Pragmatic Clinical Trials Part I

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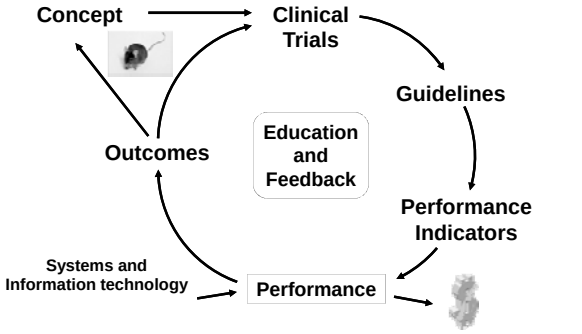
Pragmatic Clinical Trials Objectives

- 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



Califf and DeMets Circ 2002

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

Califf and DeMets Circ 2002

Sample Size

Deaths	Patients Randomized (Risk = 10%)	Chance of Type II Error*	Comments on Sample Size
0-50	< 500	> 0.9	Utterly inadequate
50-150	1000	0.7-0.9	Probably inadequate
150-350	3000	0.3-0.7	Possibly inadequate
350-650	6000	0.1-0.3	Probably adequate
> 650	10000	< 0.1	Adequate

**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

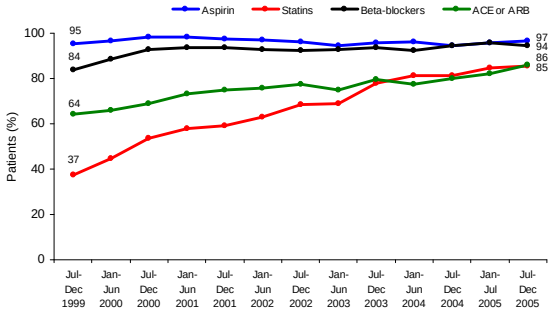
Decline in CV-Mortality

Attribution of Treatment / RF-Modification

Treatment	Decrease in Deaths by	
Initial (acute) treatment of MI / UAP	10%	Therapy 47%
Secondary prevention after MI / UAP	11%	
Treatment of heart failure	9%	
Revasc for chronic angina	5%	
Other therapies	12%	
Reduction in cholesterol	24%	RF-Mod. 44%
Reduction in BP	20%	
Reduction in smoking	12%	
Reduction in physical inactivity	5%	

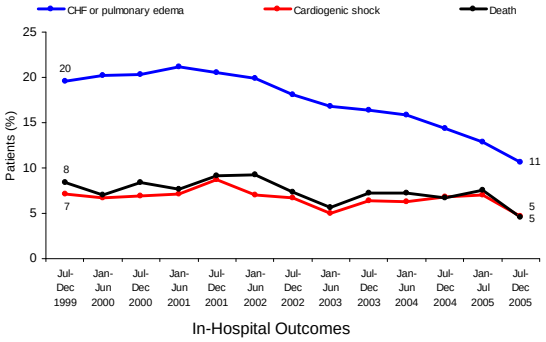
Ford et al, NEJM 2007;356:2388-98

Temporal Trends in Patients with STEMI GRACE 1999-2005 (n≅17,000)



Pharmacological Management - Class 1A Recommended Medications

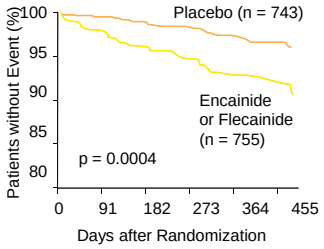
In-Hospital Outcomes with STEMI: GRACE

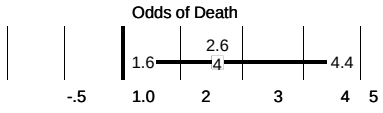


In-Hospital Outcomes

CAST

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





—Echt, NEJM, 1991

Understanding Treatment Effects

Observational Studies vs Clinical Trial Evidence

	Observation	Trial Results
Estrogen for 2° prev	50% ↓ MI	↑ MI first yr
Vitamin E for 2° prev	50% ↓ MI	15 %↑ CHF
Folate/B6 for 2° prev	50% ↓ MI	0-20%↑ death/MI
Increase Hgb in ESRD	50% ↓ death	34%↑ D/MI/HF/stroke
PPI for pts on clopidogrel	25-50% ↑ CV events	No effect

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

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."

