II INTERNATIONAL SUMMER SCHOOL

Rare disease and orphan drug registries

Registry types, Aims, Building a registry, Management, and Sustainability

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Disclosures

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- Jesse's Journey
- Families of SMA Canada
- Starratt Family Foundation
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- Genzyme Canada

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- Muscular Dystrophy Canada

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Disclosures

I am an expert in patient registries

"An expert is a person who has found out by his own painful experience all the mistakes that one can make in a very narrow field" - Niels Bohr

Objectives

1. Registry types

2. Aims

3. Building a registry

4. Management of Operations

5. Sustainability

Registry development
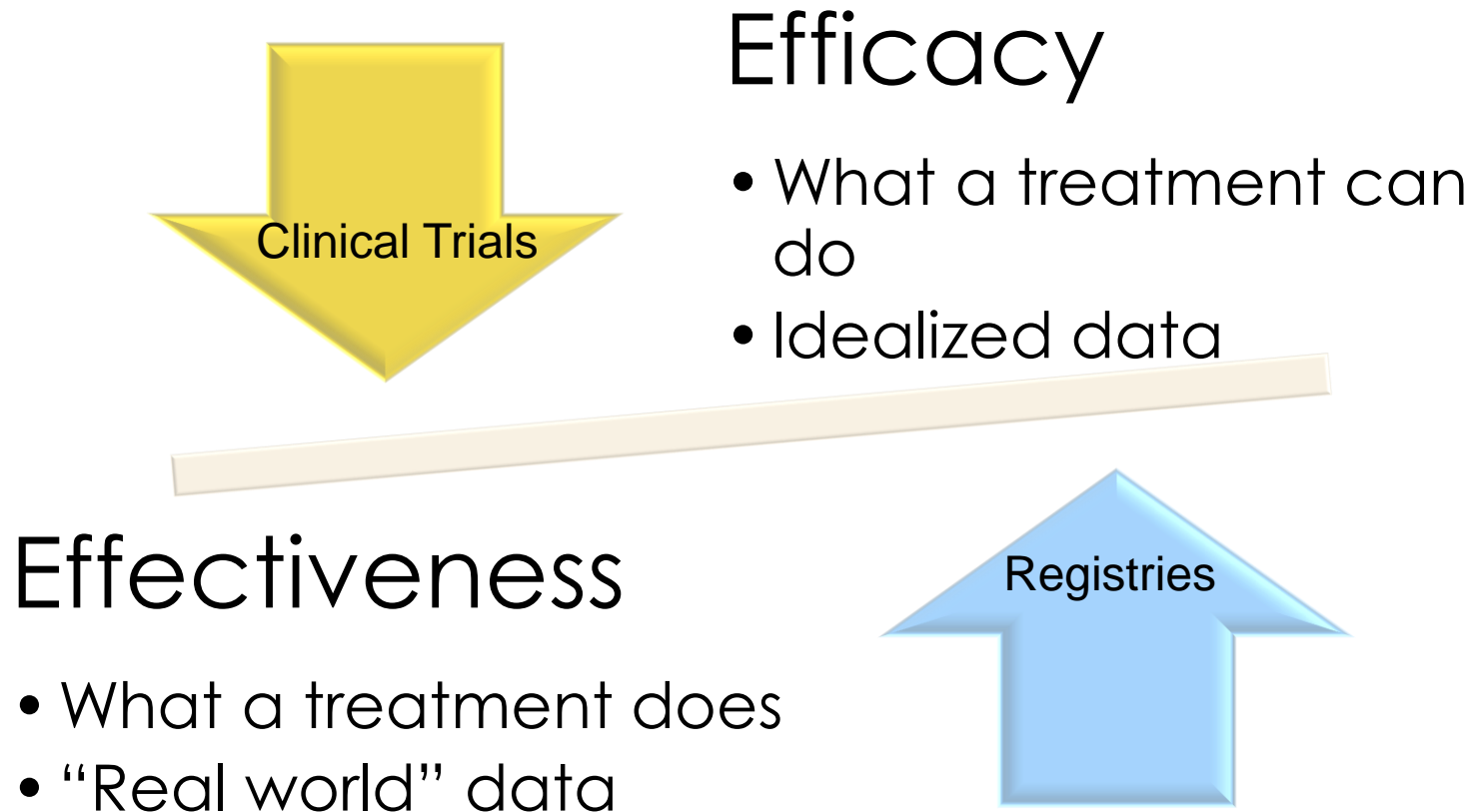
Where to begin?

Barriers

Time consuming

Expensive

Gustave Doré
Dante in the Dark Wood

Definition of a Clinical Registry

- A system used to organize or catalogue patient information for research, administrative, regulatory or governmental purposes

Registry data

Efficacy

- What a treatment can do
- Idealized data

Clinical Trials

Effectiveness

- What a treatment does
- "Real world" data

Registries

First Question

- Is a registry the appropriate method?

- What are the types of registries?

Types of Registries

- By drivers
  - Physician driven
  - Patient driven

- By method of data collection
  - Web-based
  - Electronic chart-based
  - Clinic-based

Pro's and Con's to each driver and method

Conventional and Innovative Roles for Registries

- Conventional
  - Trial readiness (Canadian Neuromuscular Disease Registry)
  - Natural history (Pompe disease)
  - Quality improvement (stroke care)
  - Disease subgroup characterization (pituitary and lung tumors)
  - Post-marketing surveillance (cardiovascular stents)
  - Monitoring of clinical outcomes (everolimus in cardiac transplant patients)

Forced Vital Capacity by Age across DMD subjects in the CNDR
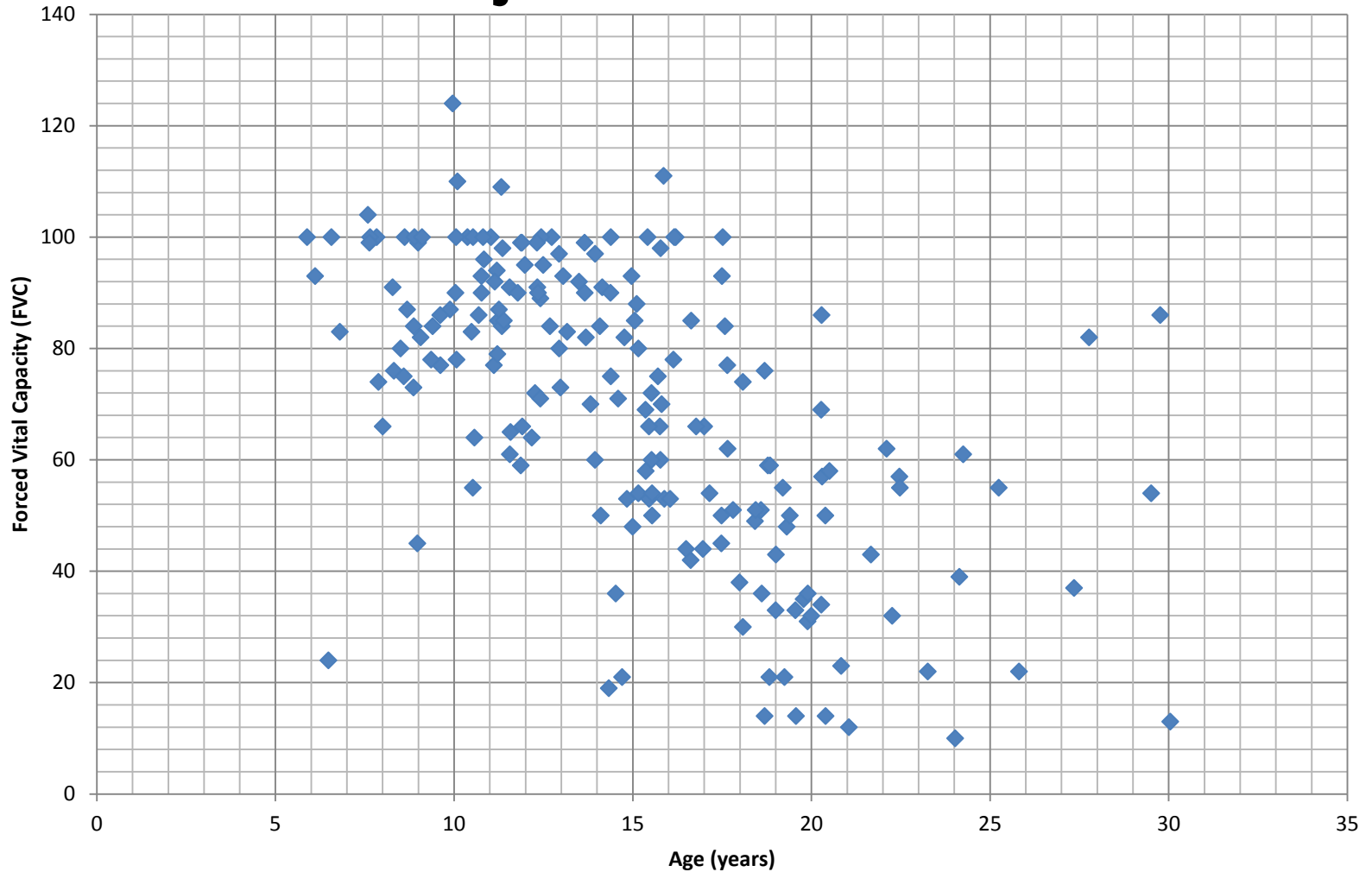
Conventional and Innovative Roles for Registries

