CTTI Registry Trials Project: Literature Review

March 30, 2016

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Literature Review Purpose

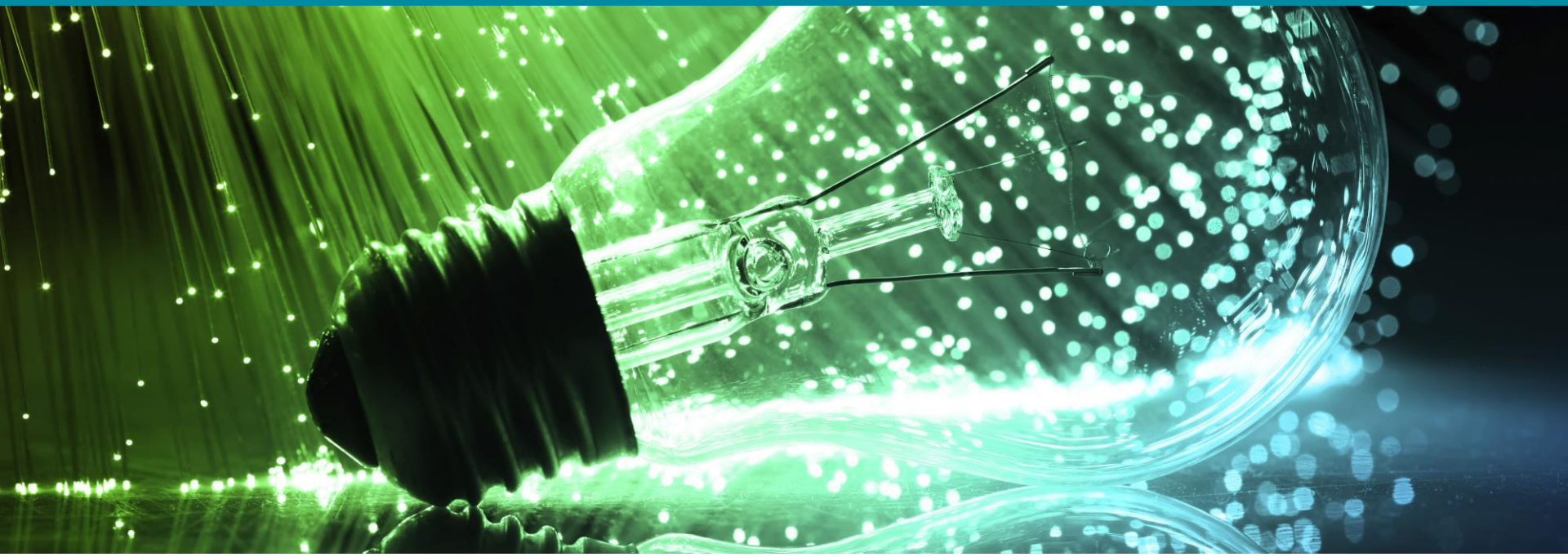
- Provide an overview of the ways in which clinical registries are used to:
  - facilitate and conduct clinical trials
  - illuminate future directions for registry integrated trials
- Assemble examples of existing registry trials
- Compile commentaries and other literature related to use of registries 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

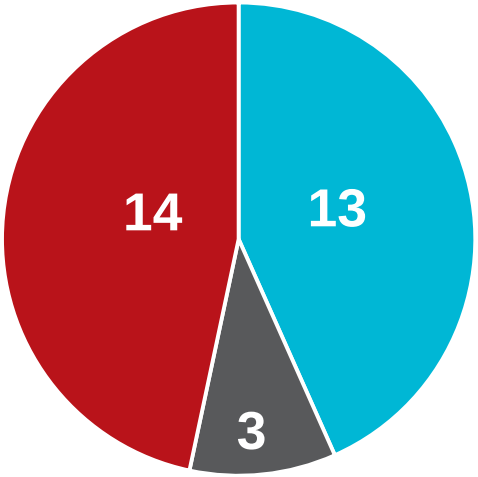
Inclusion Criteria

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



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)

