right placebo for your drug
  
  Methotrexate: Infuvit® Adult diluted with sodium chloride to match the yellow color of the MTX
  
  Rosiglitazone: manufacturer provided same placebo they used in RCT

- Study drugs often have to be shipped across state borders, the drug shipments are subject to the legislation of the receiving state.
  
  - IDS requires licensure for each state to which it will need to ship drug.
Placebo Problems: Do We Always Need to be Blinded

- Comparative effectiveness trials as which drug works better in routine clinical practice
  - With equipoise, physician and patient should not have a preference for which drug to use (other than cost)
  - Random selection of treatment without blinding could answer comparative effectiveness questions
Things to Consider if Using Open Label Design

• Will drop outs differ by treatment given knowledge of assigned treatment
  – Equipoise is critical

• Will assessment of outcomes differ given knowledge of assigned treatment
  – Open label trials can be single blinded
  – Using analytes (e.g. CRP or calprotectin) reduces risk of bias in open labeled trials
The Budget Issue

- Contract and budget negotiations take always longer

- Calculate 6-8 months for budget and contract negotiations with universities

- MERIT-UC: Despite pre-negotiations in the year before MERIT-UC started, at start of the study only 6 sites were ready (after 9 months) and it took another 12 months until all sites were ready to enroll.

- Make a detailed budget, which is easier to negotiate.

- MERIT-UC: Budget planning in 2008, need for updating reimbursement in 2014
## Need for Detailed Budget

<table>
<thead>
<tr>
<th></th>
<th>Screening Period</th>
<th>Induction Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening, Week</td>
<td>Week</td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mayo score</td>
<td>$100</td>
<td></td>
</tr>
<tr>
<td>Partial Mayo Score 📷</td>
<td></td>
<td>$50</td>
</tr>
<tr>
<td>Medical History</td>
<td>$225</td>
<td>$50</td>
</tr>
<tr>
<td>AE query</td>
<td></td>
<td>$50</td>
</tr>
<tr>
<td>Concomitant meds</td>
<td>$100</td>
<td>$50</td>
</tr>
<tr>
<td>Physical Exam</td>
<td>$225</td>
<td>$225</td>
</tr>
<tr>
<td>Coordinating Lab and other Tests</td>
<td>$50</td>
<td>$225</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td></td>
<td>$600</td>
</tr>
<tr>
<td>Chest-xray</td>
<td></td>
<td>$100</td>
</tr>
<tr>
<td>EKG (if needed in the context of odanetron)</td>
<td></td>
<td>$100</td>
</tr>
<tr>
<td>Total</td>
<td>$700</td>
<td>$1,250</td>
</tr>
<tr>
<td>Patient reimbursement</td>
<td>$50</td>
<td>$150</td>
</tr>
<tr>
<td>Total + Patient Reimbursement</td>
<td>$750</td>
<td>$1,400</td>
</tr>
<tr>
<td>Total direct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient care (no F&amp;A)</td>
<td>1,400.00</td>
<td></td>
</tr>
<tr>
<td>Non-patient care (for F&amp;A)</td>
<td>6,000.00</td>
<td></td>
</tr>
</tbody>
</table>
## Costs for Procedures, Labs and Personnel...

<table>
<thead>
<tr>
<th>Procedure / Fees</th>
<th>Mean</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper-endoscopy + biopsy</td>
<td>2682</td>
<td>5500</td>
</tr>
<tr>
<td>Colonoscopy + biopsy</td>
<td>3235</td>
<td>6000</td>
</tr>
<tr>
<td>Sigmoidoscopy + biopsy</td>
<td>1983</td>
<td>3851</td>
</tr>
<tr>
<td>MR-Enterography</td>
<td>2312</td>
<td>3851</td>
</tr>
<tr>
<td>CT-Enterography</td>
<td>1745</td>
<td>6032</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>187</td>
<td>491</td>
</tr>
<tr>
<td>Coordinator / hr</td>
<td>94</td>
<td>250</td>
</tr>
<tr>
<td>PI / hr</td>
<td>177</td>
<td>300</td>
</tr>
<tr>
<td>Clinic space / hr</td>
<td>119</td>
<td>200</td>
</tr>
<tr>
<td>Pharmacy start up</td>
<td>2037</td>
<td>2893</td>
</tr>
<tr>
<td>Site start up</td>
<td>4698</td>
<td>8000</td>
</tr>
</tbody>
</table>

n=15 academic IBD centers, questionnaire answered in 2014
Budget Strategies

• Same fixed price per completed subject for all sites
  – Otherwise risk that expensive sited enroll more than less expensive sites → budget shortfall

