Pragmatic Clinical Trials
Part I
Christopher B. Granger, MD
Professor of Medicine, Division of Cardiology
John P. Vavalle, MD
Fellow, Cardiovascular Disease
Duke University Medical Center

Pragmatic Clinical Trials
Objectives
• Module I: Understand the importance of large randomized clinical trials and the current barriers that are limiting their conduct
  – Large randomized clinical trials form the foundation of evidence-based medicine
  – The fact that most of our guidelines are based on “lower levels” of evidence underscores the need to improve our clinical trial productivity
  – Limitations with current large clinical trials

Pragmatic Clinical Trials
Objectives
• Module II: Describe potential solutions to improve the conduct and capacity of pragmatic trials
  – Proposed strategies to overcome current limitations and expand capacity for pragmatic clinical trials
  – Provide examples of successful pragmatic trials
The Cycle of Clinical Therapeutics

- Concept
- Clinical Trials
- Outcomes
- Guidelines
- Education and Feedback
- Performance Indicators
- Performance
- Systems and Information technology

Therapeutic Principles

- Treatment effects usually modest
- Subgroup analyses are unreliable
- Unintended targets common
- Long-term vs. short-term effects may differ
- Combinations are unpredictable
- Class effect may not be valid
- Most treatments produce a mixture of benefits and risks

Sample Size

<table>
<thead>
<tr>
<th>Deaths</th>
<th>Patients Randomized (Risk = 10%)</th>
<th>Chance of Type II Error*</th>
<th>Comments on Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-50</td>
<td>&lt; 500</td>
<td>&gt; 0.9</td>
<td>Utterly inadequate</td>
</tr>
<tr>
<td>50-150</td>
<td>1000</td>
<td>0.7-0.9</td>
<td>Probably inadequate</td>
</tr>
<tr>
<td>150-350</td>
<td>3000</td>
<td>0.3-0.7</td>
<td>Possibly inadequate</td>
</tr>
<tr>
<td>350-650</td>
<td>6000</td>
<td>0.1-0.3</td>
<td>Probably adequate</td>
</tr>
<tr>
<td>&gt; 650</td>
<td>10000</td>
<td>&lt; 0.1</td>
<td>Adequate</td>
</tr>
</tbody>
</table>

*Probability of failing to achieve p < .01 if risk reduction = 25%

— Yusuf, Prog in CV Disease, 1985
Therapeutic Principles

• Applying the results of clinical trials is beneficial

Califf and DeMets Circ 2002

Decline in CV-Mortality

Attribution of Treatment / RF-Modification

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Decrease in Deaths by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial (acute) treatment of MI / UAP</td>
<td>10%</td>
</tr>
<tr>
<td>Secondary prevention after MI / UAP</td>
<td>11%</td>
</tr>
<tr>
<td>Treatment of heart failure</td>
<td>9%</td>
</tr>
<tr>
<td>Revasc for chronic angina</td>
<td>5%</td>
</tr>
<tr>
<td>Other therapies</td>
<td>12%</td>
</tr>
<tr>
<td>Reduction in cholesterol</td>
<td>24%</td>
</tr>
<tr>
<td>Reduction in BP</td>
<td>20%</td>
</tr>
<tr>
<td>Reduction in smoking</td>
<td>12%</td>
</tr>
<tr>
<td>Reduction in physical inactivity</td>
<td>5%</td>
</tr>
</tbody>
</table>

Therapy 47%

RF-Mod. 44%


Temporal Trends in Patients with STEMI

GRACE 1999-2005 (n=17,000)

Pharmacological Management - Class 1A Recommended Medications
In-Hospital Outcomes with STEMI: GRACE

CAST
1st DSMB: blinded, p<.05
2nd: same trend: 56 vs 22 deaths
Moricizine continued for 1 y

Understanding Treatment Effects
Observational Studies vs Clinical Trial Evidence

<table>
<thead>
<tr>
<th>Observation</th>
<th>Trial Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen for 2o prev</td>
<td>50% ↓ MI ↑ MI first yr</td>
</tr>
<tr>
<td>Vitamin E for 2o prev</td>
<td>50% ↓ MI 15% ↑ CHF</td>
</tr>
<tr>
<td>Folate/B6 for 2o prev</td>
<td>50% ↓ MI 0-20% ↑ death/MI</td>
</tr>
<tr>
<td>Increase Hgb in ESRD</td>
<td>50% ↓ death 34% ↑ D/MI/HF/stroke</td>
</tr>
<tr>
<td>PPI for pts on clopidogrel</td>
<td>25-50% ↑ No effect</td>
</tr>
<tr>
<td></td>
<td>CV events</td>
</tr>
</tbody>
</table>
Current State of Clinical Trials

