Embedding Clinical Trials within Registries: How Feasible?

A project of the Clinical Trials Transformation Initiative (CTTI)

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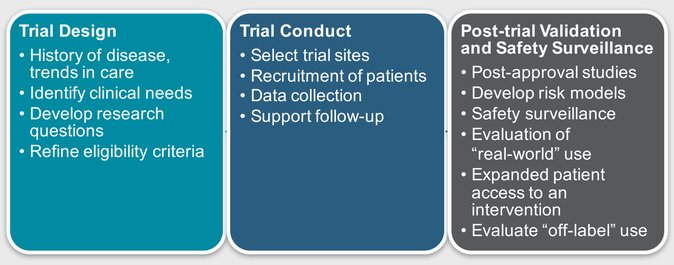
Background

- Well-controlled clinical trials are necessary to assure the safety and efficacy of drugs, biologics, and devices that enter the marketplace.
- Costs and inefficiencies have led many to suggest that the clinical trials enterprise needs to be modified and modernized.[1-3]
- Registries may be designed to serve several purposes (Fig. 1).

Figure 1: Common Registry Uses to Facilitate Clinical Trials



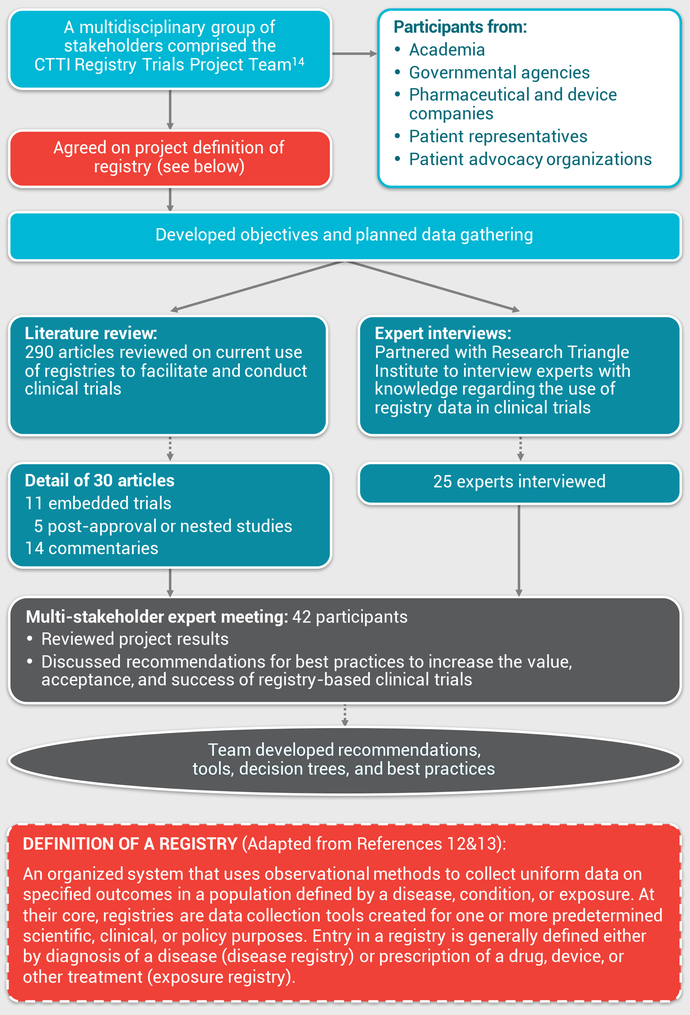
- Embedding clinical trials within registries offers opportunities to evaluate an intervention in a population broader than the typical randomized clinical trial, increase operational efficiencies, and potentially decrease clinical trial costs.[4-6]
  - Examples: Thrombus Aspiration in ST-Elevation myocardial infarction (TASTE)[7] and Study of Access Site for Enhancement of PCI for Women (SAFE-PCI for Women)[8]
- The U.S. Food and Drug Administration (FDA) has signaled its commitment to developing policies regarding the use of what is being called "real-world evidence" (e.g. registries, electronic health records, and claims databases) across a wide spectrum of research including interventional trials.[9-11]

Objectives

- Identify the essential characteristics and capabilities of registries needed for the conduct of high quality clinical trials.
- Provide a conceptual framework for assessment and design of embedded clinical trials within registries that would be acceptable to regulatory authorities.

Methods

Figure 2: Registry Trials Project Methods



DEFINITION OF A REGISTRY (Adapted from References 12&13):

An organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a disease, condition, or exposure. At their core, registries are data collection tools created for one or more predetermined scientific, clinical, or policy purposes. Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug, device, or other treatment (exposure registry).

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Results

- Registries can be more widely used for clinical trials
- Key factors to consider suitability for regulatory purposes:
  - "Relevancy", "Reliability", "Robustness"
  - Assurances of patient protections
  - Interoperability and/or ability to reconfigure
- Recommendations for three registry frameworks:
  - Can an **EXISTING REGISTRY** be appropriate for embedding clinical trials (**Table 1**)?
  - What elements must be present for an **EXISTING REGISTRY** to support embedded clinical trials (**Table 2**)?
  - What are the requirements for a **NEW REGISTRY** to be suitable for embedding clinical trials (**Table 3**)?