• Prorated for early discontinuation

• Limit the number of screen failures that will be reimbursed per randomized participant
Turnover at Sites and the Need for Monitoring

MERIT-UC:
• 4 years of the recruitment period, 42 sites
  - turnover of >140 coordinators and 6 principal site investigators.

Monitoring is necessary to ensure the quality of data, the correct conduct of the trial and the completeness of study relevant documents at sites.

• can be conducted remotely for many document related requirements
• only in person visit can find discrepancies between real and documented data
Collaborator Interest Curve

- Grant Proposal
- Start-up
- Mid-study Blues
- Analysis phase
<table>
<thead>
<tr>
<th>Author or study acronym</th>
<th>Recruitment period (months)</th>
<th>Disease</th>
<th>Design</th>
<th>Drug</th>
<th>Patients enrolled</th>
<th>Number of study sites</th>
<th>Location of sites</th>
<th>Patients / site / year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis</td>
<td>2002-2006 (39)</td>
<td>UC</td>
<td>Randomized, double blind</td>
<td>Rosiglitazone vs placebo</td>
<td>105</td>
<td>15</td>
<td>U.S.</td>
<td>2.2</td>
</tr>
<tr>
<td>Osterman</td>
<td>2008-2012 (41)</td>
<td>UC</td>
<td>Open-label, randomized</td>
<td>Increase 5-ASA vs stable 5-ASA in patients with increased fecal calprotectin</td>
<td>119</td>
<td>14</td>
<td>U.S.</td>
<td>2.5</td>
</tr>
<tr>
<td>Carbonnel METEOR</td>
<td>2007-2013 (72)</td>
<td>UC</td>
<td>Randomized, double blind</td>
<td>Methotrexate vs placebo</td>
<td>111</td>
<td>26</td>
<td>France, Austria, Belgium, Italy Finland, Greece.</td>
<td>0.7</td>
</tr>
<tr>
<td>MERIT-UC</td>
<td>2012-2016 (52)</td>
<td>UC</td>
<td>Randomized, double blind</td>
<td>Methotrexate vs placebo</td>
<td>179</td>
<td>42</td>
<td>U.S.</td>
<td>1.0</td>
</tr>
<tr>
<td>Dassopoulos</td>
<td>2005-2007 (29)</td>
<td>CD</td>
<td>Randomized, double blind</td>
<td>weight-based vs. individualized azathioprine dosing</td>
<td>50</td>
<td>12</td>
<td>U.S., Canada</td>
<td>1.7*</td>
</tr>
<tr>
<td>Cosnes</td>
<td>2005-2010 (66)</td>
<td>CD</td>
<td>Open-label, randomized</td>
<td>Azathioprine vs conventional management</td>
<td>132</td>
<td>24</td>
<td>France</td>
<td>1.0</td>
</tr>
<tr>
<td>Panes</td>
<td>2006-2009 (42)</td>
<td>CD</td>
<td>Randomized, double blind</td>
<td>Azathioprine vs placebo</td>
<td>131</td>
<td>31</td>
<td>Spain</td>
<td>1.2*</td>
</tr>
</tbody>
</table>
Problem Competing Industry Studies - Industry sponsored interventional phase 2 and phase 3 studies*

Conceptualization of MERIT-UC

Start recruitment in MERIT-UC

* as listed on ClinicalTrials.gov.
How to Keep the “Hype”

• Newsletter
• Email to coordinators/investigators
• Phone calls with coordinators
• Personal contact during meeting with PI

Probably a combination of all works best, but regular phone calls with coordinators really help to keep you informed about problems at sites.
Encouragement

- Frequent (positive) updates
  - Recruitment statistics
  - Related publications
- Facilitation of activities
- Intermediate rewards
  - Publications from the work
  - Reimbursement for activities
- Peer pressure
  - Recruitment statistics