- Innovative
  - Examining the impact of a diagnostic test on patient management (i.e. PET scanning on management of cancer patients)
  - Clinical instrument development (i.e. management of hospitalized patients with heart failure)
  - Serving as a ureteral stent removal reminder system to Urologists

Registry-Based RCTs

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
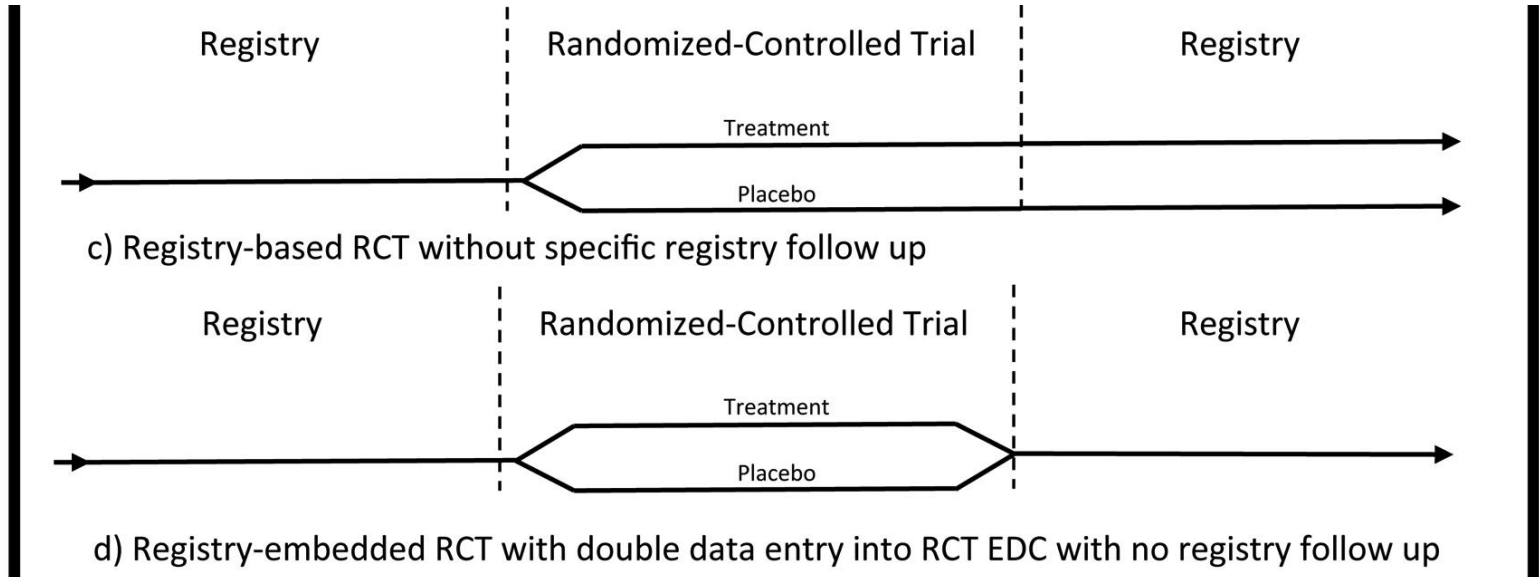
the effects of unmeasured con-

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 rare diseases such as hypertrophic cardiomyop-

Lauer MS, D'Agostino RB, New England Journal of Medicine, September 1, 2013

An example ... RB-RCT

- The Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial

- Operated within the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) registry

- RCT of 7244 subjects at an incremental cost of US$300,000 or US$50 per subject

  - Frobert O et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med. 2013;369(17):1587-97.
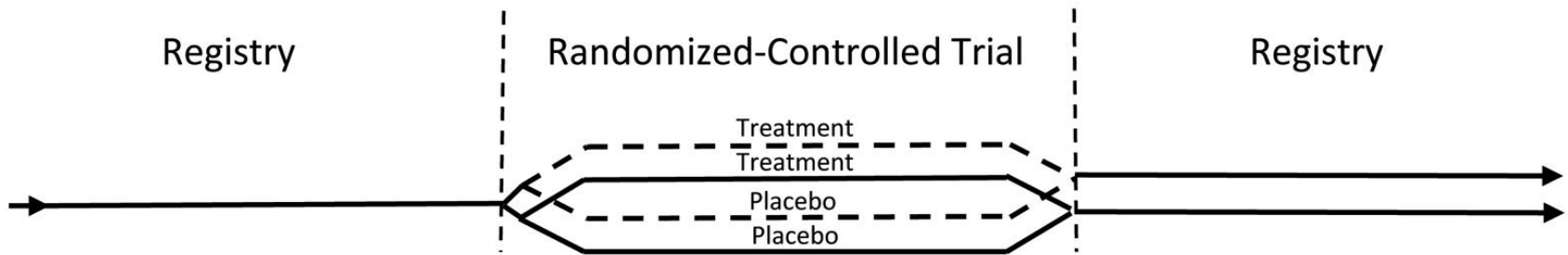
Types of Registries for Registry-Based Clinical Trials

| Registry | Randomized-Controlled Trial | Registry |

Treatment

Placebo

c) Registry-based RCT without specific registry follow up

| Registry | Randomized-Controlled Trial | Registry |

Treatment

Placebo

d) Registry-embedded RCT with double data entry into RCT EDC with no registry follow up

d) Registry-embedded RCT with double data entry into RCT EDC with no registry follow up

Registry | Randomized-Controlled Trial | Registry

Treatment
Treatment
Placebo
Placebo
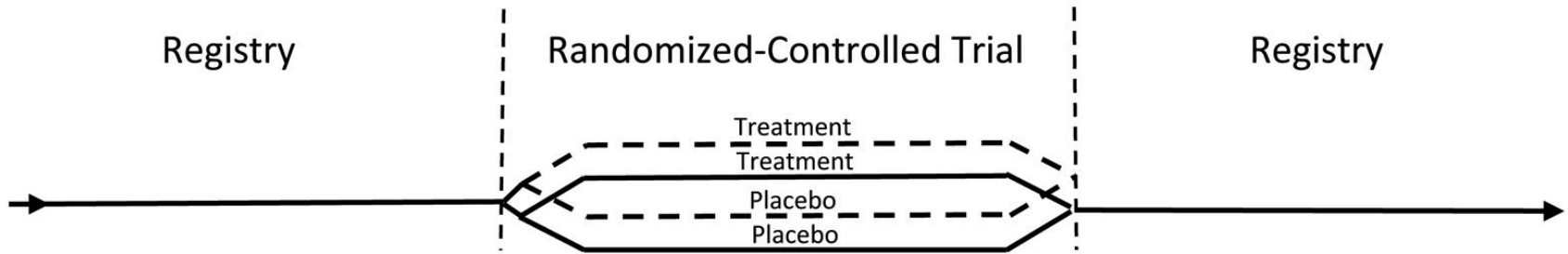
e) Registry-embedded RCT with double data entry into RCT EDC with registry follow up

