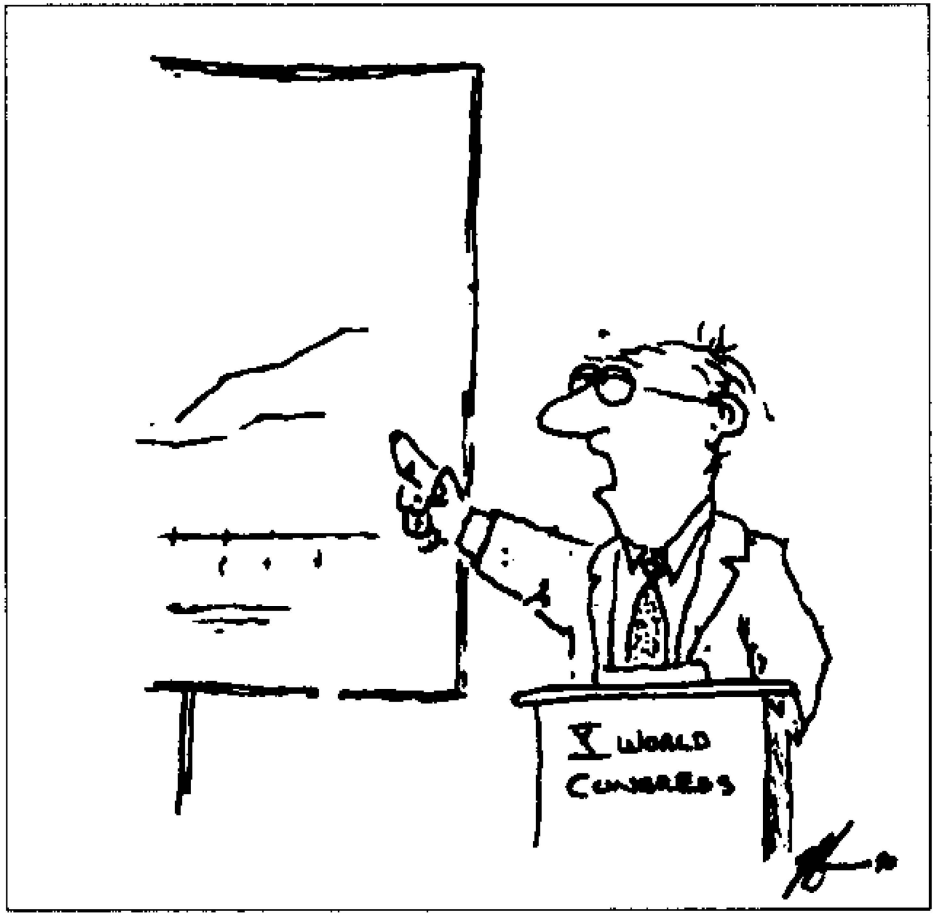
Background points

- The randomized trial is the best tool for defining modest effects of medical treatments in an unbiased and reliable way
- Large randomized trials have become increasingly expensive and complex
- This has limited the number of trials that can be done with available resources
- Relatively few of our commonly used treatments have been adequately studied: only 20% of guideline recommendations are based on “level of evidence A”
- Much of the complexity and cost in large randomized trials does not improve quality

CTTI Project: Facilitating the use of a Large Simple Trial (LST) design

- **The goal of the large simple trial (LST) design is to efficiently test the efficacy and/or effectiveness and/or safety of an intervention with regard to a clinically meaningful outcome. The LST design is streamlined to focus on outcomes, rather than mechanisms, by striving for a generous sample size with the lowest possible cost per patient. It has the following characteristics.**
- **Inclusion/exclusion criteria are unambiguous and easily applied.**
- **Primary endpoint is unambiguous and directly related to the patient's health and well-being (not a surrogate)**
- **Dosing, mechanism, and potential adverse effects of intervention are generally well understood**
- **Sample size and statistical power to detect a modest but still clinically meaningful treatment effect. (10,000 patients, 1,000 events)**
- **Streamlined data collection and monitoring**

The LST design is especially well-suited for comparative effectiveness research (CER), but the two terms are not synonymous. For example, the large simple trial of the Salk vaccine in the 1950s was an efficacy trial.



"This randomized, double-blind trial involving over 20,000 patients was conducted over a 10 year period. Unfortunately we've forgotten why."

Selected Elements of Quality in LSTs

- Adequate number of events to answer question with confidence
- In a practice setting to make results generalizable
- With proper randomization
- With reasonably complete follow-up and ascertainment of primary outcome
- With aggregate safety assessment
- With a plan for ongoing measurement, feedback, improvement of quality measures during trial conduct
- With safeguards against bias in determining clinically relevant outcomes (like blinding)
- With protection of rights of research patients

LST Project

Project questions:

- Given that LSTs provide the best means to answer certain important clinical questions, why are sponsors not regularly performing large simple trials and submitting results to FDA for review?
- Are there real or perceived obstacles to performing them?
- What can be done to facilitate and/or incentivize the use of this trial design?
- This project is in line with the some of the concepts embodied in the Quality by Design project designing the protocol around a research question, focusing on what matters and streamlining data collection

LST project

Objectives:

- To obtain a deeper understanding of sponsors' current barriers for LSTs
- To facilitate an informed discussion of practices and challenges in conducting LSTs
- To issue recommendations for future approaches that will support the intent and use of LSTs

Introduction: Goals and Anticipated Outcome

Purpose: "To develop recommendations to facilitate and promote the adoption of LST designs for regulatory submissions or other purposes."

Key Objectives

- Discuss findings from a survey of practices
- Discuss strategies that companies are using to implement LSTs
- Discuss the challenges to LSTs

This meeting in context

Sensible guideline meeting Wash DC	Jan 2007
Pragmatic trial meeting CMTP	Spring 2009
Sensible guideline meeting Oxford UK	Sep 2009
Sensible guideline meeting Toronto	May 2012
ESC clinical trial workshop London	June 2012
IOM LST workshop	Nov 2012

What is different with this meeting?

- Quantitative data about perceived barriers and opportunities
- Strong FDA and industry participation
- Focus on key what are the most important barriers and what are opportunities to overcome those barriers
- Use of specific examples