• Large randomized trials are necessary to determine which treatments work
• But, complexity and costs are increasing
• And, layers of regulatory approval, challenges in funding, and contracting complexity are growing

Yusuf S et al. Clinical Trials 2008

Current State of Clinical Trials

• “For a scientific method that is at the heart of evidence-based medicine, there is no good evidence that the layers of complexity, approvals, processes, and laws to protect subjects have actually achieved their purpose.
• “What is clear is that such processes are extremely expensive and delay studies.”

Randomized Studies - RCT

Strengths

➢ Adequately designed trials with sufficient power are, by far, the most reliable tool to estimate the effects of treatments on clinical outcomes
➢ Since the main determinant of outcome is baseline risk (much of which is not able to be measured), randomization to provide equal groups at baseline is the key to providing an unbiased estimate of effect
Randomized Studies - RCT

**Weaknesses**
- Expensive
- Long time to plan and complete
- Selected populations may not be representative
- Selected study centers may not be representative
- Surrogate outcomes are often used that may not reflect impact on clinical outcomes (late lumen loss, TLR vs. Angina, MI)
- When sponsored by industry, only studies with economic interest will be performed

Registry studies

**Strengths**
- Unselected populations – generalizable
- Typical and representative care setting
- Can measure how treatments are used in actual practice and how guidelines are being implemented
- Clinically important endpoints – hard endpoints possible
- Large cohorts of consecutive patients provides large numbers of events to measure small outcome differences, even for infrequent events
- Less expensive

Registry studies

**Weaknesses**
- Confounding factors impossible to adjust for despite complex statistical models
- Data quality not as good
- Missing variables
- Advanced statistics with multivariable analyses - difficult to understand
Rank of reliability of evidence source to define modest treatment effects

1. Large pragmatic randomized trials
2. Meta-analyses of randomized trials
3. Registry studies
4. Meta-analyses of registry and randomized studies
5. Meta-analyses of registry studies

Developing the Best Evidence

A new therapy is best evaluated via randomized controlled trials (RCT)…..provided such trials are:
   – Adequately sized
   – In representative patient populations
   – With typical providers and care setting
   – With meaningful outcome endpoints
**Progress in clinical trials**

**1950-1990**: False POSITIVES increasingly well controlled by randomisation

**1990-2000**: False NEGATIVES increasingly well controlled by “mega-trials” and “meta-analyses”

**2000 & beyond**: Increasing regulation (without appropriate interpretation) may prevent many important public health questions from being answered reliably

---

**Unfortunately, a small proportion of evidence comes from RCTs**

---

**Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines**

---

**Level of Evidence A**

*Current Guidelines*  

*Guidelines expressing Level of Evidence*

---

Tricoci P et al. JAMA 2009;301(8):831-841
ACC/AHA Guidelines

• “Recommendations with level of evidence A are mostly concentrated in class I, but only 245 of 1305 class I recommendations have level of evidence A (median, 19%).”

• “Recommendations issued in current ACC/AHA clinical practice guidelines are largely developed from lower levels of evidence or expert opinion.”

• “The proportion of recommendations for which there is no conclusive evidence is also growing.”

Tricoci P et al. JAMA 2009;301(8):831-841

RCT Have Limitations

• Practical issues and $ often limit trial size
• Differences between trial and community
  — In practice patients: older, more comorbid disease
  — Provider/setting: Expert vs usual practice
• Surrogates often used (e.g., BP lowering, effect on LDL) and unclear if these translate into patient outcome.
• Certain questions not easily subject to RCT
  — Unethical, impractical, or clinical question doesn’t translate well to protocol evaluation

Problem # 1:
National Heterogeneity
National Regulatory Barriers

• Need for multiple submissions
• Divergent decisions/requests
• Differences in adverse event reporting requirements
• Different requirements for privacy protection and collection/use of DNA

Are national health authorities becoming more activist?