Registry | Randomized-Controlled Trial | Registry

Treatment
Treatment
Placebo
Placebo

Registry Aims

- Natural history of disease

- Treatment/device safety

- Outcome measure validation

- Trial readiness

- Molecular epidemiology

- Etc, etc, etc

Objectives and Impact

- ☐ Focused objectives are critical

- ☐ Should reflect expected impact

- ☐ Example: clinical trial recruitment tool
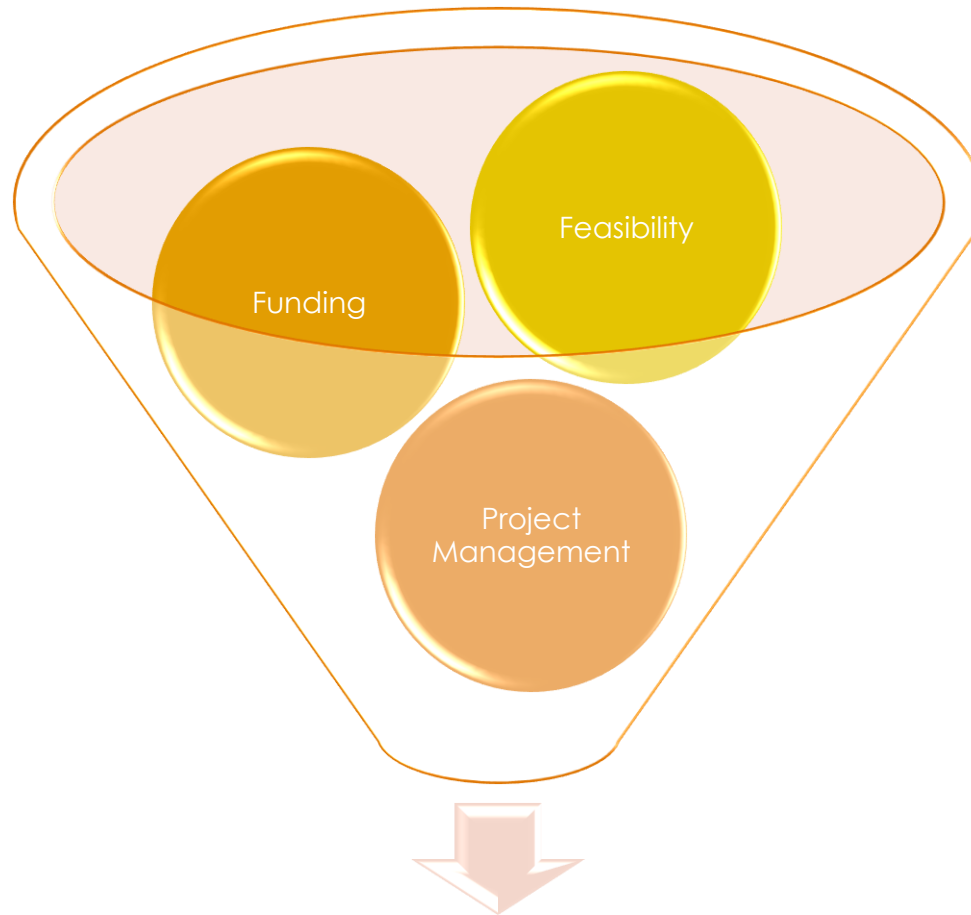
| Impact:
More efficient testing of potential therapies | Objective:
Accelerated recruitment into clinical trials | Registry Design:
Up to date clinical information for each participant | Registry Design:
Clinic-based dataset based on clinical trial inclusion/exclusion criteria |

Start Building a Registry from the Desired Impact or Outcome

Funding

Feasibility

Project Management

Sustainability and Impact

ALS Clinical Trial Recruitment
University of Calgary

2009	2010	2011	2012	2013
4	3	3	4	21

Launch of ALS-CNDR

Building a registry

Patient Perspectives: Motivating factors for patient participation in registries

- Altruistic attitudes – the perception of benefit to the greater good even beyond immediate individual benefit or the potential for individual benefit

- That data will be used by responsible people for legitimate purposes – participants desire clear purposes for collecting data and clear methods for its release

- Advancement in research and the possibility of elucidation of treatment or cure, and subsequently improved quality of life

Korngut L et al. Perspectives on Neurological Patient Registries: A literature review and focus group study. BMC Medical Research Methodology 2013, 13 :135

Patient Perspectives: Motivating factors for patient participation in registries

- ☐ Desire for prompt information after diagnosis

- ☐ Perception of equal communication with health practitioners and researchers

- ☐ Other factors influencing participation include satisfaction with care, age, education, gender and recruiting site

Korngut L et al. Perspectives on Neurological Patient Registries: A literature review and focus group study. BMC Medical Research Methodology 2013, 13 :135

Building a Registry

- Design
  - Begin with your primary objective
  - Can have many secondary objectives
  - Design the registry to address your objectives in a cost-effective manner with minimal participant and investigator burden

The Steps

- Determine Desired Impact or Outcome

- Purpose of Registry

- Research Questions/Objectives

- Inclusion/Exclusion criteria

- Target population and sampling methodology

The Steps

- Anticipated size and duration of the registry

- Data collection and analysis

- Data dictionaries and coding manuals

- Sources of registry data

- How to use the paper and/or electronic case report form and archiving

- Roles of registry personnel and corresponding job descriptions/qualifications required

The Steps

- Legal and ethical documentation (confidentiality agreements; data-sharing agreements and ethics certificates and submissions)

- Data management policies and agreements governing data management (contractor agreements; database administrator position description etc).

The Steps

- Recruitment/withdrawal procedures including copies of appropriate consent/withdrawal forms and how they should be retained/copied/archived.

- Procedures for promoting and subsequently evaluating data quality.

