



Expert Meeting on Large Simple Trials (LSTs)

Executive Summary of Expert Meeting held May 13 and 14, 2013

Hilton Washington DC, Rockville, MD

CTTI MISSION: To identify and promote practices that will increase the quality and efficiency of clinical trials

Meeting materials, including agenda, participant list and presentations, are available on the Clinical Trials Transformation Initiative (CTTI) website at: <https://ctti-clinicaltrials.org/expert-meeting-on-large-simple-trials-lsts/>

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MEETING BACKGROUND

On May 13–14, 2013, the Clinical Trials Transformation Initiative (CTTI) held an expert meeting in Rockville, MD to develop recommendations to facilitate and promote the adoption of large simple trial (LST) designs for regulatory submissions or other purposes. A broad array of engaged stakeholders including regulators, government sponsors of clinical research, members of academia and industry, patient advocates, clinical investigators, and other interested parties gathered to discuss strategies for implementing LSTs, challenges associated with LSTs, and findings from a survey of practices.

MEETING OBJECTIVES

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

Introduction

The randomized clinical trial (RCT) is the gold standard for evaluating the risks and benefits of medical therapies in an unbiased and reliable way. However, large randomized trials have become increasingly and prohibitively expensive and complex, and most clinical trials fail to provide enough evidence (level of evidence A) to adequately inform medical decision making.¹ The majority of clinical trials registered between 2007 and 2010 involved small sample sizes and large budgets, and were characterized by the use of surrogate endpoints and heterogeneity in methodological approaches, including reported use of randomization, blinding, and data monitoring centers.² The United States is ranked 37th in terms of the quality of its health care and first in terms of cost.³ Innovative work is crucial for transforming clinical trials and shifting the paradigm to a system that is more economical, less complicated, and more focused on clinically relevant endpoints in a real-world integrated setting.⁴

Adoption of an LST design may be appropriate for some trials, such as with a moderately sized but clinically important treatment effect or in the case of a prevalent disease. Post-approval safety and efficacy studies could also be simplified, especially if the intervention is a one-time intervention or is easily administered. The LST design has key characteristics that make it more efficient and inexpensive, including unambiguous and easily applied inclusion and exclusion criteria; unambiguous primary endpoints related to the patients' health and well-being; well-understood dosing, mechanism and potential adverse

events; sample size and statistical power to detect clinically relevant treatment effects; and streamlined data collection and monitoring.

Because large trials are inherently not simple, it may be more reasonable to consider strategies for streamlining clinical trials, including being more thoughtful about site selection, having a more focused case report form (CRF), collecting selected adverse events (AEs) rather than all AEs after an adequate safety database has been established, and monitoring and following-up more efficiently. Clinical trials could be further simplified by moving to electronic health record (EHR)-based data collection and using registries.

Barriers to Simplifying and Streamlining Clinical Trials

Currently, neither industry nor government sponsors are dedicating a large percentage of available research resources to conduct LSTs. To learn why researchers and sponsors aren't implementing LSTs more often, a web-based survey about the real and perceived barriers of using LSTs was generated and distributed to stakeholders in different sectors of the clinical trials enterprise. CTTI targeted 89 respondents and received 53 completed surveys. In addition, meeting attendees were asked to identify 3 challenges or barriers that limit increased adoption of LST designs and strategies to overcome them.

▶ Regulatory burden and safety reporting

One of the most important barriers is the perception of ongoing regulatory burden. The US Food and Drug Administration (FDA) and industry share the concern that regulators will require more granular data after a trial is completed, although respondents were willing to support simplified trial designs if they allowed for achievement of regulatory goals.

To this end, FDA has developed guidance to help streamline monitoring and safety data collection. In August 2013, FDA published *Guidance for Industry: Oversight of clinical investigations, a risk based approach to monitoring*.⁵ FDA suggests that all sponsors consider the use of alternative monitoring approaches, such as the use of centralized monitoring and reliance on technological advances (e.g., e-mail, webcasts, online training modules). In February 2012, FDA drafted the guidance for industry: *Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Post-approval Clinical Investigations*.⁶ In this guidance, FDA recommends selective, targeted safety data collection for medical products during late stage development or during the post-market stage based on what is already known about a medical product's safety profile.

FDA emphasizes the importance of collaborating with the review division as a protocol is being developed and developing a consensus around the data variables that need to be collected. The streamlined protocols should explicitly highlight what will not be collected. FDA noted that when reviewing a streamlined protocol, FDA reviewers focus on key questions, such as what is required for a robust determination of efficacy; what are the unique features of the trial population that may call for special attention; have safety issues been generally

consistent across other trials and drugs in class; and what questions will FDA reviewers have if the trial was to fail.

