Agenda

- Clinical Trials Transformation Initiative
  - Sara Calvert, CTTI

- Introduction to the CTTI Registry Trials Project
  - Jules Mitchel, Target Health

- Project Recommendations & Examples
  - John Laschinger, FDA

- Questions & Answers
CTTI Strengths

Public-Private Partnership
Co-founded by Duke University & FDA
Involves all stakeholders
80+ members

MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials
Introduction to the CTTI Registry Trials Project
# Project Team

<table>
<thead>
<tr>
<th>Team Leaders</th>
<th>Team Members</th>
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<tr>
<td>John Laschinger (FDA/CDRH)</td>
<td>Lauren McLaughlin (MJFF)</td>
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<td>James Tcheng (Duke)</td>
<td>Chunrong Cheng (FDA)</td>
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<td>Theodore Lystig (Medtronic)</td>
<td>Magnus Petersson (AstraZeneca)</td>
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<td>E. Dawn Flick (Celgene)</td>
<td>Alan Clucas (Pfizer)</td>
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<td>Christopher Dowd (CFF)</td>
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<td>Nicolle Gatto (Pfizer)</td>
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<td>Steve Mikita (Patient Representative)</td>
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<td>Kristen Miller (FDA)</td>
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<td>Daniel Mines (Merck)</td>
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<td>Jules Mitchel (Target Health)</td>
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<td>Arlene Swern (Celgene)</td>
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<td>Sunil Rao (Duke)</td>
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<td>Emily Zeitler (Duke)</td>
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<td><strong>Project Manager</strong></td>
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<td>Sara Calvert (current)</td>
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<td>Steve Mikita (former)</td>
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<tr>
<td><strong>Executive Committee Champion</strong></td>
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<td>Michael Lauer (NIH)</td>
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ISSUES

- Data collected in clinical registries may overlap with data needed to support traditional clinical trials
- As a result, integrating clinical trials within observational data registries could offer valuable opportunities to:
  1. Avoid duplicate data collection
  2. Increase operational efficiencies
  3. Decrease clinical trial costs
- However, questions exist about how to:
  1. Identify appropriate registries
  2. Ensure data quality/comparability
  3. Meet regulatory/legal requirements
  4. Protect privacy/security
  5. Clarify the processes needed for implementation
Project Overview

PURPOSE
- Provide recommendations for registry assessment and design regarding their suitability for conducting embedded clinical trials

ANTICIPATED IMPACT
- Clinical trial stakeholders will collaborate to utilize prospective patient registries to facilitate high quality, efficient registry-embedded clinical trials
Project Scope

SCOPE

- Registry-embedded clinical trials

OUTSIDE OF SCOPE (Limitations)

- Other examples of large datasets to facilitate clinical trials (e.g., electronic health records and claims databases)
For the purposes of Registry Trials Project, an adapted version of EMA’s and AHRQ’s definitions of a registry is being used:

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

Sources:
- EMA: Guideline on good pharmacovigilance practices (GVP).
Methods

Multi-stakeholder CTTI Registry Trials Project Team Formed

LITERATURE REVIEW:
290 articles reviewed on uses of registries to facilitate and conduct clinical trials

Detail of 30 articles:
- 11 embedded trials
- 5 post-approval studies
- 14 commentaries

EXPERT INTERVIEWS:
Partnered with RTI to interview experts regarding use of registry data in clinical trials

25 Experts Interviewed:
Academia (9), Government (4), Patient Groups (4), Professional Society (3), Other (3), Industry (2)

MULTI-STAKEHOLDER EXPERT MEETING:
42 participants

Team developed recommendations, tables, and decision trees
Project Findings

- Clear role for registries in creating a sustainable infrastructure to conduct clinical trials

- Depending on type/characteristics, some registries are more appropriate than others for conducting clinical trials

- Designing or altering registries so that they are fit for purpose for embedding clinical trials involves several considerations
  - e.g., patient protections, interoperability, data quality
Registry Trials Recommendations
Disclosures & Disclaimer

John C. Laschinger, M.D.

I am a full time employee of the FDA. I have no financial conflicts of interest to report.

The views expressed in this presentation are those of the presenter and do not represent the official policies of the FDA.
Developed recommendations, which include decision trees and tables, to assist in:

1) Evaluating an **existing** registry’s suitability for conducting clinical trials

2) Designing a **new** registry in which to conduct a clinical trial
**Tools | Decision Trees & Tables**

**Tables provide:**
- Requirements
- Recommendations
- Suggested Good Practices

**Decision Trees are:**
- NOT intended as checklists
- Intended as visual guides to evaluate *existing* registries:
  - historical use and performance,
  - suitability for embedding wide spectrum of clinical trials including RCT’s
Recommendations for Existing Registries

To determine if an existing registry is appropriate for embedding clinical trials, we recommend the following 2 step process:

**Step 1**: Evaluation of historical evidence generated:
- Prior record of successful use
- Fit to purpose and high quality
  - Relevant
  - Robust
  - Reliable

*See Decision Tree 1 and Table 1*
Decision Tree 1 (Excerpt)

Does an appropriate registry exist for the condition and its treatment?

