

Dear Colleague,

The Clinical Trials Transformation Initiative (CTTI) would like to invite you to participate in a project that will help facilitate the use of Large Simple Trial designs for regulatory or other purposes. Your participation will entail completing the attached survey.

CTTI is a public–private partnership with a mission to identify and promote practices that will increase the quality and efficiency of clinical trials. To this end, CTTI conducts collaborative projects to generate empirical information about how clinical research is currently conducted and to identify ways to improve quality and efficiency. CTTI members represent a range of stakeholders from government, industry, patient and consumer organizations, investigator groups, academia, and other interested parties. More detailed information about CTTI may be found at www.ctti-clinicaltrials.org.

Large Simple Trials feature streamlined approaches to data collection and monitoring, highly generalizable results, and unambiguous and clinically important outcome measures. Despite these attractive characteristics, sponsors do not frequently elect to use large simple trials to establish the efficacy, effectiveness, and/or safety of their products.

The attached survey link ([individual hyperlink](#)) is part of a project designed to identify why large simple trial designs, when deemed an appropriate design for the intended purpose of the trial, are not more frequently used to generate evidence for regulatory submissions or other purposes. Your organization's feedback will be very helpful in providing insights on current practices in designing the use of Large Simple Trials. Office and Division Directors within the Office of New Drugs (OND) at FDA are also completing a parallel survey to provide complementary information on the regulatory role of Large Simple Trials. CTTI also intends to engage representatives from industry, academia, and government (NIH) with experiences in designing and performing large simple trials to review the survey results and facilitate an informed discussion of the perceived and real barriers that have limited the adoption of large simple trial designs and possible approaches to facilitating their use. Those who complete the attached survey will also be invited to the CTTI expert meeting with other stakeholders, including FDA.

Feedback you provide will be kept confidential and your organization's response will be aggregated with those from others for analysis. The collective results of the surveys will be reviewed and discussed by invited experts at a meeting to be held May 13-14, 2013, in the Washington, DC area. CTTI plans to publish a summary of current practices as well as recommendations to address barriers to the conduct of large simple trials for regulatory submissions and other purposes derived during the expert meeting.

Sincerely,

The CTTI LSTs Project Team Working Group:
Patrick Archdeacon, Food and Drug Administration
David Gordon, National Institutes of Health, NHLBI
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Large Simple Trials Survey

MODULE 1

DEMOGRAPHICS, FOR ALL GROUPS

PROGRAMMER: ADMINISTER MODULE 1 TO ALL SAMPLE MEMBERS

PROGRAMMER NOTE: D1 MUST BE ANSWERED. HARDCHECK MESSAGE TO READ, "A response to this question is required"

D1. These initial questions ask about your background. Which of the following best describes you/your organization? Please select one.

- 1 Industry
- 2 Clinical Research Organization
- 3 Academic Research Organization
- 4 NIH
- 5 VA
- 6 FDA

D2.If D1=1/Industry, How many employees work at your company?

- 1 Fewer than 500
- 2 500-5,000
- 3 Over 5,000

D3. What is your title or role in your organization?

_____ UNLIMITED TEXT

D4. [IF D1 NE 6/FDA] In what specialty areas is your organization currently developing or planning to develop treatments using large simple trials design? Check all that apply.

- Cardiology/Vascular Disease
- Dermatology
- Endocrine and Diabetes
- Gastroenterology
- Genetic Disease
- Hematology
- Hepatology (Liver, Pancreatic, Gall bladder)
- Immunology
- Infections and Infectious Diseases

- Musculoskeletal
- Nephrology
- Neurology
- Nutrition and Weight Loss
- Obstetrics/Gynecology (Women's Health)
- Oncology
- Ophthalmology
- Orthopedics
- Otolaryngology (Ear, Nose, Throat)
- Pediatrics/Neonatology
- Plastic Surgery
- Podiatry
- Psychiatry/Psychology
- Pulmonary/Respiratory
- Rheumatology
- Sleep
- Trauma (Emergency, Injury, Surgery)
- Urology
- Vaccines
- None of the above

D5 [IF D1 EQ 6/FDA] In what FDA division do you work?

- Office of New Drugs
- Office of Drug Evaluation I
- Office of Drug Evaluation II
- Office of Drug Evaluation III
- Office of Drug Evaluation IV
- Office of Antimicrobial Products
- Other

D5_OTH [IF D5=25/OTHER] What is your FDA division?

