CTTI Registry Trials Project: Literature Review
March 30, 2016
Literature Review Purpose

- Provide an overview of the ways in which clinical registries are used to:
  - Facilitate and conduct clinical trials
  - Illuminate future directions for registry integrated trials

- Assemble examples of existing registry trials

- Compile commentaries and other literature related to use of registries for clinical trials
Literature Review Methods

Two primary searches in PubMed
- Search 1 was a broad search, investigating the relationship between trials and registries
- Search 2 was a more targeted search, focusing on the role of registries in post-approval studies

SCOPUS database of abstracts and conference programs search for registry-based randomized trials from 2011-2016

Team suggested additional publications

Reviewed bibliographies of relevant publications
# Inclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of a clinical registry in any stage of clinical trial process (e.g. planning,</td>
<td>Use of electronic health records or claims databases that do not also utilize or</td>
</tr>
<tr>
<td>recruitment, long-term follow-up)</td>
<td>comment on the use of clinical data registries</td>
</tr>
<tr>
<td>Commentaries/editorials about randomized registry trials</td>
<td>Registry design</td>
</tr>
<tr>
<td>Examples of registry-based clinical trials</td>
<td>Observational research using registry</td>
</tr>
<tr>
<td>Examples of studies that could inform the future conduct of registry-based</td>
<td>Registration of clinical trials (e.g. ClinicalTrials.gov)</td>
</tr>
<tr>
<td>clinical trial (e.g. device post approval studies)</td>
<td>Published prior to January 1, 2005</td>
</tr>
<tr>
<td></td>
<td>Not available in English</td>
</tr>
</tbody>
</table>
Results
Results

- Examples, 13
- Related, 3
- Commentary, 14

Records identified through database searching:
- Search 1 n=841,
- Search 2 n=233
  (n = 1074)

Additional records identified through other sources:
(n = 44)

Records after duplicates removed:
(n = 1054)

Full-text articles assessed for eligibility:
(n = 474)

Studies included in qualitative synthesis:
(n = 290)

Full-text articles excluded, (n=184)
(Observational Research n=94,
Registries of clinical Trials n=56,
Registry design n=34)

Records excluded based on review of abstract:
(n = 580)

Subset of Registry Trial Examples, Commentaries, and Related Research (n=30)
Common Uses of Registries to Facilitate Clinical Trials

- **Clinical Trial Design**
  - History of disease, trends in care
  - Identify clinical needs
  - Develop research questions
  - Refine eligibility criteria

- **Clinical Trial Conduct**
  - Select trial sites
  - Recruitment of patients
  - Data collection
  - Support follow-up

- **Post Trial Validation and Surveillance**
  - Post approval studies
  - Develop risk models
  - Safety surveillance
  - Evaluation of “real world” use
  - Expanded patient access to an intervention
  - Evaluate “off-label” use
## Registries vs. RCTs

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Registry</strong></td>
<td><strong>Limited value for inferring causal relationships</strong></td>
</tr>
<tr>
<td>Continuous</td>
<td>Potential confounding</td>
</tr>
<tr>
<td>Descriptions of landscape, standards, treatment patterns</td>
<td>Missing data, data quality variable/questioned</td>
</tr>
<tr>
<td>Large, heterogeneous populations (generalizable)</td>
<td>Utility varies based on type of registry</td>
</tr>
<tr>
<td>Detect rare events</td>
<td>Limited interoperability</td>
</tr>
<tr>
<td>Inexpensive</td>
<td><strong>Randomization balances variation and confounding factors</strong></td>
</tr>
<tr>
<td><strong>Randomization balances variation and confounding factors</strong></td>
<td><strong>Strict eligibility criteria</strong></td>
</tr>
<tr>
<td>Detect small-to-moderate effects reliably with adequate sample sizes</td>
<td>Expensive</td>
</tr>
<tr>
<td>Good data quality</td>
<td>Logistically complex</td>
</tr>
<tr>
<td><strong>Detect small-to-moderate effects reliably with adequate sample sizes</strong></td>
<td>Discontinuous</td>
</tr>
<tr>
<td><strong>Good data quality</strong></td>
<td>Patient burden</td>
</tr>
<tr>
<td><strong>Randomization balances variation and confounding factors</strong></td>
<td>Site/Provider burden</td>
</tr>
<tr>
<td><strong>Detect small-to-moderate effects reliably with adequate sample sizes</strong></td>
<td>Misaligned industry incentives and patient need</td>
</tr>
</tbody>
</table>
Promises of Registry-based clinical trials