• Used to focus almost exclusively on ethics implementation, informed consent, etc
• Now requesting protocol design changes
• Disallowing global trials to proceed in country (Hungary: CURRENT, an ongoing AF trial)
• Requesting SAE reporting beyond that agreed to with FDA (France)
## Regional Differences: Regulatory Submission to Approval

<table>
<thead>
<tr>
<th></th>
<th>Unapproved drugs</th>
<th>Approved drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>40 days</td>
<td>30 days</td>
</tr>
<tr>
<td>Japan</td>
<td>15 days*</td>
<td>26 days*</td>
</tr>
<tr>
<td>UK</td>
<td>27 days</td>
<td>39 days</td>
</tr>
<tr>
<td>Germany</td>
<td>90 days</td>
<td>90 days</td>
</tr>
<tr>
<td>France</td>
<td>95 days</td>
<td>60 days</td>
</tr>
<tr>
<td>India</td>
<td>39 days</td>
<td>60 days</td>
</tr>
<tr>
<td>Argentina</td>
<td>80 days</td>
<td>6 months</td>
</tr>
<tr>
<td>China</td>
<td>8 months</td>
<td>11 months*</td>
</tr>
</tbody>
</table>

## Regional Differences: Reg Approval to First Patient

<table>
<thead>
<tr>
<th></th>
<th>Unapproved drugs</th>
<th>Approved drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>10 d</td>
<td>2 d</td>
</tr>
<tr>
<td>Japan</td>
<td>3 mo</td>
<td>NA</td>
</tr>
<tr>
<td>UK</td>
<td>7 mo</td>
<td>30 d+</td>
</tr>
<tr>
<td>Germany</td>
<td>60 d</td>
<td>60 d+</td>
</tr>
<tr>
<td>France</td>
<td>5 mo</td>
<td>30 d</td>
</tr>
<tr>
<td>India</td>
<td>4 mo</td>
<td>40 d</td>
</tr>
<tr>
<td>Argentina</td>
<td>5 mo</td>
<td>NA</td>
</tr>
<tr>
<td>China</td>
<td>5 mo</td>
<td>NA</td>
</tr>
</tbody>
</table>

## Summary of Regional Differences: Regulatory Submission to First Patient

<table>
<thead>
<tr>
<th></th>
<th>Unapproved Drugs</th>
<th>Approved Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>1-5 mo</td>
<td>1-3 mo</td>
</tr>
<tr>
<td>Japan</td>
<td>1-4 mo</td>
<td>---</td>
</tr>
<tr>
<td>Great Britain</td>
<td>2-3 mo</td>
<td>3-7 mo</td>
</tr>
<tr>
<td>Germany</td>
<td>5 mo</td>
<td>4-5 mo</td>
</tr>
<tr>
<td>France</td>
<td>3-8 mo</td>
<td>3-4 mo</td>
</tr>
<tr>
<td>India</td>
<td>3-5 mo</td>
<td>5-6 mo</td>
</tr>
<tr>
<td>Argentina</td>
<td>6-8 mo</td>
<td>5 mo</td>
</tr>
<tr>
<td>China</td>
<td>12 mo</td>
<td>12 mo</td>
</tr>
</tbody>
</table>
### Regional Differences: Major Issues

<table>
<thead>
<tr>
<th>Region</th>
<th>What works</th>
<th>What doesn't work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>High enrollment, low cost</td>
<td>Regulatory delays, quality assurance</td>
</tr>
<tr>
<td>N America</td>
<td>Fast regulatory approval</td>
<td>High cost, low enrollment</td>
</tr>
<tr>
<td>Europe</td>
<td>Some countries fast and efficient</td>
<td>Heterogeneity and uncertainty</td>
</tr>
</tbody>
</table>

### Problem # 2: Complexity

- Concept to submission
  - Multiple internal reviews
  - Regulatory pre-submission work
- Submission to national regulatory agencies
  - Often more than 30 countries
- Drug importation issues
- Contract and IRB
- Different types of trials require different regulatory oversight

### Large Trial Organizational Structure

- **Executive Center**
  - Study Chair
  - Study Co-Chair

- **Coordinating Center**
  - International Data Centers
    - International Co-Chair

- **Steering Committee**
  - Chairmen + NCs + RDs + experts in clinical studies

- **DSMB**

- **Events Review Committee**

- **Sponsor**
Administrative Barriers in Clinical Research: Example from Oncology