▶ **Informed consent**

Another major hurdle is the difficulty involved in obtaining informed consent and complicated consent forms. Developing clear, informative, and succinct consent forms would benefit both patients and investigators.

▶ **Data exuberance**

Another barrier was data “exuberance” (i.e., the desire to get the most information out of the trial as possible). A crucial element for streamlining clinical trials is an upfront understanding and agreement that details will remain unmeasured and that some of the questions that get raised will remain unanswered.

▶ **Focus on basic science**

There is a perception that NIH focuses primarily on basic science. Recently, however, NIH leadership wrote into a renewed program announcement that it is interested in pragmatic trials and LSTs.

▶ **Other barriers**

Other barriers included cultural barriers and stakeholder desire, patient recruitment and compliance, lack of harmonization of regulators, expensive academic incentives, and lack of consistency with clinical practice. The solutions to these barriers included designing trials with quality and simplification in mind; building a consensus between sponsors, investigators, and FDA about the appropriate, measurable data elements and the appropriate methods for data collection; and providing transparent and documented examples about what has and has not been successful.

Real-world Examples of Streamlined Trials

Because each trial is different, there are no universal answers, but substantial reductions in costs of large-scale clinical trials can be achieved without compromising quality. Meeting attendees gave real-world examples of trials that have achieved some measure of simplification.

▶ **Pragmatic trials using electronic health care records**

The Veterans Health Administration (VHA) has developed Point of Care Research: clinical trials are conducted with a substantial portion of the operations conducted by clinical staff in the course of providing routine clinical care. Randomization is embedded in the EHR and the choice of treatment is between two equivalent options. They performed a pilot study to gauge physician and patient acceptance, institutional review board and regulatory acceptance, the ability to modify EHR screens, and the opportunity to settle a substantive clinical issue. Their pilot was an open-label RCT comparing weight-based and sliding-scale insulin protocols at three VHA medical centers, and their primary endpoint

was length of stay. In the EHR, they added an option under diabetes medications that read: “No preference for insulin regimen. Consider enrollment in inpatient study of weight based vs. sliding scale protocols.” Clicking that option randomized the patient to a treatment and flagged the patient’s data for abstraction. The trial had high participation and acceptance rates from regulators, providers, and patients, and it abstracted good data from the EHR, although the quality was higher for structured than for unstructured data.

► Population-based trial with high cost efficiency

The ongoing VITamin D and Omega-3 Trial (VITAL) is a large randomized, double-blind, placebo-controlled, 2 x 2 factorial trial of vitamin D and marine omega-3 fatty acid supplements in the primary prevention of cancer and cardiovascular disease (CVD) among a multi-ethnic population of 25,000 U.S. men aged 50 and older and women aged 55 and older.⁷ The trial has almost achieved its recruitment goal of 25,000 people with 5,000 of those being African Americans. Baseline blood samples will be collected from about half the participants, with follow-up blood collection in about a quarter of the participants. Yearly follow-up questionnaires will assess treatment compliance, use of non-study drugs or supplements, occurrence of endpoints, and cancer and vascular risk factors. Self-reported endpoints will be confirmed by medical record review by physicians blinded to treatment assignment, and deaths will be ascertained through national registries and other sources.

► Examples of large trials that have been streamlined

Champion Phoenix was a large 11,000 patient percutaneous coronary intervention (PCI) trial that tested whether acute P2Y12 inhibition with a fast-acting P2Y12 inhibitor at the time of PCI reduced major adverse cardiac events.⁸ The investigators were able to reduce the per-patient cost to \$6,500, while similar trials have cost twice this much. The investigators increased the efficiency and decreased the complexity and cost of the study by aligning the design with practice, reducing the number of data variables collected per patient, working with a small number of sites, and fostering a culture of learning at the sites.

The Study of Heart and Renal Protection (SHARP) was designed to determine if low density lipoprotein (LDL)-lowering therapy reduces the risk of atherosclerotic disease in chronic kidney disease (CKD) patients.⁹ SHARP was a streamlined study that cost 60 million dollars, which is much less than other comparable trials.¹⁰ The study was streamlined in a number of ways:

1. To increase the statistical power while keeping the sample size relatively low, the study collected outcomes important for patients and sensitive to LDL lowering. Thus, the primary outcomes were major coronary events, non-hemorrhagic stroke, and any revascularization. Although data on vascular mortality and all cause mortality were collected, they were not included as primary endpoints because that would require much larger sample sizes.