- Randomization removes confounding
- Select highly qualified sites
- Quickly identify and enroll patients
- Representative sample (assuming comprehensive registry)
  - Potential to assess external validity at a faster pace
- Decrease data collection
  - Avoid or decrease need for case report form
- Obtain more complete and accurate follow-up
- Lower costs, faster timelines, earlier answers
Terminology

James et. al. define a registry-based randomized clinical trial (RRCT) as a prospective randomized trial that uses a clinical registry for one or several major functions for trial conduct and outcomes reporting.

Other terms commonly used:
- registry-based clinical trial
- embedded clinical trial
- registry trial
- interventional registry trial

James, S. et al. (2015) Registry-based randomized clinical trials—a new clinical trial paradigm
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2015.33
## RRCT Examples

<table>
<thead>
<tr>
<th>Trial name (Location)</th>
<th>Registry</th>
<th>Trial Question</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SORT OUT II-VII</strong> (Denmark)</td>
<td>Western Denmark Heart Registry and national registries</td>
<td>Six trials investigated the safety and efficacy of drug eluting stents (2 stents compared in each trial)</td>
</tr>
<tr>
<td><strong>TASTE</strong> (Sweden, Denmark, Iceland)</td>
<td>SCAAR/SWEDE-HEART/National health registries</td>
<td>Thrombus aspiration during percutaneous coronary intervention (PCI) treatment of STEMI vs PCI alone</td>
</tr>
<tr>
<td><strong>iFR-SWEDEHEART</strong> (Sweden, Denmark)</td>
<td>SCAAR/ SWEDEHEART/ National health registries</td>
<td>Instantaneous wave-free ratio (iFR) vs fractional flow reserve (FFR) strategy to assess the hemodynamic severity of coronary lesions</td>
</tr>
</tbody>
</table>

**SORT OUT**: Scandinavian Organization for Randomized Trials With Clinical Outcome  
**SCAAR**: Swedish Coronary Angiography and Angioplasty Registry
## RRCT Trial Examples

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Registry Description</th>
<th>Trial Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT-TAVI Trial REPLACE</td>
<td>Ferrarotto Hospital’s Registry of Percutaneous Aortic Valve Replacement</td>
<td>RenalGuard System with furosemide vs. normal saline on prevention of acute kidney injury (AKI) in patients undergoing transcatheter aortic valve replacement (TAVR)</td>
</tr>
<tr>
<td>(Italy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAFE-PCI for Women (U.S.A)</td>
<td>NCDR-CathPCI Registry</td>
<td>Outcomes of radial access vs femoral access in women undergoing PCI</td>
</tr>
</tbody>
</table>
TVT Registry

- A national clinical registry program for transcatheter valve therapy (TVT) devices

- Created through a partnership of The Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC), in close collaboration with the Food and Drug Administration (FDA), the Center for Medicare and Medicaid Services (CMS), and the Duke Clinical Research Institute

- Data is entered from hospitals using the National Cardiovascular Data Registry (NCDR) interface.

- Capability to connect with other data sources including CMS data, the STS Adult Cardiac Surgery Database, and other data in NCDR

- Regular reports are generated for participating institutions for benchmarking to local and national outcomes

- **Ability to embed post-approval and IDE studies**
Nested Studies & Sub-Studies

Use of existing Consortium of Rheumatology Researchers of North America (CORRONA) registry infrastructure to address a new research question

- CORRONA Registry
  - Baseline dataset collected
  - Eligible patients identified
  - Informed Consent

Additional CERTAIN Dataset

Additional T2T Dataset

Return to CORRONA
- Follow-up to assess long-term outcomes

Slide Content Source: Adapted from Leavy, M.B. DIA 2015
Summary of Concerns and Limitations, and Potential Solutions
Key requirement - Registry

“Such trials are not feasible if there is no registry …. ”

Does registry exist and contain desired data?