Table 1. Number of Steps, Individuals, and Signatures Required to Initiate a Phase II Study

<table>
<thead>
<tr>
<th></th>
<th>Community Practice Site</th>
<th>Comprehensive Cancer Center</th>
<th>CALGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of protocol sites</td>
<td>&lt; 40</td>
<td>&gt; 110</td>
<td>&gt; 170</td>
</tr>
<tr>
<td>No. of sites activated</td>
<td>13-27</td>
<td>&lt; 77</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>No. of signatures required</td>
<td>4-12</td>
<td>13-27</td>
<td>&gt; 75</td>
</tr>
<tr>
<td>Decision points</td>
<td>NA</td>
<td>NA</td>
<td>42</td>
</tr>
<tr>
<td>Processing steps</td>
<td>NA</td>
<td>NA</td>
<td>30</td>
</tr>
</tbody>
</table>

*Administrative: CALGB, Center and Locustina Group B; NA, not available; Total days from CALGB executive review to study activation:
  median: 580 days, range: 205-1,248

Sources of Delay

- Trials approved at multiple levels before going to research sites
  - Pharmaceutical company committees
  - Large academic steering committees
  - National funding agencies
  - FDA, EMEA and other national regulatory bodies
- FDA SPA (Special Protocol Assessment) can add delays
- Drug import licenses and customs: more paperwork, cost
- Patient enrollment: local contracts, ethics review, site training
Are Delays Getting Worse?
Two recent ACS and AMI Large Trials (US only)

<table>
<thead>
<tr>
<th>Protocol to:</th>
<th>Year</th>
<th>Overall*</th>
<th>Top 10%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reg Approval</td>
<td>2001-03</td>
<td>133 (93,173)</td>
<td>91 (64,138)</td>
</tr>
<tr>
<td></td>
<td>2004-05</td>
<td>140 (94,196)</td>
<td>129 (91,154)</td>
</tr>
<tr>
<td>1st Patient</td>
<td>2001-03</td>
<td>221 (165,291)</td>
<td>126 (98,210)</td>
</tr>
<tr>
<td></td>
<td>2004-05</td>
<td>241 (169,318)</td>
<td>169 (155,219)</td>
</tr>
<tr>
<td>Drug to 1st Pt</td>
<td>2001-03</td>
<td>50 (26,84)</td>
<td>28 (10,39)</td>
</tr>
<tr>
<td></td>
<td>2004-05</td>
<td>65 (37,106)</td>
<td>42 (22,55)</td>
</tr>
</tbody>
</table>

*Median days (25%,75%)

Problem #3: The industry of conducting clinical trials

- CROs commonly manage multinational regulatory submissions for pharmaceutical company sponsored trials
- CROs have little incentive to simplify processes

Problem #4: Cost

- Costs have become prohibitively expensive.
- Increasing cost is forcing sponsors to look outside of the U.S. for conducting clinical trials
Cost of Start Up per Site  
(Sponsor Costs)

<table>
<thead>
<tr>
<th>Item</th>
<th>Sponsor $$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start Up Grant</td>
<td>$3000+</td>
</tr>
<tr>
<td>Contract</td>
<td>$1000</td>
</tr>
<tr>
<td>Invest. Meetings</td>
<td>$3500</td>
</tr>
<tr>
<td>Training Materials</td>
<td>$300</td>
</tr>
<tr>
<td>Drug/IVRS/Lab</td>
<td>$2000</td>
</tr>
<tr>
<td>Reg Docs etc</td>
<td>$1500</td>
</tr>
<tr>
<td>Site Visit</td>
<td>$3000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>$14,300</strong> (minimum)</td>
</tr>
</tbody>
</table>

Global Costs- CV Megatrial  
(14,000 patients at 300 sites)

- Site Payments $150 M
- Monitoring $90 M
- Data Management + Stats $12 M
- Project/Clinical Leadership $12 M
- IVRS + Drug Distribution $10.8 M
- Analyses and publications $100,000

**Total ~ $350M++**

---

**Ethical and Scientific Implications of the Globalization of Clinical Research**

- Since 2002, the number of FDA investigators outside the US has grown by 15% annually, while the number inside the US has declined by 5.5%.
- One-third of phase 3 trials of the 20 largest US pharmaceutical companies are being conducted solely outside the US.
- For those same firms and studies, a majority of study sites (13,521 of 24,206) are outside the US.