2. The inclusion and exclusion criteria were simple. The study enrolled patients aged 40 years and older with a history of CKD and no history of myocardial infarction.
3. Because the treatment lowers LDL cholesterol, instead of tracking tablets, the study tracked compliance by measuring the lipid profile of all patients at randomization, at 2.5 years, and in a 10% subsample of patients at 1 and 4 years.
4. After consultation with the FDA, SHARP limited the collection of non-serious AEs, and collected all SAEs and any permanent and temporary discontinuations, and pre-specified the SAEs that required adjudication. In addition, they did not have a clinical adjudication committee, but used trained physicians as adjudicators.
5. The final way SHARP streamlined the study was to build in quality to reduce the need for monitoring. The study included nurse training, built-in checks of the data entry system, use of the database to check the performance of sites, and involvement of monitors only at sites that experienced problems.

The Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial investigated whether patients with low LDL and elevated levels of high-sensitivity C-reactive protein are at increased vascular risk and whether these patients would benefit from a statin.¹¹ The JUPITER trial had many of the qualities of an LST and its primary endpoint was time to first occurrence of a major cardiovascular event. The investigators added secondary endpoints to consider efficacy (incident diabetes mellitus, venous thrombotic events, and bone fractures) and safety (total mortality, non-cardiovascular mortality, and adverse events). These additional secondary endpoints added a level of complexity, but also provided valuable information.

FDA provided its perspective on the SHARP and JUPITER trials. FDA stated that the timing of protocol development for both these trials was close to the time of approval of the drugs, so the trials informed safety and efficacy. In addition, both trials were blinded trials designed to test the superiority of a treatment, and a simplified trial design was possible. Because substantial post-marketing data existed, the collection of safety information could be streamlined.

Approaches to Big Data and Patient-Reported Outcomes

Using registry and EHR data in clinical trials is technically simple; randomization can be embedded in the EHR, and data collection can be coordinated with standard practice at the point of care. However, study coordinators and sites may need to change workflow to identify and track patients using EHR, and some additional infrastructure may be needed. The standardization of definitions across all data sets would make it easier to combine data. In addition, new informatics tools and groups are working on clinical workflows, and there are abundant opportunities to use these tools.

Research could be initiated to determine if data from EHRs and registries are similar to data collected on CRFs. Although big data may be able to generate robust information and new insights, stakeholders should understand the limitations of the data. Large data sets, like those used in health maintenance organizations (HMOs), could be used to validate EHR data. The Patient Centered Outcomes Institute (PCORI) could partner with FDA to research and discuss requirements for acceptable evidence and ways to modernize clinical trials, and it could provide funding for large informatics trials. PCORI now funds development of research methods that are more patient-centered, and could also meet with groups that have incorporated patient-recorded outcomes to champion their use.

Powerful studies can be done at low cost when patients are involved. For example, the PatientsLikeMe program (<http://www.patientslikeme.com/>) provides a platform on which patients can share and learn from real-world outcome-based data. Non-randomized trials can be designed using this platform, and all the data are input by the patients themselves using a validated instrument, so the cost of the trials are minimal. There are critical questions about the accuracy of patient-reported data; however, there is speculation that the large sample sizes will overcome quality issues.

MEETING ACTION ITEMS

1. Promote and expand the FDA guidances on monitoring and safety data collection.
2. Draft a commentary targeted to the *Journal of the American Medical Association* to facilitate and promote the adoption of LST and streamlined designs and address the FDA guidance.
3. Provide concrete examples and processes for LSTs and streamlined trials. AHRQ is compiling a registry of registries, and CT.gov could house best practice examples of streamlined protocols and operations.

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ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership to identify and promote practices that will increase the quality and efficiency of clinical trials. The CTTI vision is a high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

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References

1. DeMets DL, Califf RM. A historical perspective on clinical trials innovation and leadership: where have the academics gone? *JAMA* 2011;305(7):713–4.
2. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *JAMA* 2012;307(17):1838–47.
3. Murray CJL, Frenk J. Ranking 37th--measuring the performance of the U.S. health care system. *N Engl J Med* 2010;362(2):98–9.
4. Antman EM, Harrington RA. Transforming clinical trials in cardiovascular disease: mission critical for health and economic well-being. *JAMA* 2012;308(17):1743–4.
5. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Oversight of clinical investigations, a risk based approach to monitoring [Internet]. 2013; Available from: <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf>
6. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations [Internet]. 2012; Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291158.pdf>
7. Manson JE, Bassuk SS, Lee I-M, et al. The VITamin D and OmegA-3 Trial (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemp Clin Trials* 2012;33(1):159–71.
8. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* 2013;368(14):1303–13.
9. Sharp Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. *Am Heart J* 2010;160(5):785–794.e10.
10. Eisenstein EL, Lemons PW 2nd, Tardiff BE, Schulman KA, Jolly MK, Califf RM. Reducing the costs of phase III cardiovascular clinical trials. *Am Heart J* 2005;149(3):482–8.
11. Hsia J, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *J Am Coll Cardiol* 2011;57(16):1666–75.