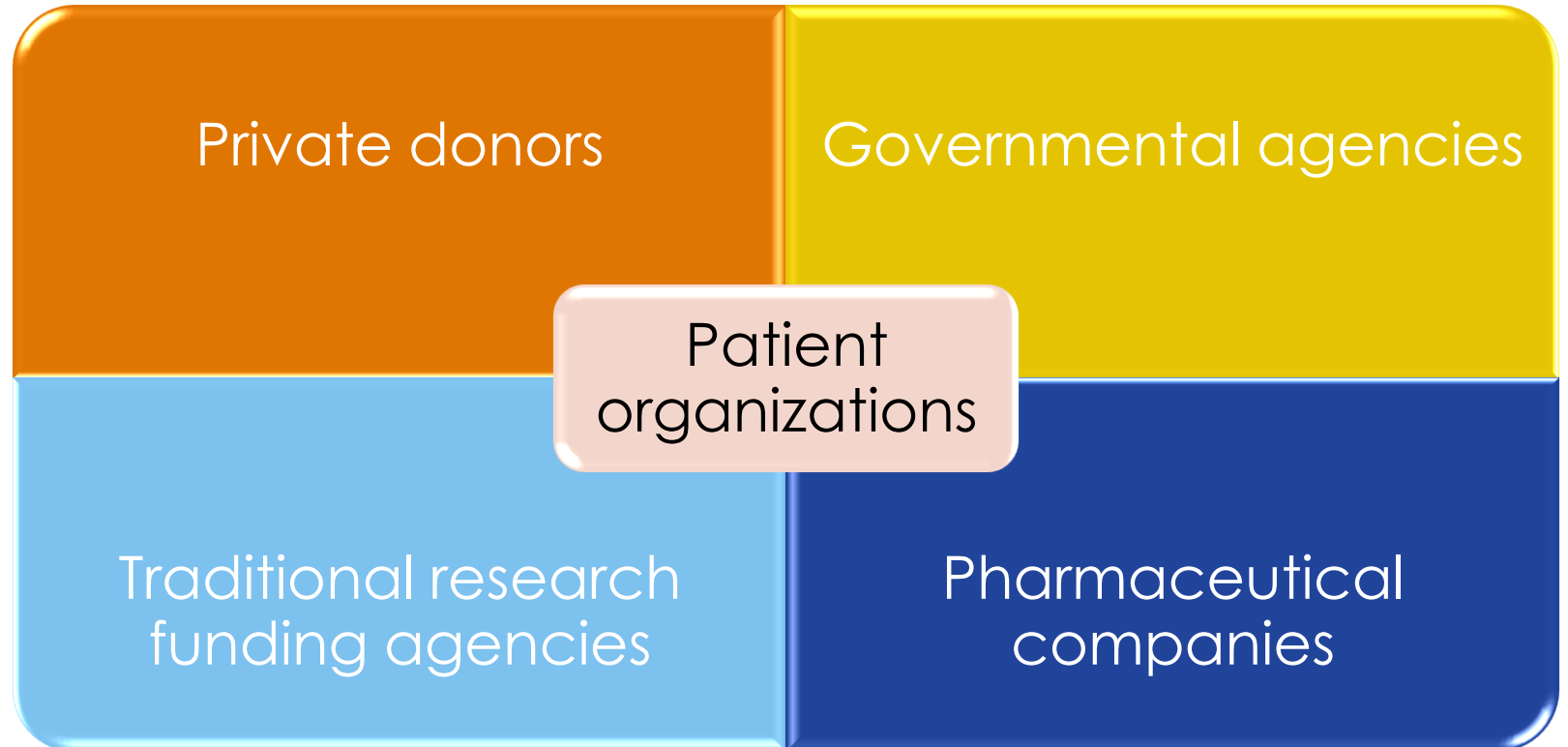- How patient identification codes are assigned, how duplicate records are prevented

The Steps

- Procedures for access to data for research purposes (internal and external).

- Data security measures and procedures in the event of a security breach.

- Registry governance structure and roles.

Funding
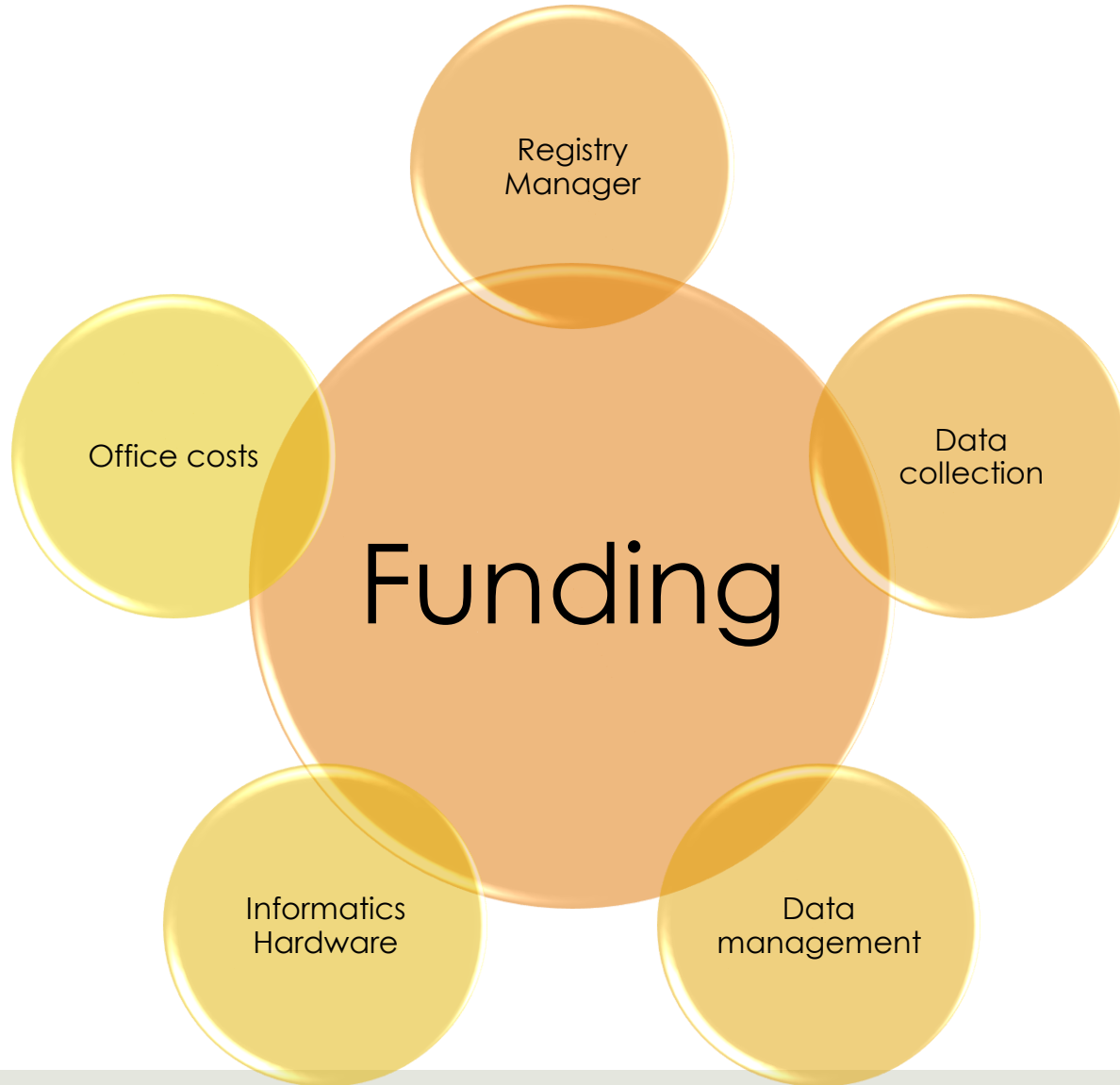
Potential Funding Sources

Private donors

Governmental agencies

Patient organizations

Traditional research funding agencies

Pharmaceutical companies

Registry Operation

Project Management
- Project plan
- Project milestones
- Implementation
- Budget
- Human resources

Research
- Defining objectives
- Research applications of data
- Recruitment
- Data analysis