- YES
- NO

Are there endpoints in the existing data source that measure product outcomes relevant to the intended use?

- NO
- YES

Can linked data sources be used to provide needed endpoints/data?

- NO
- YES

Existing registry data insufficient as primary evidence source

Is evidence derived from analysis of existing registry data sufficient to allow the clinical or regulatory decision needed based on sound clinical judgment?

- NO (Drugs)
- NO (Devices)

Are safety data adequate and post-market data collection will provide additional needed evidence for effectiveness (i.e., pre- to post-market balance)?

- NO
- YES

Is there sufficient evidence of medical community acceptance (i.e., used for one or more of the following)?

- High patient and site participation rates
- Used for benchmarking and performance improvement
- Used to set practice guidelines, make standard-of-care decisions
- Generates peer-reviewed publications
- Allows validated predictive risk modeling
- Sufficient for signal recognition and assessment

- NO
- YES
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

<table>
<thead>
<tr>
<th>REQUIREMENTS</th>
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<tr>
<td><strong>RELEVANCY AND ROBUSTNESS</strong></td>
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<tr>
<td><strong>RELIABILITY</strong></td>
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<tr>
<td><strong>ASSURANCE OF PATIENT PROTECTIONS</strong></td>
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**Recommendation:**
Data are adequate in scope and content

**Suggested Good Practices:**
- Assess whether data and evidence that are generated can address the question at hand (i.e., fit for purpose)
- Connectivity: Establish whether there are linkages, or the ability to link to other existing datasets for additional data not captured directly in the registry
Recommendations for Existing Registries

Step 2*: Evaluating an existing registry for elements needed to conduct a clinical trial:

- Suitable platform exists – step 1
- Core data needed to answer the question at hand is acquired - relevant
- Additional critical data can be acquired:
  - Reconfigure or modular add-on data forms
  - Linkages to other datasets
- Data privacy and security, timely accessibility
- Strict adherence to patient protections standards
- Appropriate analytic methodologies available

*See Decision Tree 2 and Table 2
Additional Decision Tree for Regulatory Studies:

An appropriate registry exists for the condition of interest and its treatment.

The historical evidence produced by the registry is regarded as ROBUST 
(See Decision Tree 1)

The historical evidence produced by the registry data is regarded as RELIABLE 
(See Decision Tree 1)

The pre-defined data elements needed to answer the clinical questions are collected.

Use of a registry platform as the primary data collection tool may be inadvisable or inadequate for evidence generation.

Are adequate patient protections in place, including appropriate informed consent?

Are patient privacy and data confidentiality maintained?

Consider use of existing registry as data collection platform

Use of the registry platform as the primary data collection tool may be inadvisable or inadequate for evidence generation

Are patient privacy and data confidentiality maintained?

YES

NO

YES
TABLE 2: EXISTING REGISTRY – Suitability Assessment

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

<table>
<thead>
<tr>
<th>REQUIREMENTS</th>
<th>Recommendation:</th>
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<tbody>
<tr>
<td>ABILITY TO SUPPORT PROPOSED CLINICAL TRIAL</td>
<td>Considerations for patient privacy and data confidentiality</td>
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<tr>
<td>RELEVANCY (FIT FOR PURPOSE)</td>
<td></td>
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<tr>
<td>RELIABILITY (SUFFICIENT DATA QUALITY)</td>
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<tr>
<td>ACCESSIBLE DATA, and PROVIDE PATIENT PRIVACY AND DATA CONFIDENTIALITY</td>
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**Suggested Good Practice:**
Assure informed consent adequately describes data accessibility and maintenance of patient privacy and data confidentiality.
Recommendations for New Registries

To design a new registry as a reusable platform suitable for embedding clinical trials,

• Follow:
  • Software guidelines - industry and regulatory,
  • Additional Guidance documents provided by regulatory agencies,
• Develop methods to maintain standards and compliance in real world use

*See Table 3
### TABLE 3: DESIGNING A NEW REGISTRY

Designing a new registry with the capability of embedding a clinical trial suitable for regulatory purposes

<table>
<thead>
<tr>
<th>REQUIREMENTS</th>
<th>Recommendation:</th>
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<tr>
<td><strong>RELEVANCY AND INTEROPERABILITY</strong></td>
<td>The registry design document should articulate the vision, mission, reason, and value proposition of the registry</td>
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<tr>
<td>CLEARLY ARTICULATE PURPOSE</td>
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<tr>
<td>DEFINE AND DESCRIBE PARTICIPANT CHARACTERISTICS</td>
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<tr>
<td>SELECT CLINICALLY RELEVANT DATA ELEMENTS</td>
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<tr>
<td>RELIABILITY</td>
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<tr>
<td>PATIENT PROTECTIONS AND INPUT</td>
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Alternative options to trial embedded in one registry