Yusuf S et al. Clinical Trials 2008

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

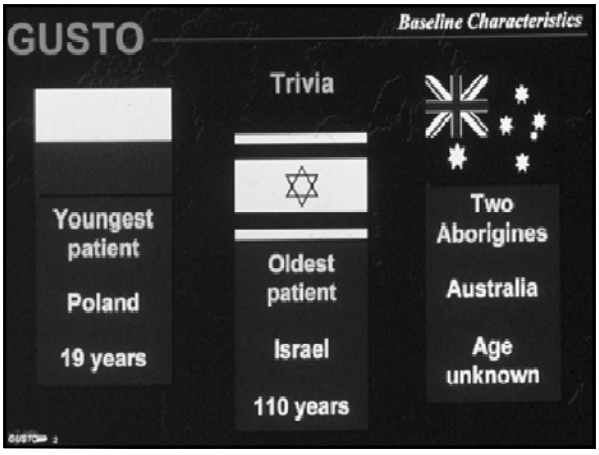
1. Large pragmatic randomized trials
2. Meta-analyses of randomized trials
3. Registry studies
4. Meta-analyses of registry and randomized studies
5. Meta-analyses of registry studies

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

ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 27 topics, including a total of 2196

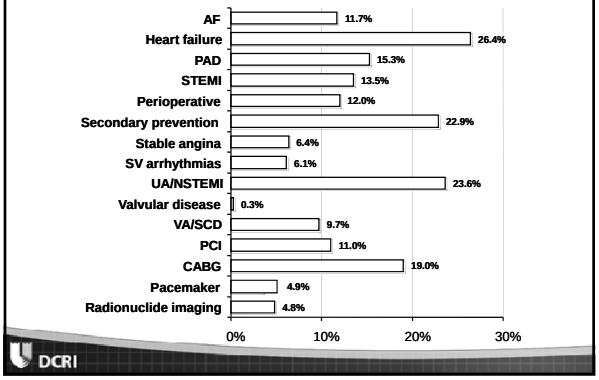
CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions

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

Level of Evidence A

Current Guidelines*

*Guidelines expressing Level of Evidence



DCRI

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

SFDA State Food and Drug Administration,P.R.China

European Medicines Agency

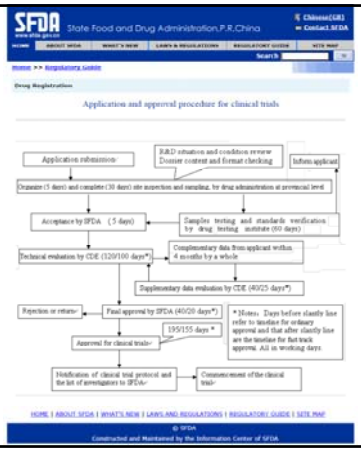
FDA U.S. Food and Drug Administration

Pmda Pharmaceuticals and Medical Devices Agency, Japan

ANMAT

National Health Surveillance Agency ANVISA 10 anos

भारतीय आयुर्विज्ञान अनुसंधान परिषद INDIAN COUNCIL OF MEDICAL RESEARCH CDSCO



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

	Unapproved drugs			Approved drugs	
	AF 2007	ACS 2009	Diab 2009	ACS 2006	ACS 2009
US	40 days	30 days	68 days	30 days	12 months*
Japan	15 days*	26 days*		---	---
UK	27 days	39 days		30 days	30 days
Germany	90 days	90 days		60 days	3 months
France	95 days	60 days		30 days	3 months
India	39 days	60 days	110 days	5 months	4 months
Argentina	80 days	6 months		3 months	3 months
China	8 months	11 months*		10 months	10 months

Regional Differences: Reg Approval to First Patient

	Unapproved drugs			Approved drugs	
	AF 2007	ACS 2009	Diab 2009	ACS 2006	ACS 2009
US	10 d	2 d	92 d	2 mo	NA
Japan	3 mo	NA		---	--
UK	7 mo	30 d+		2 mo	6 mo
Germany	60 d	60 d+		2 mo	1 mo
France	5 mo	30 d		2 mo	1 mo
India	4 mo	40 d	31 d	1 mo	1 mo
Argentina	5 mo	NA		2 mo	2 mo
China	5 mo	NA		3 mo	2 mo

Summary of Regional Differences: Regulatory Submission to First Patient

	Unapproved Drugs	Approved Drugs
US	1-5 mo	1-3 mo
Japan	1-4 mo	---
Great Britain	2-3 mo	3-7 mo
Germany	5 mo	4-5 mo
France	3-8 mo	3-4 mo
India	3-5 mo	5-6 mo
Argentina	6-8 mo	5 mo
China	12 mo	12 mo

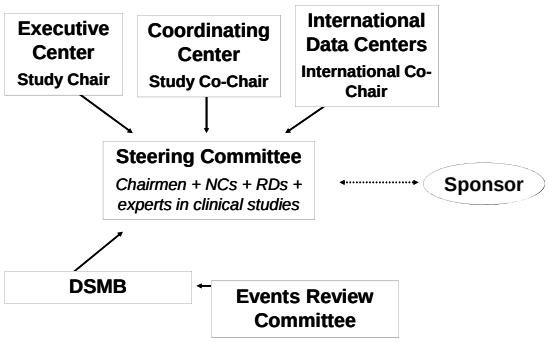
Regional Differences: Major Issues

	What works	What doesn't work
Asia	High enrollment, low cost	Regulatory delays, quality assurance
N America	Fast regulatory approval	High cost, low enrollment
Europe	Some countries fast and efficient	Heterogeneity and uncertainty