Table 1: Existing Registry—Historical Assessment

Evaluate if historical evidence generated by an existing registry is robust, relevant, and reliable, with assurance of patient protections

RECOMMENDATIONS
RELEVANCY AND ROBUSTNESS
Data are relevant: • Adequate in scope and content • Generalizable: Registry reflects high site- and patient- participation rates compared with total population
Data are robust—acceptable for use in one or more of the following: • Validated risk prediction • Quality assurance • Performance improvement • Benchmarking • Informing practice guidelines • Post-market surveillance • Generating peer-reviewed publications • Comparative effectiveness research
RELIABILITY
Design: Registry designed to capture reliable data from real-world practice
Patient population: Should be limited to those with specific diseases, conditions, or treatment exposure(s)
Data collection forms: Should be standardized
Datasets: Should be able to be mapped to industry standards to allow for more direct comparison of data analyses
Timing of endpoints/outcomes: Should be documented
Timing of data collection: Data collection/entry can occur at any time
Data completeness and accuracy: Should be complete, accurate, and attributable
ASSURANCE OF PATIENT PROTECTIONS
• Documentation of informed consent or IRB waiver of informed consent is needed for access to the data • Patient privacy must be assured

Table 2: Existing Registry—Suitability Assessment

Evaluate elements in an existing registry needed to conduct clinical trials (Please note: Table 1 assessment must be made before Table 2 assessment.)

RECOMMENDATIONS
ABILITY TO SUPPORT PROPOSED CLINICAL TRIAL
1. Registry focused on patient population, disease and intervention of interest
2. Evaluate if historical data in registry are robust and reliable (see Table 1)
RELEVANCY (FIT FOR PURPOSE)
1. Assignment of therapy: Processes must be integrated for identification, assignment, and documentation of eligible participants
2. Adequacy of data: Assure available data elements collected in the registry generate the information/evidence needed to answer the question at hand
3. Ensure availability of appropriate data and analysis tools
RELIABILITY (SUFFICIENT DATA QUALITY)
1. Data collection must be sufficient to support regulatory decision making
2. Data should be complete and accurate
3. Employ adequate data quality assurance procedures
4. Establish processes for accountability of study subjects
5. Source data should be available for key data elements; site-reported data without independent assessment may not provide enough accuracy for key outcomes in randomized trials
ACCESSIBLE DATA; PROVIDE PATIENT PRIVACY AND DATA CONFIDENTIALITY
1. Establish data availability to the sponsor and/or clinical investigators, with considerations for patient privacy and data confidentiality
2. Ensure availability of line-item data to regulators
3. Establish necessary associations to other data sources
4. Develop plan for data dissemination

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Table 3: Designing a New Registry

Designing a new registry with the capability of embedding clinical trials suitable for regulatory decision making

RECOMMENDATIONS
RELEVANCY AND INTEROPERABILITY
Clearly articulate purpose Design should articulate mission and value proposition of registry
Define and describe participant characteristics 1. Minimize barriers for inclusion to maximize inclusion of those with disease/condition 2. Allow for disparate treatment modalities, including drugs, biologics, devices, and combination products
Select clinically relevant data elements 1. Efficiently capture and convey information to provide evidence-based on meaningful clinical endpoints/outcomes 2. Use standard data element definitions and nomenclature 3. Must be able to: • document informed consent • document randomization/assignment of patients • configure/add data elements 4. Should be able to: • identify eligible patients for trial • accept external data if not collected in registry (e.g., EHR, reliable external datasets) • measure product performance • document adjudication/core lab determinations for key outcomes
RELIABILITY
Data collection processes must be systematic, consistent, reproducible, and reliable 1. Registry must comply with U.S. Code of Federal Regulations Title 21 Part 11 2. Data traceability must include attributability of data originators and data entry personnel, with date and time stamps for all transactions 3. Data should be usable for clinical care purposes 4. Data collection should be integrated into process of care 5. All processes must be supported by documented training of data entry personnel
Conform to informatics standards Registry should support: 1. Publication of data dictionary 2. Defined/semantic data elements 3. Use of common data elements/vocabularies 4. Use of common data model 5. If device: use of FDA's Unique Device Identifier (UDI) 6. Referential integrity via use of single source (e.g., RxNorm, GUDID)
Evaluate and assure data quality across multiple dimensions Data must be contemporaneous, accurate, legible, consistent, complete, and reliable
Assure valid design across multiple stakeholder analyses 1. Data should support pre-/post-market regulatory/other evidentiary needs 2. Data ownership access to trial-specific data should be established before start of trial 3. Site-based users, registry should support: • Quality assurance • Risk reduction • Benchmarking on risk-adjusted outcomes 4. Anticipate distributed query/aggregate analysis
PATIENT PROTECTIONS AND INPUT
Patient protections must be assured Assure patient protections by: 1. Documentation of appropriate informed consent 2. Data confidentiality policies 3. System security compliance/audits 4. Published explanation of intended? data uses 5. Training of data entry personnel 6. IRB oversight/review
Incorporate patient-reported information within the registry 1. Provide guidelines for participants to report 2. Provide technologies/structures to support participants' queries

Registry Trials Project Conclusions

- CTTI developed a conceptual framework and created tools to assist in: 1) **EVALUATING AN EXISTING REGISTRY'S** suitability for conducting clinical trials; and 2) **DESIGNING A NEW REGISTRY** in which to conduct clinical trials.
- Project recommendations will be released on May 18, 2017 during a CTTI webinar: www.ctti-clinicaltrials.org/briefing-room/webinars.
- CTTI encourages researchers and those engaged with registry development to interact with regulators to ensure that data generated from a registry trial are acceptable for regulatory purposes.