_____ UNLIMITED TEXT

MODULE 2
INDUSTRY, CRO, ARO, NIH, VA

PROGRAMMER: ASK MODULE 2 WHEN D1=1, 2, 3, 4, 5

S1. These next questions ask about how clinical trials get designed at your organization. Which departments of your organization are involved with selecting the clinical trial design for Phase 3 trials? Check all that apply.

- Research and Development
- Marketing
- Global Safety
- Regulatory Affairs
- Strategy
- Compliance
- Board of Directors/CEO
- Legal
- Other

S1_OTH. [IF S1=OTHER] What other department(s)?
_____ UNLIMITED TEXT

S2. How often do you use an existing protocol model to plan new studies?

- 1 Never
- 2 Rarely
- 3 Sometimes
- 4 Most of the time
- 5 All of the time

S3. What outside experts are involved in the clinical trial design process? Check all that apply:

- Clinical Investigators/Academicians
- Contract Research Organizations
- Patient Advocates
- Other External Consultants
- Investors
- Business Partners
- Other

S3_OTH. [IF S3=OTHER] What other outside experts?
_____ UNLIMITED TEXT

S4. Who in your organization has final signatory authority? Check all that apply.

- Product lead (research and development)
- Head of research and development
- Head of strategy
- CEO
- Someone else

S4_OTH. [IF S4=SOMEONE ELSE] Who has final signatory authority?

_____ UNLIMITED TEXT

S5. Which areas or departments of your organization conduct an assessment of risk management principles before committing to a clinical trial design? Check all that apply.

- Research and Development
- Marketing
- Global Safety
- Regulatory Affairs
- Strategy
- Compliance
- Board of Directors/CEO
- Legal
- Other

S5_OTH. [IF S5=OTHER] What other department(s)?

_____ UNLIMITED TEXT

S6. Please describe the types of clinical trials that you/your organization have been involved with. Check all that apply.

- Phase 1/Feasibility
- Phase II
- Phase III pivotal
- Phase IV/Post Marketing
- Non-IND/IDE Studies
- Other

S6_OTH [IF S6=OTHER] What other types of clinical trials?

_____ [UNLIMITED TEXT]

PROGRAMMER: S7 BELOW SHOULD DISPLAY ONLY THOSE TWO OR MORE OPTIONS CHECKED IN S6.

S7. What is the most common type of clinical trial that your organization conducts?

S8. What size trials does your organization typically conduct with respect to **number of sites**?

- 1 Under 49
- 2 50-99
- 3 100-199
- 4 Over 200

S9. What size trials does your organization typically conduct with respect to **number of subjects**?

- 1 Under 100
- 2 100-499
- 3 500-1,499
- 4 1500-4,999
- 5 5000-9,999
- 6 Over 10,000

S10. Does your organization conduct clinical trials internationally?

- 1 YES
- 2 NO

PROGRAMMER: RANDOMIZE RESPONSES FOR S11

S11. On what criteria does your organization base its choice for a particular trial? Check all that apply.

- Previous trials conducted with same investigational product (same inclusion/exclusion, endpoints, etc., for consistency and ability to combine data)
- Trial Phase
- Trial size
- Geographic region involved
- Regulatory goal of trial (e.g., supportive data to be submitted to FDA, pivotal data for an initial application [NDA, BLA, PLA], or request for a label change)
- Whether a key opinion leader is involved and wants data for academic sub studies
- Amount of money available to dedicate to the trial
- Constraints on trial timeline imposed by other organizational goals

PROGRAMMER: S12 BELOW SHOULD DISPLAY ONLY CHECKED OPTIONS FROM S11.

S12. Which is the **most** important criterion?

S13. How does your organization decide on a clinical trial design? _____ [UNLIMITED TEXT]

PROGRAMMER, DISPLAY LSTDEF BEFORE S14. SEE FINAL PAGE.

PROGRAMMER NOTE: S14 MUST BE ANSWERED. HARDCHECK MESSAGE TO READ, "A response to this question is required"

S14. Does your organization conduct large simple trials, as defined above?

- 1 YES
- 2 NO

S15. [IF S14=YES] What percent of trials have a large simple trial design?

- 1 Less than 5%
- 2 5-14%
- 3 15%-24%
- 4 25%-50%
- 5 Greater than 50%

S16. [IF S14=YES] What percentage of the organization's overall budgeted dollars for trials is spent on trials that have a large simple trial design?