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

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

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

Studies included in qualitative synthesis (n = 290)

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

	Advantages	Disadvantages

Registry	• Continuous
	• Descriptions of landscape, standards, treatment patterns
	• Large, heterogeneous populations (generalizable)
	• Detect rare events
	• Inexpensive
		• Limited value for inferring causal relationships
		  • Potential confounding
		  • Missing data, data quality variable/questioned
		• Utility varies based on type of registry
		• Limited interoperability

	• Randomization balances variation and confounding factors • Detect small-to-moderate effects reliably with adequate sample sizes • Good data quality	• Strict eligibility criteria • Expensive • Logistically complex • Discontinuous • Patient burden • Site/Provider burden • Misaligned industry incentives and patient need

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

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

SORT OUT: Scandinavian Organization for Randomized Trials With Clinical Outcome

SCAAR: Swedish Coronary Angiography and Angioplasty Registry

CTTI

RRCT Trial Examples

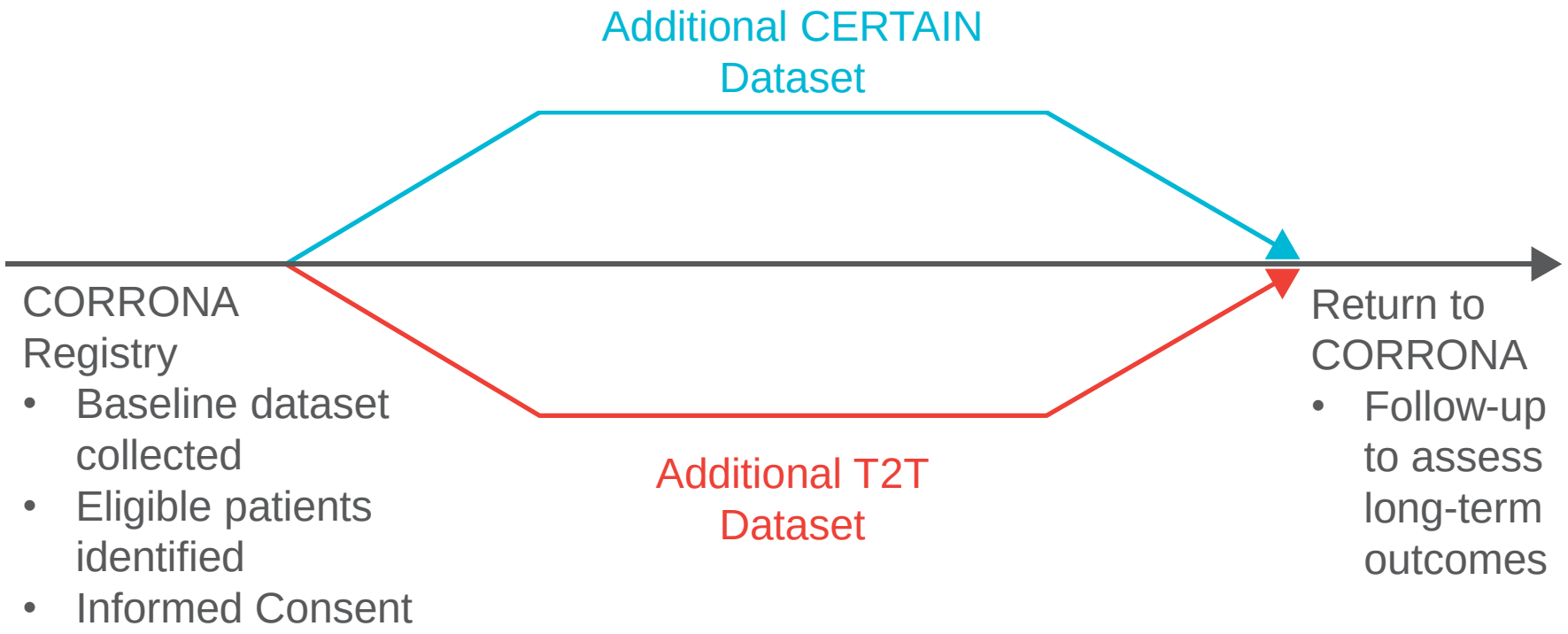
PROTECT-TAVI Trial REPLACE (Italy)	Ferrarotto Hospital's Registry of Percutaneous Aortic Valve Replacement	RenalGuard System with furosemide vs. normal saline on prevention of acute kidney injury (AKI) in patients undergoing transcatheter aortic valve replacement (TAVR)
SAFE-PCI for Women (U.S.A)	NCDR-CathPCI Registry	Outcomes of radial access vs femoral access in women undergoing PCI