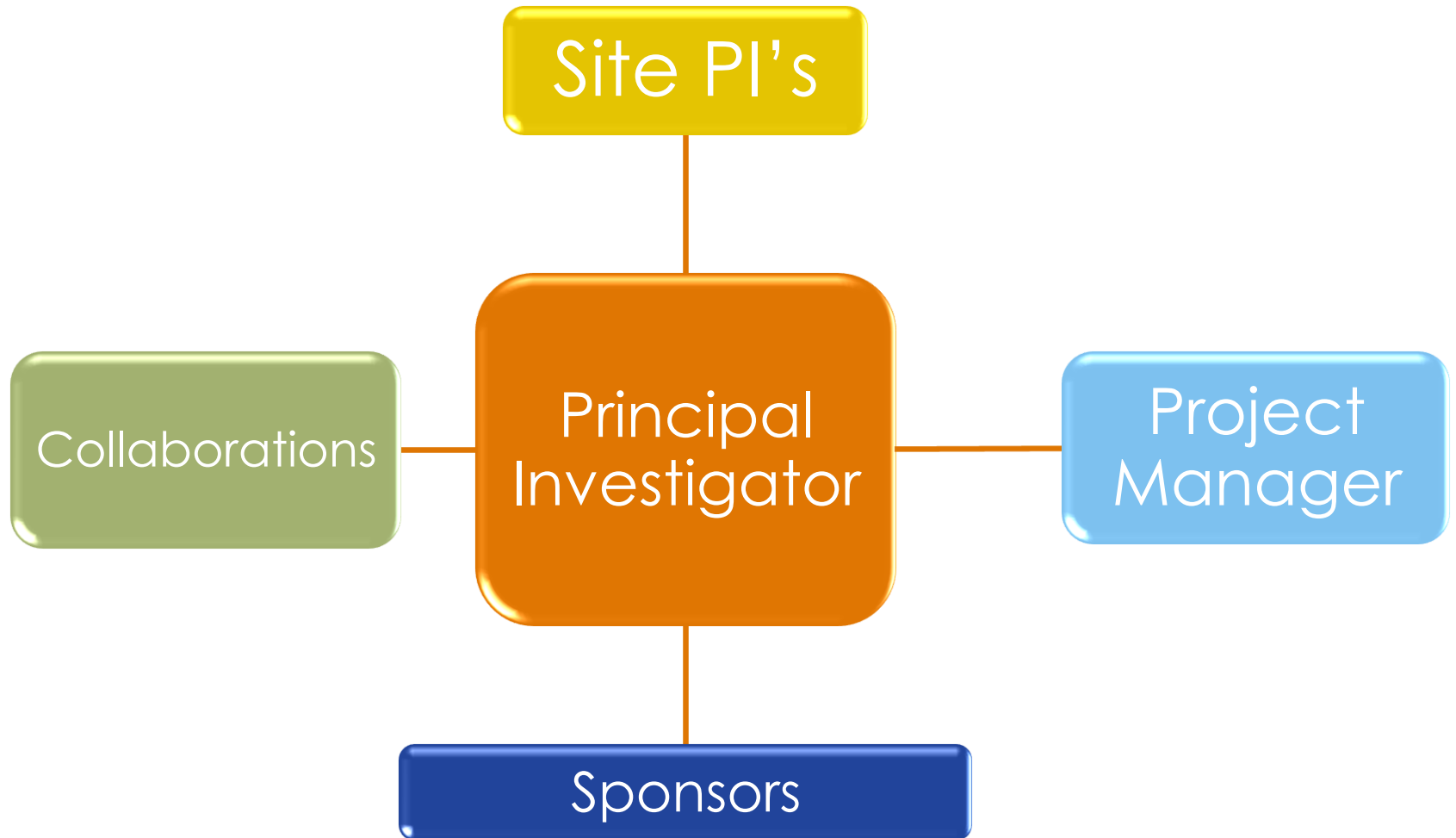**Project management is a very different skill from research!**

Registry Operation

- Considerable overlap between research and project management
    - Data set derivation
    - Database capacity and optimization
    - Clinical and research utility
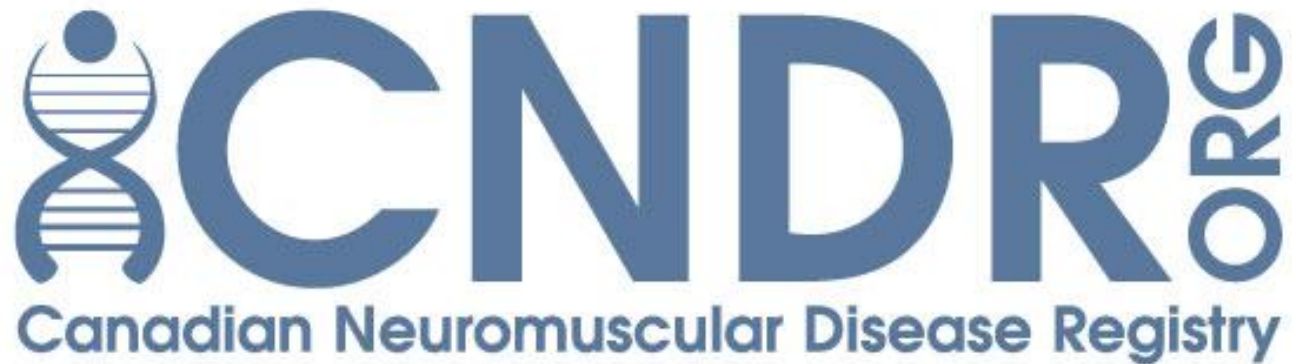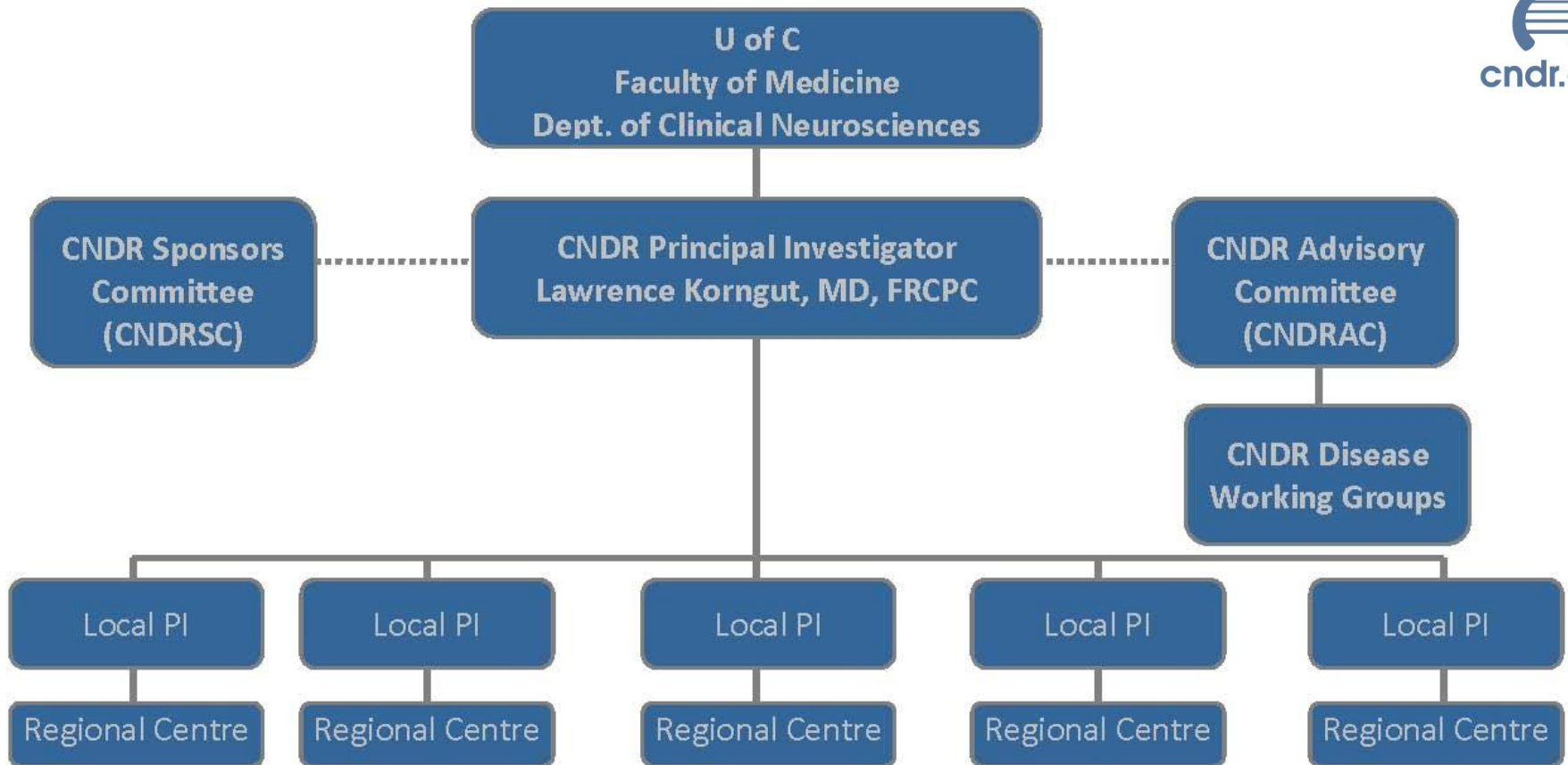   - Quality control and monitoring