- It is unusual for an existing registry to provide *all* evidence
  - Registries (and/or other data sources) can be combined
  - Consider hybrid trial option- part registry, part standard CRF
  - New registries should allow for study specific data to be added to registry data collection

- Use registry for trial facilitation
  - Trial feasibility assessment
  - Selecting sites and/or identifying and recruiting patients
  - Collecting available baseline and/or follow-up data

- Consider creating new registry - if anticipate repeated use of registry as sustainable platform for multiple clinical trials
Registry-based randomized clinical trials—a new clinical trial paradigm

Stefan James, Sunil V. Rao and Christopher B. Granger

Abstract | Randomized clinical trials provide the foundation of clinical evidence to guide physicians in their selection of treatment options. Importantly, randomization is the only reliable method to control for confounding factors when comparing treatment groups. However, randomized trials have limitations, including the increasingly prohibitive costs of conducting adequately powered studies. Local and national regulatory requirements, delays in approval, and unnecessary trial processes have led to increased costs and decreased efficiency. Another limitation is that clinical trials involve selected patients who are treated according to protocols that might not represent real-world practice. A possible solution is registry-based randomized clinical trials. By including a randomization module in a large inclusive clinical registry with unselected consecutive enrolment, the advantages of a prospective randomized trial can be combined with the strengths of a large-scale all-comers clinical registry. We believe that prospective registry-based randomized clinical trials are a powerful tool for conducting studies efficiently and cost-effectively.

James, S. et al. Nat. Rev. Cardiol. 12, 312–316 (2015); published online 17 March 2015; doi:10.1038/nrcardio.2015.33

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D’Agostino, Sr., Ph.D.

The randomized trial is one of the most powerful tools clinical researchers possess, a tool that enables them to evaluate the effectiveness of new (or established) therapies while accounting for United States and abroad have collected vast amounts of data from patients with acute coronary syndromes, stable coronary disease, and heart failure, as well as from patients with any disease.
RRCT’s - Examples


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Laschinger JC

*IFR vs. FFR*
The SWEDEHEART Trials
Registry-based Randomized Controlled Trials (RRCT)

Linked Registries and Data Sources in SWEDEHEART Trials

- **Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies**
  - Sub registry: The **Swedish Coronary Angiography And Angioplasty Registry (SCAAR)**

- Danish National Patient Registry and Western Denmark Heart Registry

- National Population Registries – Sweden and Denmark

- Modular On-line Questionnaire – granular procedural data
SWEDHEART RRCT I – TASTE Trial
Proof of Concept

TASTE Trial (Thrombus Aspiration in ST Elevation Myocardial Infarction)

Important Features:
• Automated Patient Identification
• Randomization and Informed Consent

The TOTAL costs of TASTE:
US $300,000 or $50 per patient
≈ 2% of a conventional RCT ($2000 +/- pt.)

SWEDHEART RRCT II

*iFR vs. FFR*+

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**Results confirmed by simultaneous DEFINE-FLAIR traditional RCT (ACC 2017)**

**Long Term Follow-up:**
- Hard Outcomes
- Linked Procedure/Population Registries

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- Modular add-on for granular procedure data
- Adjudication of Key Endpoints

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*physiologically guided coronary-artery revascularization strategy*

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NEJM 376;1813-1823

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Available CV Device Registries - US

Cardiovascular Device and Procedure Registries - US
- Reliable, Relevant, Robust
- Harmonized Definitions
- Linkages established
- History of RWE for:
  - Label Expansion
  - Post Approval Studies
- Sustainable – QA/PI uses
- Risk prediction, Benchmarking

Available CV Device Registries - US

- InterMACS
- IMACS
- PediMACS
- Adult Cardiac Surgery
- Congenital Cardiac Surgery
- SSA Death Master File
- STS National Database
- AAC National Cardiovascular Disease Registries
- Government Datasets
- Joint STS/ACC Registry
- CMS Administrative Dataset
- Implantable Cardioverter Defibrillator
- LA Appendage Occlusion
- STS/ACC TVT Registries
- Cath-PCI
- AF Ablation
- IMPACT
- CDC National Death Index
- Gov’t UDI Database

Legend:
- STS National Database
- AAC National Cardiovascular Disease Registries
- Government Datasets
- Joint STS/ACC Registry
Summary

Registries can be more widely used for clinical trials

CTTI recommendations assist in:

1. EVALUATING AN EXISTING REGISTRY
2. DESIGNING A NEW REGISTRY
   as reusable platforms for conducting clinical trials

Key factors to consider suitability for regulatory purposes
- “Relevancy”, “Reliability”, “Robustness”
- Assurances of patient protections
- Interoperability and/or ability to reconfigure

Researchers/Registry developers should interact with regulators to ensure that data generated from a registry trial are acceptable for regulatory purposes
Questions?
THANK YOU.

For more information contact Sara Calvert
Sara.calvert@duke.edu
919-280-6207

www.ctti-clinicaltrials.org