Source: Glickman, SW et al. NEJM 2009
**DCRI Global Enrollment: Selected Trials: 1990-2010**

<table>
<thead>
<tr>
<th>Trial</th>
<th>US/CN</th>
<th>WE</th>
<th>EE</th>
<th>LA</th>
<th>A-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO (41,021)</td>
<td>56%</td>
<td>7%</td>
<td>21%</td>
<td>8%</td>
<td>NA</td>
</tr>
<tr>
<td>GUSTO IIb (12,142)</td>
<td>30%</td>
<td>10%</td>
<td>48%</td>
<td>4%</td>
<td>10%</td>
</tr>
<tr>
<td>GUSTO III (15,060)</td>
<td>32%</td>
<td>13%</td>
<td>37%</td>
<td>1%</td>
<td>11%</td>
</tr>
<tr>
<td>PURSUIT (10,748)</td>
<td>38%</td>
<td>3%</td>
<td>39%</td>
<td>16%</td>
<td>5%</td>
</tr>
<tr>
<td>ASSENT 2 (16,949)</td>
<td>21%</td>
<td>6%</td>
<td>54%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>PARAGON B (5235)</td>
<td>29%</td>
<td>5%</td>
<td>42%</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>VALIANT (14,814)</td>
<td>27%</td>
<td>7%</td>
<td>28%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>SYNERGY (10,027)</td>
<td>56%</td>
<td>16%</td>
<td>10%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>APEX (5745)</td>
<td>31%</td>
<td>6%</td>
<td>31%</td>
<td>22%</td>
<td>NA</td>
</tr>
<tr>
<td>EARLYACS (9492)</td>
<td>24%</td>
<td>7%</td>
<td>50%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>TRACER (12,636)</td>
<td>21%</td>
<td>5%</td>
<td>45%</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>ASCEND (7143)</td>
<td>38%</td>
<td>6.5%</td>
<td>7%</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>IMPROVE-IT (18,143)</td>
<td>32%</td>
<td>6%</td>
<td>40%</td>
<td>9%</td>
<td>25%</td>
</tr>
<tr>
<td>ROCKET-AF (14,269)</td>
<td>13%</td>
<td>5%</td>
<td>14%</td>
<td>38%</td>
<td>14%</td>
</tr>
</tbody>
</table>

**US Clinical Research Strengths**

- Large country with well-developed health care system
- Large numbers of patients with common diseases
- Tradition of academic leadership
- Training programs
- NIH/NHLBI
- US focus of global pharma and device companies
- Global regulatory leadership (FDA)

**US Cardiovascular Clinical Research Weaknesses**

- Research not well integrated into practice; financial pressures in practice (applies both to academic and private settings)
- Workforce shortage (MDs and RNs)
- Training programs largely not focused on training clinical investigators
- Poor research infrastructure
- Litigation society/risk aversion
- Media coverage of research issues such as COI
- Lack of infrastructure (IT) across country (inability to link clinical practice with research)
- Lack of common data standards
- Lack of support for sustaining investigator networks
- Biostatistics shortage
US Cardiovascular Clinical Research

Threats

• US economy and ability to leverage research funds
• Commercial CROs with profit mandate not patient mandate (CROs sell research services, they do not do research)
• Inability to compete with financial demands of clinical practice ("no time for research")
• Lawyers (increasingly complex regulations, contracts, etc)
• Inability to attract/train/retain next generation

US Cardiovascular Clinical Research

Opportunities

• New knowledge on basic discovery side is moving rapidly; need new methods to move through the translational hurdles
• Technology to understand –omics
• Ability to better characterize populations, diseases and predict response to therapies
• Societal need for evidence to guide care and policy
• Keen societal interest in engaging academics in clinical research and education
• IT capable of linking global community; makes collaboration easier than ever
• Retool training programs

Pragmatic Trials

• Goal: stimulate reform and simplification of clinical trials procedures, while enhancing patient safety and autonomy, improving the scientific validity and integrity of trials and making them more affordable.

• In Module II, we will discuss ways to address current limitations and how pragmatic trials can be designed to overcome some of the present barriers
References & Resources