Operational Roles: Project Manager
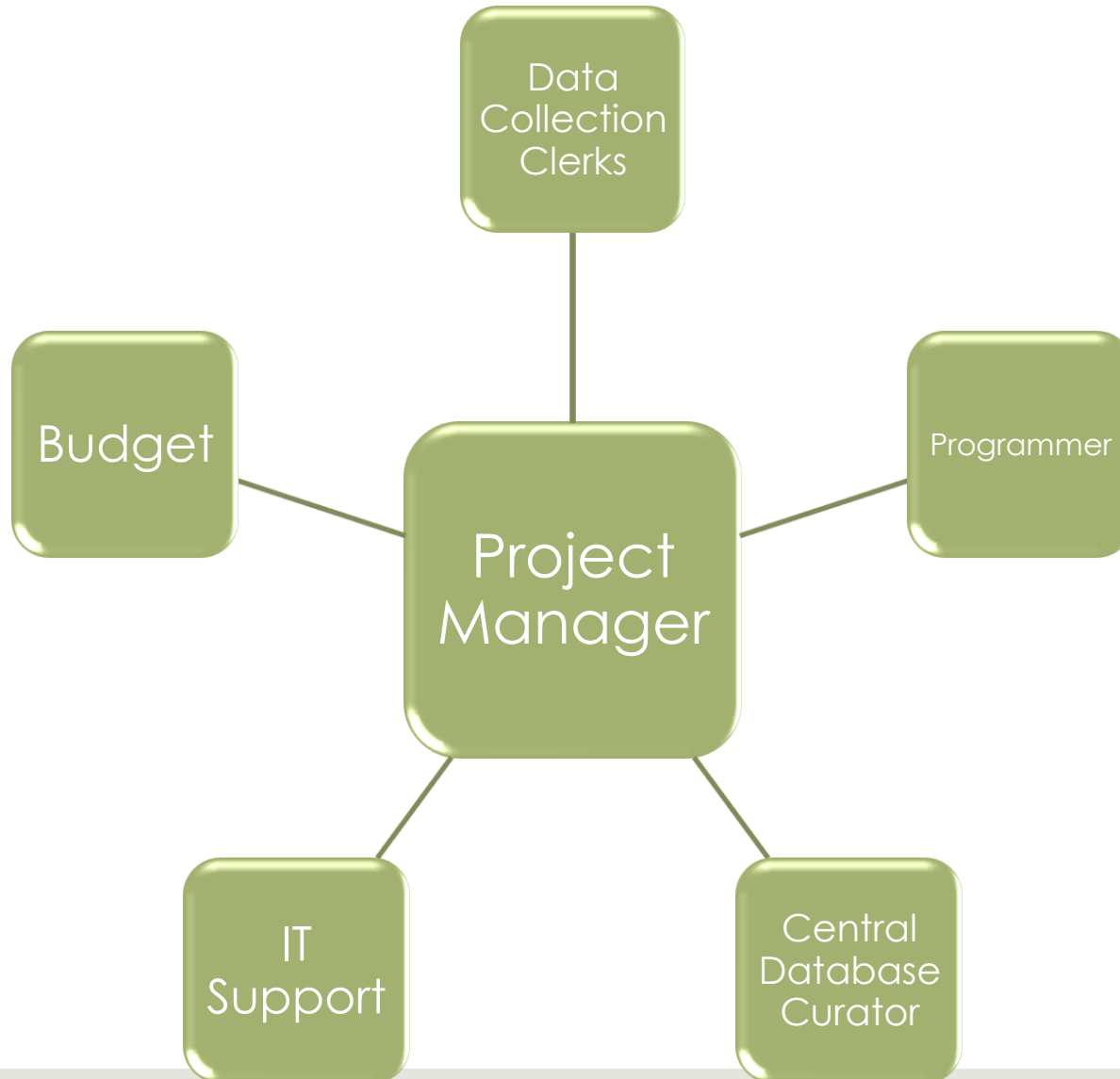
Operational Roles: PI

Management: An Example

CNDR Organizational Structure

Management Roles

Rapid identification of subject meeting clinical trial inclusion/exclusion criteria

De-identified aggregate data available for national level studies

CNDR Webserver
University of Calgary
VIA Secure Portal
Login

Data Entry Clerk

Data Entry Clerk

Data Entry Clerk

Data Entry Clerk

NMC Clinician

NMC Clinician

NMC Clinician
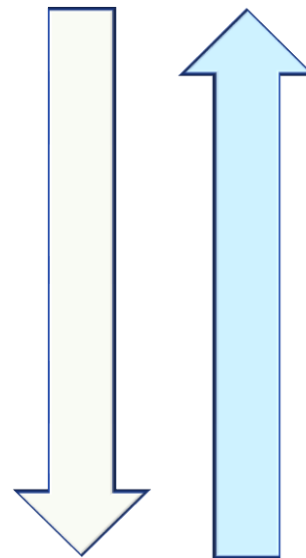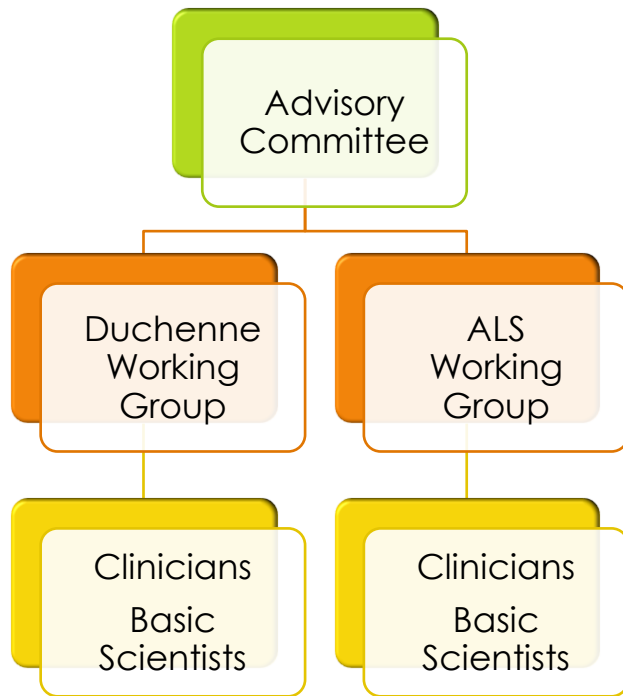
NMC Clinician