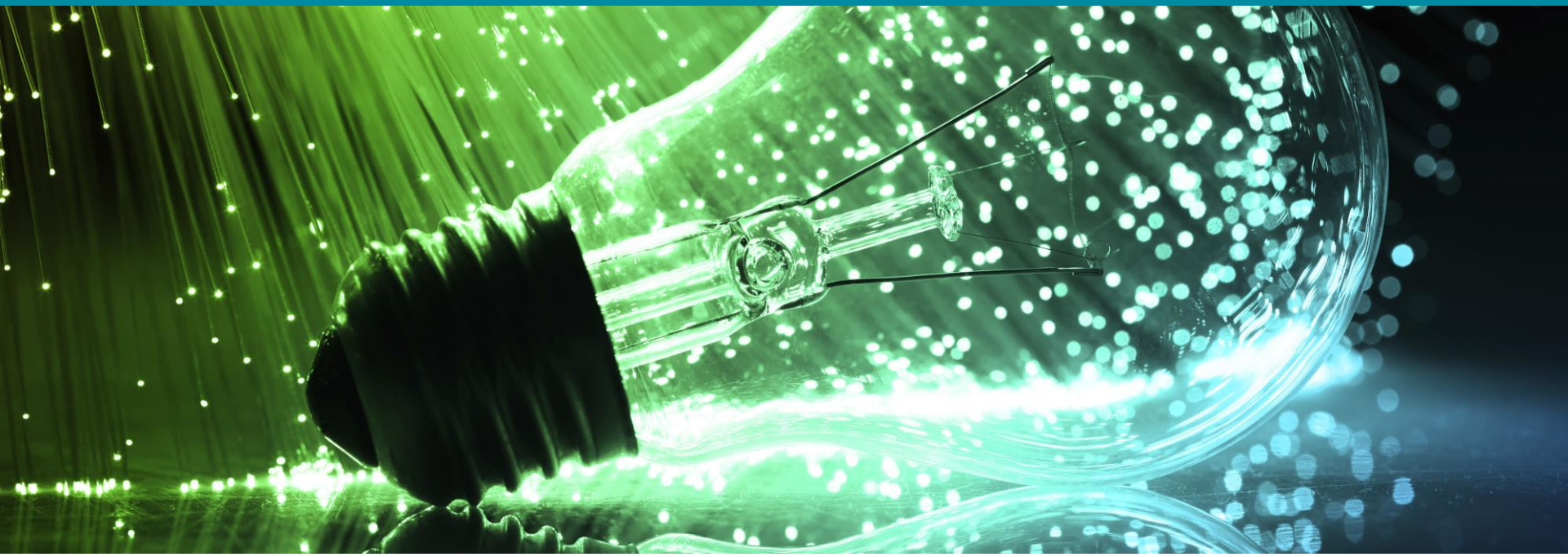
TVT Registry

- 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





Summary of Concerns and Limitations, and Potential Solutions

Key requirement - Registry

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

- Baker and Kramer, NEJM 2014;370:681-2.

- 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

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

Incomplete Data

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

- Determine is 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 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 site 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
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  - Christopher Dowd
  - Dawn Flick
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  - John Laschinger
  - Steve Mikita
  - Kristen Miller
  - Daniel Mines
  - Emily Zeitler

Thank you.

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