If not, is establishing a new registry cost-effective?
- Purpose, cost, ability to use for several research purposes
### Consider type of registry

<table>
<thead>
<tr>
<th>Types of Registries</th>
<th>Enrollment Point/Cohort</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>Patients with specific disease or condition</td>
<td>Alzheimer's Disease Registry</td>
</tr>
<tr>
<td>Disease Surveillance</td>
<td>Identification of new cases to estimate incidence or prevalence</td>
<td>The Surveillance, Epidemiology, and End Results (SEER)</td>
</tr>
<tr>
<td>Exposure</td>
<td>Follows patients starting a specific treatment longitudinally for outcomes</td>
<td>Cath-PCI registry</td>
</tr>
<tr>
<td>Risk management programs</td>
<td>All patients treated with a specific pharmaceutical/ biologic product to ensure safe use conditions</td>
<td>REMS programs (Accutane, Clozapine, etc.)</td>
</tr>
<tr>
<td>Directory of Potential Trial</td>
<td>Identification of patients who may qualify for clinical trial</td>
<td>Many patient advocacy group registries serve disease and directory roles</td>
</tr>
<tr>
<td>Participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population-based databases</td>
<td>Usually established by countries</td>
<td>Israeli Army database Swedish Registries</td>
</tr>
<tr>
<td>Data collected with Biospecimen</td>
<td>Cross sectional or longitudinal data collected in relation to biological specimen</td>
<td>Alzheimer's Disease Neuroimaging Initiative</td>
</tr>
<tr>
<td>Repositories</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Incomplete Data

Is data required for a clinical trial collected in the registry and at the time frame required for a trial?

- Determine if the registry is appropriate for trial purposes
- Design new registries to collect data needed for future trials, including meeting quality/regulatory requirements
- Design simple trials that only require data from the registry
- Link to other registries or data sources
- Collect some data with standard case report form
- Add trial specific screens to registry platform
- Provide benefit/incentives to sites to participate in registry and provide quality data
Data Quality

Are the data entered into the registry accurate or auditable for regulatory purposes?

- Compare to other data sources
- Critically assess need for monitoring and adjudication
- Build in processes for monitoring accuracy of data
  - Training of abstractors
  - Regular audits on subset of data
  - System for generated logic checks
  - Use of central adjudication committee
Data Interoperability

Can registry data be linked to other databases?

- Less of an issue in countries with nationalized databases and electronic health records
- Use of common patient and/or device identifiers
- Use of data standards and definitions
- Use of common data elements
Representativeness

Are there systematic differences between those who are/are not in registry and those who do/do not participate in trial?

- Determine if participants in registry and data collected is sufficient and appropriate for study purposes
- Link participation in registry as condition of treatment payment or condition to prescribe the treatment
- Provide benefit/incentives to site to participate in registry and provide quality data
- Compare those randomized to those in the registry who were not randomized
Informed Consent

Was informed consent obtained for participation in registry?

What was covered in informed consent?

When is informed consent required?

- Obtain separate consent for participation in RCT
- When possible obtain consent for research/permission to contact for research when patient enters registry
- Use novel (but validated) methods to simplify consent processes
Privacy Considerations

Are patients aware of privacy/disclosures?

- Separate personal and other information in registry
- Post privacy policy accessible to potential registrants detailing:
  - purpose of the registry
  - who will have access to data
  - how the data will be used
  - how long the data will be maintained
  - how the potential registrant can withdraw from the registry
Costs and Operational Adjustments

Who funds registry costs, operational adjustments needed for clinical trial, and clinical trials costs?

- Frequent communication between collaborators
  - Collaboration between typical competitors may be a challenge

- May need multiple sponsors
  - Registry may be funded by membership fees from institutions participating in registry
  - For investigational trials – industry sponsor(s) can pay or share payment for the trial

- Define and determine upfront: the cost and party responsible for registry maintenance and tasks required for clinical trials
Summary

- Registry-based trials can decrease costs and increase efficiencies compared to standard RCTs.
- Type and purpose of registry is important to determine if embedding a clinical trial is possible and appropriate.
- Strategies to improve quality and efficiency in RCTs also apply to registry based trials.
Thank you team!

- Emily Gao and Katelyn Blanchard
- Registry Trials Project Team
- Literature Review Working Group
  - Chunrong Cheng
  - Christopher Dowd
  - Dawn Flick
  - Nicolle Gatto
  - John Laschinger
  - Steve Mikita
  - Kristen Miller
  - Daniel Mines
  - Emily Zeitler
Thank you.

Sara Calvert
sara.calvert@duke.edu