NMC Clinician

NMC Clinician

NMC Clinician

NMC Clinician

Each site retains all data for research and clinical use

Subject data updated at each visit

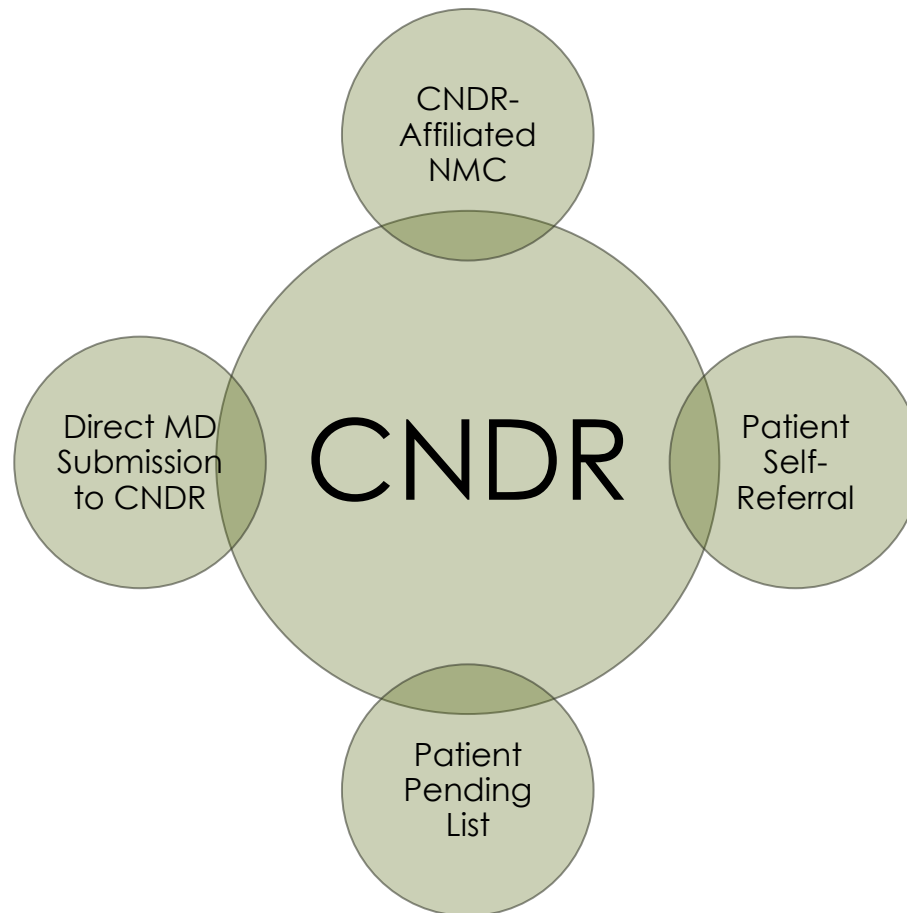cndr.org

CNDR Working Groups

Advisory Committee

Duchenne Working Group

ALS Working Group

Clinicians
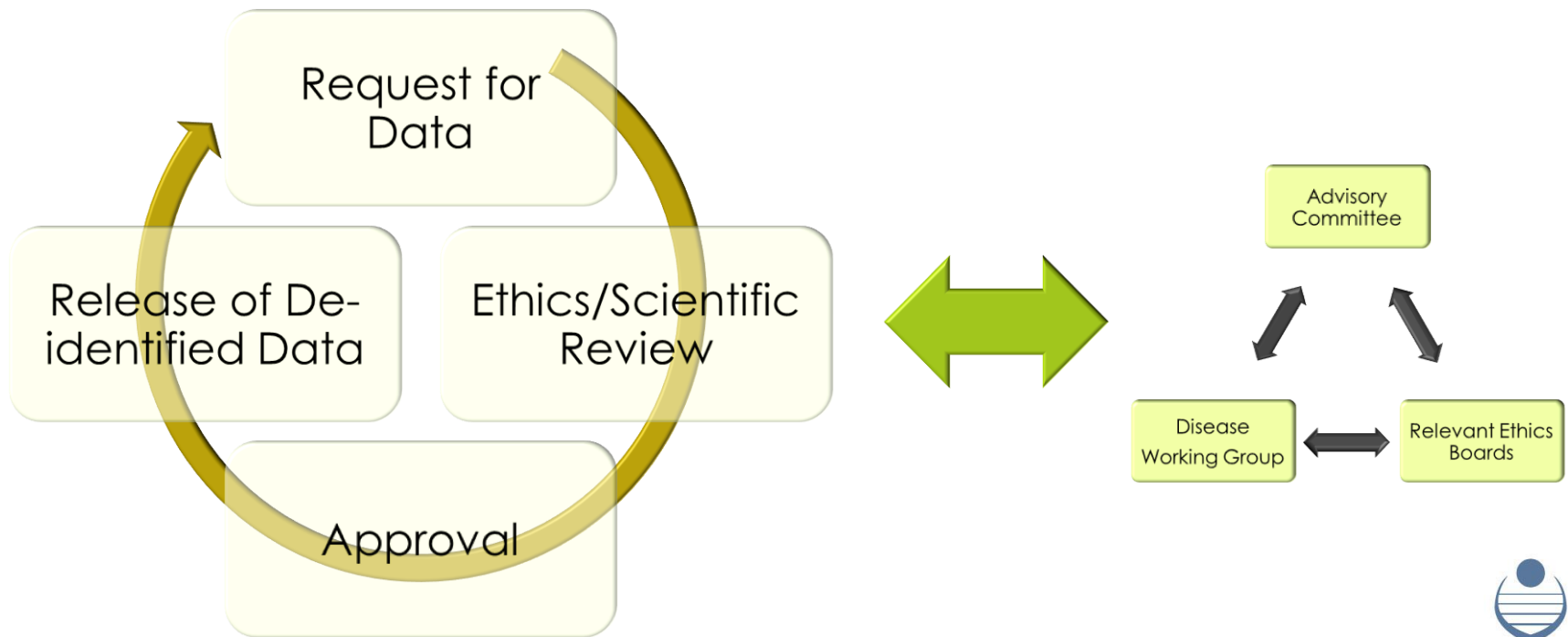Basic Scientists

Clinicians
Basic Scientists

Scientific Review

- Dataset generation
- Dataset maintenance
- Study inquiry review

cndr.org

Patient Enrollment

Data Access to Investigators

Recruitment for Clinical Trials

Clinical trial inquiry
- Inclusion and exclusion criteria

Database Scan
- Subject identification

Site and Subject Notification

cndr.org
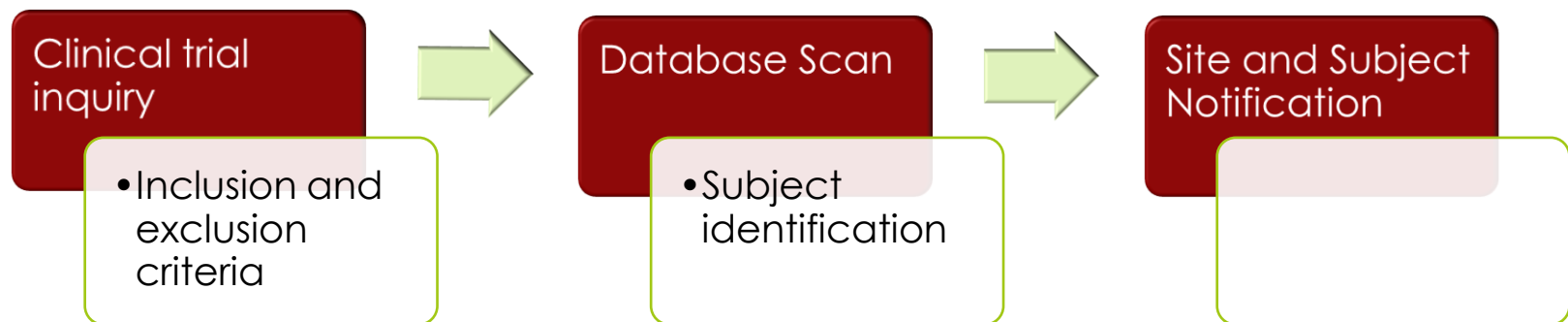
Operational and Organizational Complexity

- Registries can be complex
  - Clear operationalization of procedures is required
  - Detailed operating manuals are invaluable
  - Standardization of data collection, entry and management is essential

Registry Sustainability

The
journal
Canadian Journal of Neurological Sciences

A REFERENCE DOCUMENT

Neurological Registry
Best Practice Guidelines

A Peer-Reviewed Practical Guide to Patient Registry Development and Operations in Canada