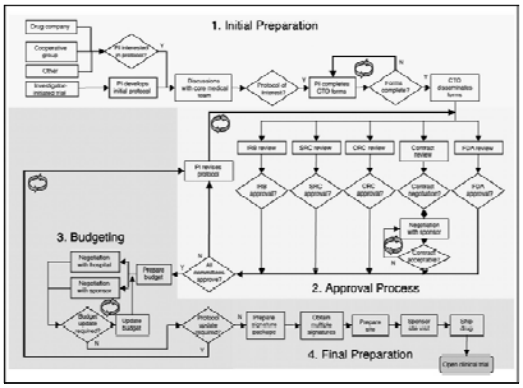
Problem # 2: Complexity

- 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



Process flow map for opening an oncology clinical trial



Dilts, D. M. et al. J Clin Oncol; 24:4545-4552 2006

Administrative Barriers in Clinical Research: Example from Oncology

Table 1. Number of Steps, Individuals, and Signatures Required to Activate a Phase III Study

	Community Practice Site*	Comprehensive Cancer Center*	CALGB
No. of process steps	< 60	> 110	> 370
No. of groups or individuals involved	13-27	< 27	> 30
No. of signatures required	4-12	13-27	> 70
Decision points	NA	NA	42
Processing loops	NA	NA	29

Abbreviations: CALGB, Cancer and Leukemia Group B; NA, not available.
*See Dilts et al.[3]

Total days from CALBG executive review to study activation:
median: 580 days, range: 295-1,248

Dilts, DM et al. Journal of Clinical Oncology Oct. 2006

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)

Protocol to:	Year	Overall*	Top 10%*
Reg Approval	**2001-03**	**133 (93,175)**	**91 (64,138)**
	2004-05	**140 (94,196)**	**129 (91,154)**
1st Patient	**2001-03**	**221 (165,291)**	**126 (98,210)**
	2004-05	**241 (169,318)**	**169 (155,219)**
Drug to 1st Pt	**2001-03**	**50 (26,84)**	**28 (10,39)**
	2004-05	**65 (37,106)**	**42 (22,55)**

***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)

Item	Sponsor $$
Start Up Grant	$3000+
Contract	$1000
Invest. Meetings	$3500
Training Materials	$300
Drug/IVRS/Lab	$2000
Reg Docs etc	$1500
Site Visit	$3000
TOTAL	$14,300 (minimum)

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++

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Ethical and Scientific Implications of the Globalization of Clinical Research

Seth W. Glickman, M.D., M.B.A., John G. McHutchison, M.D., Eric D. Peterson, M.D., M.P.H., Charles B. Cairns, M.D., Robert A. Harrington, M.D., Robert M. Califf, M.D., and Kevin A. Schulman, M.D.

- 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

	US/CN	WE	EE	LA	A-P
GUSTO (41,021)	56%- 7% 21%	8%	NA	7%	
GUSTO IIb (12,142)	30%- 10%	49%	NA	NA	10%
GUSTO III (15,060)	32%- 13%	37%	6%	1%	11%
PURSUIT (10,748)	38%- 3%	39%	16%	5%	NA
ASSENT 2 (16,949)	21%- 6%	54%	5%	4%	8%
PARAGON B (5225)	29%- 5%	42%	11%	4%	9%
VALIANT (14,814)	27%- 7%	28%	30%	6%	3%
SYNERGY (10,027)	56%- 16%	14%	5%	5%	4%
APEX (5745)	31%- 6%	31%	22%	NA	10%
EARLYACS (9492)	24%- 7%	50%	11%	0%	8%
TRACER (12,636)	21%- 5%	45%	12%	7%	10%
ASCEND (7143)	38%- 6.5%	7%	14%	9%	25%
IMPROVE-IT (18,143)	32%- 6% 6%	40%	9%	25%	
ROCKET-AF (14,269)	13%- 5% 14%	38%	14%	16%	

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

1. Califf et al. Integrating quality into the cycle of therapeutic development. Journal of the American College of Cardiology.2002; 40(11). ISSN 0735-1097/02.
2. Dilts, DM, et al. Invisible barriers to clinical trials: The impact of structural, infrastructural, and procedural barriers to opening oncology clinical trials. Journal of Clinical Oncology. 2006; 24:4545-4552.
3. Dilts, DM et al. Processes to activate phase III clinical trials in a cooperative oncology group: The case of cancer and leukemia group B. Journal of Clinical Oncology. 2006;24(28):4553-4557.
4. Echt DS. Mortality and morbidity in patients receiving Encainide, Flecainide or Placebo. N Engl J Med. 1991;324(12):781-8.
5. Ford et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. N Engl J Med.2007;356:2388-98.
6. Glickman, SW et al. Ethical and Scientific Implications of the Globalization of Clinical Research. N Engl J Med. 2009;360:816-823.
7. State Food and Drug Administration. Drug Registration. Available at http://eng.sda.gov.cn/WS03/CL0769/61659.html. Accessed on January 31, 2012.
8. Tricoci P et al. Scientific evidence underlying the ACC/AHA clinical practice guidelines. JAMA 2009;301(8):831-841.
9. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: An overview of the randomized trials. Progress in Cardiovascular Diseases. 1985;XXVII(5):335-371.