- 1 Less than 5%
- 2 5-14%
- 3 15-25%
- 4 25%-50%
- 5 Greater than 50%

S17. [IF S14=YES] Under what circumstances does your organization conduct large simple trials? Check all that apply.

- Post-marketing studies required by regulatory agency
- Post-marketing studies not required by regulatory agency
- Global mega-trials for drug approval
- Global mega-trials for supplemental approval (e.g., new indication)
- Practice-based studies to supplement information for practicing clinicians
- Other

S17_OTH. [IF S17=OTHER] Please describe _____
UNLIMITED TEXT

PROGRAMMER: RANDOMIZE RESPONSES FOR S18

S18. [IF S14=NO] Now think about your organization's rationale for not conducting large simple trials. Please rate the concern for each of the following factors on a scale of 1-5, where 1 = not concerned and 5 = very concerned.

Expense

Ability to recruit investigators and/or patients

Willingness of FDA to accept LSTs in primary support of regulatory submissions

Willingness of regulators in the rest of world to accept LSTs in primary support of regulatory submissions

Risk that regulators may demand more granular information after the trial is completed

Possible negative audit findings by regulatory inspectors after the trial is completed

Possible demands for more granularity or other desire for different design from a key opinion leader serving as PI for the trial

Difficulties predicting outcomes relative to smaller conventional trials using surrogate endpoints familiar from Phase 2 trials

Marketing or other strategy concerns

S18a. [IF S14=NO] Is there any other reason your organization does not conduct large simple trials?

1 YES

2 NO

S18_OTH. [IF S18a=YES] Please describe the other reason your organization does not conduct large simple trials. _____ UNLIMITED TEXT

S18_OTH_RATE [IF S18a=YES] Please rate your concern for that reason on a scale of 1-5, where 1 = not concerned and 5 = very concerned.

S19. Has your organization ever started with the intent to conduct a LST and ended up with a large, complex trial with high costs and prolonged timelines?

1 YES

2 NO

S20. [IF S19=YES] What were the drivers of complexity? For each, rate on a scale of 1-5, where 1 = not concerned and 5 = very concerned.

Fear that regulators could ask for more granular information after the trial is completed

Demands from a key opinion leader serving as PI for the trial

Desire to minimize risk of negative audit findings by regulatory inspectors at the end of a trial

Lack of global harmonization requirements

PROGRAMMER NOTE: S21 MUST BE ANSWERED. HARDCHECK MESSAGE TO READ, "A response to this question is required"

S21. [IF S14=YES] In the past 10 years, has your organization's experience with LST been:

- 1 Positive
- 2 Negative
- 3 Both positive and negative

S22. [IF S21=1 OR 3] What were the reasons you had a positive experience with a LST? Please rate the **importance** of each of the following factors on a scale of 1-5, where 1 = not at all important and 5 = very important.

- 1 Efficiencies in terms of costs
- 2 Clear demonstration of efficacy/effectiveness
- 3 Clear demonstration of comparative effectiveness
- 4 Positive reception at regulatory agencies

S22a. Is there any other reason for your positive experience with a LST?

1 YES

2 NOS22_OTH. [IF S22a=YES] Please describe another reason for the positive experience _____
UNLIMITED TEXT

S22_OTH_RATE [IF S22a=YES] Please rate the importance of this reason on a scale of 1-5, where 1 = not at all important and 5 = very important.

S23. [IF S21=2 OR 3] What has been your organization's experience with LST failures? Thinking about your organization's experience with LST failures, how much of a problem was each of the following? Please rate each factor on a scale of 1-5, where 1=not a big problem and 5=a very big problem.

- 1 Cost overruns
- 2 Failure of study to demonstrate efficacy/effectiveness
- 3 Inability to recruit patients/investigators/sites

- 4 Inability to collect quality data or excessive loss to follow up
- 5 Negative interactions with regulatory agencies

S23a. Was there any other reason for your negative experience with a LST?

- 1 YES
- 2 NO

S23_OTH. [IF S23a=YES] Please describe another reason for the negative experience _____ UNLIMITED TEXT

S23_OTH_RATE [IF S23a=YES] Please rate the importance of this reason on a scale of 1-5, where 1 = not at all important and 5 = very important.