Acknowledgements

Lead PI: Lawrence Korngut
Co-PIs: Nathalie Jetté, Tamara Pringsheim

Registry Literature Review Flowchart

Identification

| Abstracts Identified through MEDLINE (n= 5699) | Abstracts Identified through Cochrane CENTRAL (n= 162) | Abstracts Identified through Cochrane SR (n= 0) | Abstracts Identified through PubMED (n= 5946) | Abstracts Identified through EMBASE (n= 2128) | Abstracts Identified through PsychINFO (n= 240) | Abstracts Identified through ABI Inform (n= 406) | Abstracts Identified through BIOSIS Previews (n= 4325) | Abstracts Identified through PAIS (n= 96) |

Total Abstracts (n=19002)

Abstracts after duplicates removed (n=6435)

Screening

Registry terms in subject & abstract (n=3994)

Registry terms in title (n=2441)

Selected for inclusion by RA:
Canadian (n=39)
Compare Methodology (n=28)
Development (n=287)
Feasibility (n=208)
*Impact (n=1368)
Innovation (49)
Perceptions (n=52)
Privacy (n=27)
Recruitment (n=46)
Toolkit (n=26)
Validation (n=82)
Total without duplicates (n=1880)

Excluded by RA (n=2114)

Excluded by RA (n=124)

Selected for inclusion by RA:
Canadian (n=39)
Compare Methodology (n=41)
Development (n=340)
Feasibility (n=201)
*Impact (n=765)
Innovation (32)
Perceptions (n=27)
Privacy (n=27)
Recruitment (n=50)
Toolkit (n=10)
Validation (n=149)
Total without duplicates (n=2317)

Excluded by second reviewer (n=3787)

*Impact articles were not screened for full text review

Selected for Full Text Review (n=410; some articles address more than one topic):

| Compare Methodology (n=34) | Development (n=170) | Feasibility (n=90) | Innovation (n=23) | Perceptions (n=37) | Privacy (n=30) | Recruitment (n=37) | Toolkit (n=22) | Validation (n=79) |

Included

| 7 | 28 | 24 | 19 | 24 | 19 | 23 | 5 | 62 |

Neurological Registry Feasibility and Sustainability

*Tamara Pringsheim[1], Ruth Ann Marrie[2], Elizabeth Donner[3],
Michael Shevell[4], Darren Lam[1], Lundy Day[1], Megan Johnston[1],
Nathalie Jette[1,5], Lawrence Korngut[1]*

- The feasibility and sustainability of a registry depend on many factors
  - researchers, clinicians, administrators and participants.

- The development and maintenance of a successful registry may be improved by considering the following elements in the design and implementation of registry procedures

Literature Review

- Factors that negatively affect feasibility (sustainability)
  - Confidentiality/privacy issues
  - Barriers to participation
  - Issues related to multiple centres and locations
  - Issues related to human and financial resources
  - Poor data
  - Quality(non-uniform, missing, or incomplete data), and potential
  - Bias

Literature Review

- Factors that enhance feasibility (sustainability)
  - Clear purpose
  - Data collection
  - Stakeholder engagement
  - Communication
  - Finances
  - Human resources
  - Change management

Literature Review

- Data collection practices that promote feasibility (sustainability)
  - Minimum core dataset
  - Data entry
  - Consent
  - Collaboration
  - Innovation
    - Harmonization of data collection
    - Incentives for patient participation

Feasibility (Sustainability) Recommendations

✓ Have adequate advance planning and infrastructure (including human and monetary resources)

✓ Incorporate minimal data collection time and frequency while tailoring the mode of data collection to participant needs.

✓ Pilot test data collection practices to ensure they work as designed.

Feasibility (Sustainability) Recommendations

- ✓ Have a diverse advisory board representing ethics, legal, operational, participant and sponsor interests.

- ✓ Employ regular communication amongst all stakeholders.

- ✓ Utilize graduated consent, and other participant retention tools such as a registry website and newsletter.

Feasibility (Sustainability) Recommendations

✓ Regularly engage providers through training meetings, regular data reports and presentations at conferences.

✓ Cultivate long-term funding through activities that raise

✓ Act in a transparent manner.

Feasibility (Sustainability) Recommendations

✓ Utilize common data elements to enhance registry compatibility.

✓ Link with vital statistics to determine whether patient has died and address other accessible information that may be of interest (seek patient consent for this).

✓ Address challenges associated with recruitment and retention of members of minority groups to ensure representativeness.

Important Points about Sustainability

- Aspects of sustainability are
    - Feasibility
    - Funding
    - Effective operation
    - Usefulness of data
    - Impact

The "Impact" Cycle of Sustainability
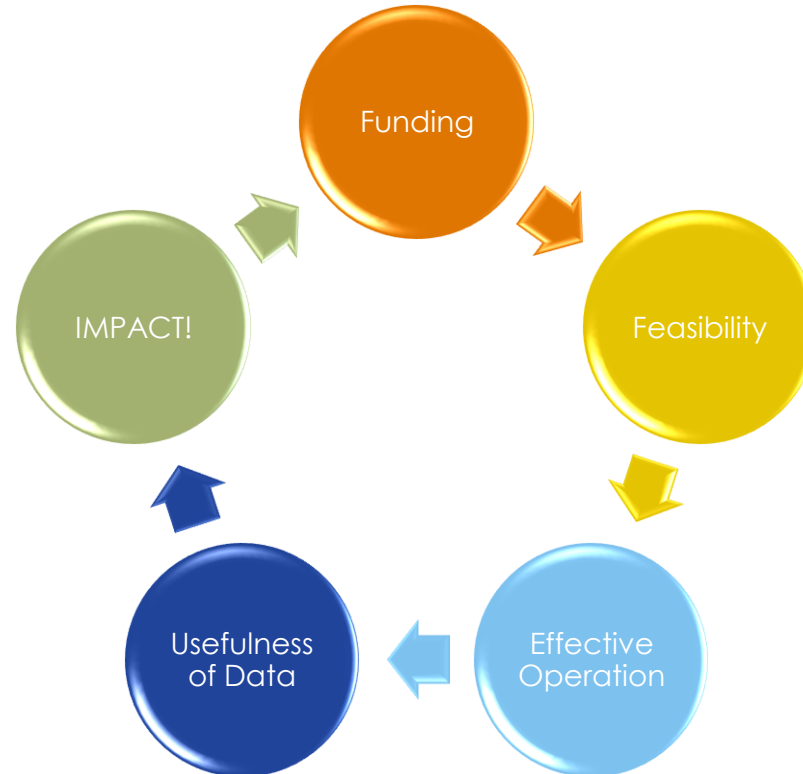
Canadian Registry Network
Réseau canadien de registres

1. Best practice guidelines

2. Implementation toolkit

3. Case report/data set metaregistry

4. Seek funding for common infrastructure/technology

5. Collaborate

6. Data linkages

7. Reduce cost

8. www.canadianregistrynetwork.org

Connecting
researchers *everywhere*
Rapprocher
les chercheurs *partout*

Canadian Registry Network
Réseau canadien de registres

The Canadian Cerebral Palsy Registry

The Canadian Neuromuscular Disease Registry (CNDR)

The North American Research Committee on

Multiple Sclerosis (NARCOMS) Registry

The Ontario Stroke Registry

The Quebec Myotonic Dystrophy Registry

The Rick Hansen Spinal Cord Injury Registry (RHSCIR)

Canadian Hydrocephalus Clinical Research Network (under development)

The Southern Alberta Dementia Registry (under development)

The Sudden Unexplained Death in

Epilepsy (SUDEP) Registry (under development)

Connecting
researchers *everywhere*
Rapprocher
les chercheurs *partout*

You can access the Toolkit website at

canadianregistrynetwork.org

Connecting
researchers *everywhere*
Rapprocher
les chercheurs *partout*

Team Members

- Megan Johnston,
  - Director, Canadian Neuromuscular Disease Network
  - Project Manager, Canadian Neuromuscular Disease Registry

- Janet Petrillo
  - Clinical Research Co-ordinator

- Jose Martinez
  - Clinical Research Co-ordinator

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