Pragmatic Trial Designs – Capturing Endpoints and Integrating Data from Non-Linked Sources

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Conflict of Interest Statement –
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Capturing Cardiovascular Endpoints

• **Approach with traditional clinical trials**
  - During study visits, site personnel administer questions to patients about hospitalizations related to potential CV endpoints (and maintain contact with relatives for death notifications)
  - Potential hospitalizations related to endpoints and deaths prompt submission of CRF endpoint pages and collection of source documents for central adjudication
  - Complicated query processes involving SAE’s and other key data fields to prompt reporting of unreported endpoints
Capturing Cardiovascular Endpoints

- **Options with pragmatic clinical trials**
  - Central longitudinal follow-up via telephone contact with collection of medical records for patient-reported hospitalizations (no site personnel involved)
  - Electronic surveillance of integrated national health record databases in countries with a single payer system using coding algorithms for endpoint identification and confirmation
  - Hybrid electronic surveillance methods with multi-tiered query processes and coding algorithms to identify and confirm all potential endpoints
Central Follow-Up to Capture CV Endpoints

• TRANSLATE ACS Registry
  – 12,366 patients with STEMI or NSTEMI treated with PCI at 233 U.S. hospitals between April, 2010 and October, 2012

• ARTEMIS Cluster Randomized Trial
  – Approximately 11,000 patients with STEMI or NSTEMI at 300 U.S. hospitals – study is ongoing and enrollment has completed

• Endpoints centrally assessed by DCRI Call Center in both studies include cause of death, MI, stroke, bleeding, and unplanned revascularization
  – Single physician adjudication of potential endpoints

*Am Heart J 2011;162:844-51, Am Heart J 2016;177:33-41*
Index acute MI hospitalization

Follow-up Interviews

Bill Collection

Medical Record Collection

Site Responsibilities
- Consent patient for central follow-up
- Enter data from index hospitalization

Central Call Center Follow Up
- validated events
- medication use
- health outcomes
- health care costs

Single Adjudication of Endpoints
- Cause of death
- Myocardial infarction
- Revascularization
- Stroke
- Bleeding

Follow-Up Interviews at 1, 3, 6, 12, and 15 months
National Health Records to Capture CV Endpoints

• Countries with integrated, single payer health care systems (Sweden, UK, Denmark, New Zealand) have several advantages including:
  – Complete capture of longitudinal health information
  – Government support for country-specific research
  – Pre-existing platforms that facilitate prospective studies
  – Innovative research spirit ➔ experimentation with pragmatic trials
Number of cases annually: 80 000

RIKS-HIA 73 CCU hospitals, 100%
SCAAR 30 PCI hospitals, 100%
Percutaneous valves 7 hospitals, 100%
Heart surgery 7 hospitals, 100%
Secondary prevention 65 hospitals, 85%

>200 variables

(Baseline data, procedural and outcome measures)

At monitoring: 95-96% agreement between files and registry.
### Data entry on line by the operator

- **Administrative data**
  - Datum för procedur: 2013-09-03
  - Typ av registrering: Angio + PCI
  - Journilded: 2 Akutfall på kontorstid
  - Remitterande enhet: Uppsala

- **Clinical background and prior CV disease**
  - Längd (cm): 175
  - Vikt (kg): 104
  - S-Kreatinin (mikromol/L): 96
  - Kreatinin clearance: 92.3

- **Angiographic background data**
  - Behandlad hypertoni: 1 Ja

### Automatic linkage with population registry

### Automated data checks
Registry-RCT vs. Traditional RCT

- Combines the advantages of an ongoing clinical registry with the rigor of a randomized trial
  - Utilizes data already collected by registries to facilitate trial conduct
- Complement to classical RCT, but no formal definition

Registry-RCT
Evaluation of therapeutic options used in routine clinical care

Traditional RCT
Approval of experimental pharmaceutical agents and medical devices
All-cause mortality up to 1 year

HR up to 1 year 0.94 (0.78 – 1.15), P=0.57

Outcomes 1 Year after Thrombus Aspiration for Myocardial Infarction

Bo Lagerqvist, M.D., Ph.D., Ole Fröbert, M.D., Ph.D., Göran K. Olvecrona, M.D., Ph.D., Thórarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Patrik Alström, M.D., Jonas Andersson, M.D., Ph.D., Fredrik Calais, M.D., Jörg Carlsson, M.D., Ph.D., Olov Collste, M.D., Matthias Göteborg, M.D., Ph.D., Peter Hårdhammar, M.D., Dan Ioanes, M.D., Anders Kallryd, M.D., Rickard Linder, M.D., Ph.D., Anders Lundin, M.D., Jacob Odenstedt, M.D., Elmir Omerovic, M.D., Ph.D., Verner Puskar, M.D., Tim Tödt, M.D., Ph.D., Eva Zelleroth, M.D., Ollie Östlund, Ph.D., and Stefan K. James, M.D., Ph.D.
Ongoing Registry-RCTs in Sweden

VALIDATE (n=6000)
- Bivalirudin versus Heparin in NST and ST- Elevation myocardial infarction in patients on modern antiplatelet therapy in SWEDHEART

DETOX-AMI (n=7000)
- DETermination of the role of OXygen in Acute Myocardial Infarction,

SWEDEPAD (n=2480)
- SWEdish Drug Elution trial in Peripheral Arterial Disease. DES vs BMS and DEB vs POBA.