S25. Describe the pros and cons of LSTs versus other clinical trial approaches.
_____ [UNLIMITED TEXT]

S26. Describe perceived and actual barriers to LSTs.
_____ [UNLIMITED TEXT]

S27. Describe what your organization considers key principles of LST design.
_____ [UNLIMITED TEXT]

PROGRAMMER: RANDOMIZE RESPONSES FOR S28

S28. In your opinion, what factors might affect reliability of trial results in LSTs? Check all that apply.

- Number of patients
- Number of sites
- Location of sites
- Protocol complexity
- Number or nature of inclusion and exclusion criteria
- Presence of randomization
- Investigators' compliance with protocols
- Completion of follow up
- Nature of efficacy outcomes
- Level of ascertainment of key study outcomes, quality of data, etc.

S29. What are the regulatory policy barriers to conducting LSTs?
_____ [UNLIMITED TEXT]

S30. Have you ever submitted data from an LST?

- 1 YES
- 2 NO

S31. [IF S30=YES] What has been your experience with working with regulators using this trial design? What obstacles did you face?

_____ [UNLIMITED TEXT]

S32. [IF S30=YES] What lessons learned or best practices would you pass along to colleagues who conduct LSTs?

_____ [UNLIMITED TEXT]

S33. What factors determine your organization's use or nonuse of LST?

_____ [UNLIMITED TEXT]

**MODULE 3
INDUSTRY, NIH, VA**

PROGRAMMER: ASK MODULE 3 WHEN D1 D1=1, 4, 5

PROGRAMMER NOTE: SRINTRO MUST BE ANSWERED. HARDCHECK MESSAGE TO READ, "A response to this question is required"

SRINTRO. The next questions ask about entities that you may contract with to support clinical trials. Do you contract with...

- 1 CROs
- 2 AROs
- 3 Both
- 4 Neither

PROGRAMMER: IF SRINTRO= NEITHER, SKIP TO THANK YOU/CLOSE SCREEN.
RANDOMIZE TWO BANKS OF QUESTIONS: SR1-SR7, SR8-SR14.

SR1. [IF SRINTRO=1 OR 3] Do you see contracting with Clinical Research Organizations (CROs) as a barrier to LSTs?

- 1 YES
- 2 NO

SR2. [IF SR1=1] Please describe how contracting with CROs poses a barrier.
_____ [UNLIMITED TEXT]

SR3. [IF SRINTRO=1 OR 3] Please describe how CROs introduce simplification and reduce cost _____ [UNLIMITED TEXT]

SR4. [IF SRINTRO=1 OR 3] How do CROs introduce barriers that increase cost?
_____ [UNLIMITED TEXT]

SR5. [IF SRINTRO=1 OR 3] In your judgment, does greater complexity in a clinical trial lead to out of scope costs by CROs?

- 1 YES
- 2 NO

SR6. [IF SR5=YES] Please describe how complexity in a clinical trial leads to out of scope costs by a CRO. _____ [UNLIMITED TEXT]

SR7. [IF SRINTRO=1 OR 3] Do you have a preferred provider partnership with a CRO?

1 YES

2 NO

SR8. [IF SRINTRO=2 OR 3] Do you see contracting with Academic Research Organizations (AROs) as a barrier to LSTs?

1 YES

2 NO

SR9. [IF SR8=1] Please describe how contracting with AROs poses a barrier.

_____ [UNLIMITED TEXT]

SR10. [IF SRINTRO=2 OR 3] Please describe how AROs introduce simplification and reduce cost _____ [UNLIMITED TEXT]

SR11. [IF SRINTRO=2 OR 3] How do AROs introduce barriers that increase cost?

_____ [UNLIMITED TEXT]

SR12. [IF SRINTRO=2 OR 3] In your judgment, does greater complexity in a clinical trial lead to out of scope costs by AROs?

1 YES

2 NO

SR13. [IF SR12=YES] Please describe how complexity in a clinical trial leads to out of scope costs by an ARO. _____ [UNLIMITED TEXT]

SR14. Do you have a preferred provider partnership with an ARO?

1 YES

2 NO

MODULE 4 REGULATORS

PROGRAMMER: ASK MODULE 4 WHEN D1 EQ 6/FDA. DISPLAY LSTDEF BEFORE REG1 (SEE FINAL PAGE)

PROGRAMMER NOTE: REG1 MUST BE ANSWERED WHEN D1 EQ 6. HARDCHECK MESSAGE TO READ, "A response to this question is required"

REG1. Does your division ever receive NDA submissions that are primarily supported by large simple trials, as defined above?