IFR SWEDHEART (n=2000)
- Instantaneous Wave-Free Ratio versus Fractional Flow Reserve in ACS

PROSPECT-2 (n=1200, hybrid trial)
- Providing Regional Observations to Study Predictors of Events in the Coronary Tree.
  Evaluate future events from cholesterol plaques detected by near infrared spectroscopy

DISCO (n=2480)
- Evaluate if patients with out of hospital cardiac arrest should undergo routine coronary angiography

U-CARE (n=500)
- Evaluation of internet based cognitive behavioural therapy (iCBT) versus usual care in patients with depression/anxiety post MI.
Hybrid Approaches to Capture CV Endpoints

• In fragmented health care systems that have multiple, non-integrated EHR platforms (such as the U.S.), capturing CV endpoints through pragmatic methods is challenging

• Options that can be considered in this environment:
  – Studies conducted within a single system (VAMC)
  – Development of a research infrastructure that combines data from multiple EHR platforms (PCORnet)
Chlorthalidone Versus Hydrochlorothiazide: A New Kind of Veterans Affairs Cooperative Study

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Memphis VAMC

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Minneapolis Medical Center
PCORnet as Part of a National Evidence Generation Infrastructure

Medical Product Safety Surveillance
- FDA
  - Sentinel Coordinating Center
- Coordinating Center(s)
  - FDA, Industry
  - NIH, Industry
  - Clinical Research

Quality of Care
- Health Plans, others
  - Coordinating Center(s)

Public Health Surveillance
- CDC
  - Coordinating Center(s)

PCORnet as Part of a National Evidence Generation Infrastructure

DISTRIBUTED NETWORK GOVERNANCE

Sentinel

PCORnet

Common Data Model
- Data Standards

• Providers
  - Hospitals
  - Physicians
  - Integrated Systems

• Payers
  - Public
  - Private

• Registries
  - Disease-specific
  - Product-specific

Results

Queries

• Registries
  - Disease-specific
  - Product-specific

• Payers
  - Public
  - Private

• Providers
  - Hospitals
  - Physicians
  - Integrated Systems

PCORI, NIH, Industry
Comparative Effectiveness Research
What PCORnet Offers

PCORnet

130 health systems across the country
Over 60 data marts
Data on over 70 million patients
ADAPTABLE Study Design

Patients with known ASCVD + ≥ 1 “enrichment factor”*

Identified through EHR (computable phenotype) by CDRNs
(PPRN patients that are already a part of a CDRN are eligible to participate.)

Patients contacted with trial information and link to e-consent;†
Treatment assignment will be provided directly to patient

ASA 81 mg QD
ASA 325 mg QD

Electronic follow-up: Every 3–6 months
Supplemented with EHR/CDM/claims data

Duration: Enrollment over 24 months; maximum follow-up of 30 months

Primary endpoint:
Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke

Primary safety endpoint:
Hospitalization for major bleeding

† Participants without internet access will be consented and followed via a parallel system.
Approach to endpoint ascertainment

- Routine queries of the PCORnet common data model (CDM) to capture and classify endpoints
  - Hospitalizations identified via standardized, validated coding algorithms developed centrally and applied to the CDM
- ADAPTABLE web portal will ask about possible endpoint events (hospitalizations for MI, stroke, or major bleeding) during participant contacts (every 3–6 months)
  - Patient-reported outcomes supplement the CDM-generated hospitalization data
  - Surveillance of CMS and private health plan data for potential “out-of-network” hospitalizations
- Death ascertainment via Social Security Administration (Medicare beneficiaries) and National Death Index
E-nabling Pragmatic Research: e-data collection and e-follow-up

N=20,000

ADAPTABLE enrollee

Baseline data

Web portal follow-up
- Randomized to 3 vs 6 mos contact
- Patient-reported hospitalizations
- Medication use
- Health outcomes

PCORnet Coordinating Center follow-up
- Via Common Data Model
- Validated coding algorithms for endpoints

CMS and private health plans follow-up
- Longitudinal health outcomes
- Validated coding algorithms for endpoints

DCRI call center
- Patients who miss 2 contacts
- Patients without internet access

Death ascertainment
National Death Index (NDI) & Social Security Database

ClinicalTrials.gov: NCT02697916
Capturing CV Endpoints with Pragmatic Trials

• Multiple, streamlined operational approaches for capturing and confirming CV endpoints beyond established processes used with traditional trials
  – Central follow-up (without site personnel involved)
  – Leveraging existing longitudinal national health records
  – Hybrid electronic surveillance methods

• Completeness and accuracy of these approaches will require further validation studies to compare with traditional endpoint ascertainment and adjudication