- 1 YES
- 2 NO

REG2. [IF REG1=YES] What percent of NDA submissions to your division are supported by large simple trials?

- Less than 5%
- 5-14%
- 15%-24%
- 25%-50%
- Greater than 50%

REG3. [If REG1=YES] Under what circumstances does your division receive submissions that are supported by large simple trials? Select all that apply.

- In support of an original NDA/BLA application
- In support of an NDA/BLA application for a new indication for a previously marketed product
- In support of a change in labeling for a previously approved product, other than a new indication
- In response to a post marketing requirement
- To address an outstanding safety concern, not required by a regulatory agency

REG4. [IF REG1=NO] Have you recommended sponsors not use large simple trial designs?

- 1 YES
- 2 NO

REG5. Whether or not your division currently receives such applications, how would you describe the receptiveness of your division to NDA submissions primarily supported by large simple trials, as defined above? For each, rate on a scale of 1-5 where 1 = not receptive and 5 = very receptive.

In support of an original NDA/BLA application, where the safety profile of the drug had been previously established in traditional Phase 1 and Phase 2 trials

In support of an NDA/BLA application for a new indication for a previously marketed product

In support of a change in labeling for a previously approved product, other than a new indication

In response to a post marketing requirement

To address an outstanding safety concern, not required by a regulatory agency

REG6. If you would advise (or do advise) sponsors in your therapeutic area **not** to use large simple trials in any of the circumstances named above, what is the rationale? For each, rate on scale of 1-5 where 1 = not a concern at all and 5 = a very large concern.

Concerns about continued need for granular data to assess safety profile of product

Concerns for possibility of more granular data to assess unanticipated safety signal detected

Concerns about data integrity or adequate patient follow up

Infeasible to recruit large numbers of patients/investigators/sites

REG6a. Is there any other rationale you would advise (or do advise) sponsors in your therapeutic area not to use a large simple trials?

1 YES

2 NO

REG6_OTH SPEC [IF REG6a=YES] What is the other rationale for not advising the use of large simple trials?

1 YES

2 NO

REG6_OTH_PSEC_RATE [IF REG6_OTH=YES] Please rate the concern on a scale of 1-5 where 1 = not a concern and 5 = a very large concern.

REG7. Describe advantages of LSTs versus other clinical trial approaches. _____ [UNLIMITED TEXT]

- REG8. Describe barriers to LSTs. _____ [UNLIMITED TEXT]
- REG9. What does your division consider key principles of LST design?
_____ [UNLIMITED TEXT]
- REG10. In your opinion, what factors might affect reliability of trial results in LSTs?
_____ [UNLIMITED TEXT]
- REG11. What are the policy barriers, if any, to conducting LSTs?
_____ [UNLIMITED TEXT]
- REG12. If you have received data obtained from a LST to support approval of an investigational drug, what have been your lessons learned related to this trial design? _____ [UNLIMITED TEXT]
- REG13. What obstacles did you face? _____ [UNLIMITED TEXT]
- REG14. What lessons learned or best practices would you pass along to colleagues who conduct LSTs? _____ [UNLIMITED TEXT]

PROGRAMMER: ALL RESPONDENTS SHOULD RECEIVE A SCREEN WITH
BUTTONS FOR "BACK" AND "SUBMIT" THAT SAYS:

Thank you for your survey response. Press Submit to submit your survey responses.

AFTER SUBMISSION, DISPLAY A CONFIRMATION MESSAGE:

You successfully submitted your survey.

SCREEN LSTDEF DEFINITION OF LSTs FOR ALL GROUPS

The questions that follow refer to large simple trials, or LSTs. For the purpose of this survey, the following is our definition of an LST.

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)**
 - Does not require expensive measurements or adjudication
 - May relate to a safety issue
- **Dosing, mechanism, and potential adverse effects of intervention are generally well understood**
 - Does not require extensive monitoring
 - Not a Phase I/II trial
- **Sample size and statistical power to detect a modest but still clinically meaningful treatment effect.**
 - A minimum of 10,000 participants and 1,000 events has been proposed as a rule of thumb for CV event trials, but exact requirements depend on the specific research question.
- **Streamlined data collection and monitoring**
 - Only data directly relevant to the primary study hypothesis and overall safety are collected.
 - Can include periodic assessment of compliance by questionnaire and/or inexpensive bioassay.

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.