Necessity is the Mother of Invention

The Impetus for Observational Research in Orphan Drug Development

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WORLDWIDE CLINICAL TRIALS

SCIENTIFICALLY MINDED • MEDICALLY DRIVEN

Michael Murphy, M.D., Ph.D.

Chief Medical and Scientific Officer

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Agenda

- Introduction
  Dr. Michael Murphy
- New Perspectives in Patient Centered Recruitment and Care
  Barbara Zupancic
- Observational Research: An Operational Approach
  Lorna Graham
- Statistical Considerations in Observational Studies
  Josie Measures
- Q & A

Responding to the “Other Stakeholders”

Academia Assisted Living Insured Children

Uninsured

Care Providers

Financial Markets

Nursing Homes

Patients

Consumers

Nurses

Insurers

Labs

Physicians

Intermediaries

Women

Seniors

Regional Variation

CMS, State Medicaid

Med Tech

Unions

Global Regulation

Products & Services

Disease Management

Medicare - Medicaid

Governments

States

Bio Tech

Basic Researchers

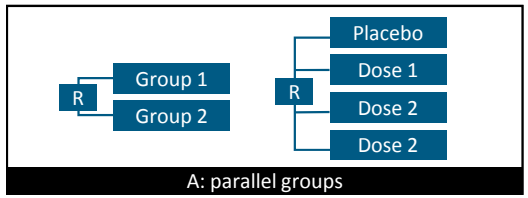
Devices

Employers

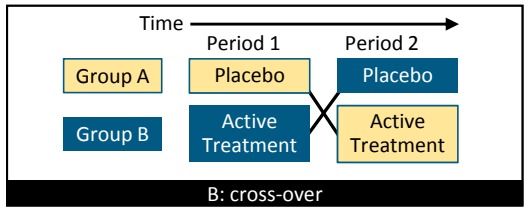
Pharma

Neither orderly nor rational, multiple stakeholders impact R&D with conflicting data needs.

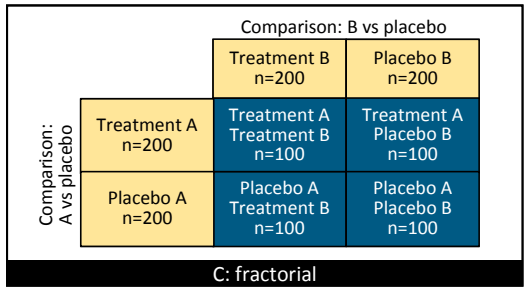
Many Options for Interventional Studies



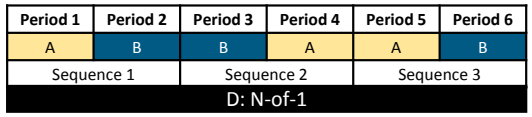
A: parallel groups



B: cross-over

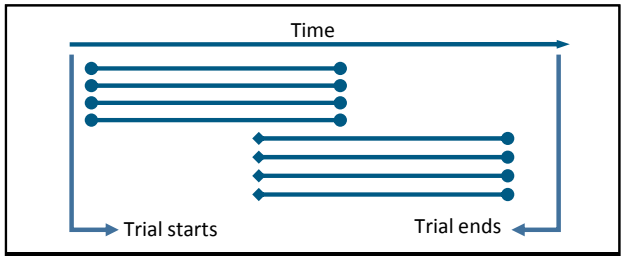


C: fractorial

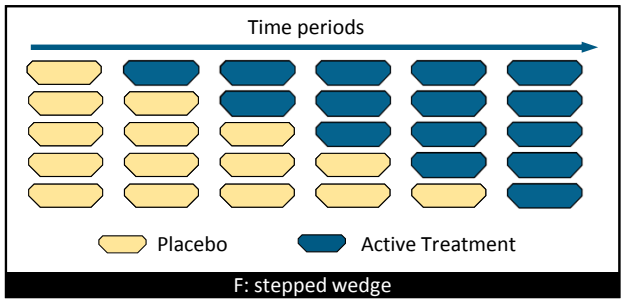


D: N-of-1

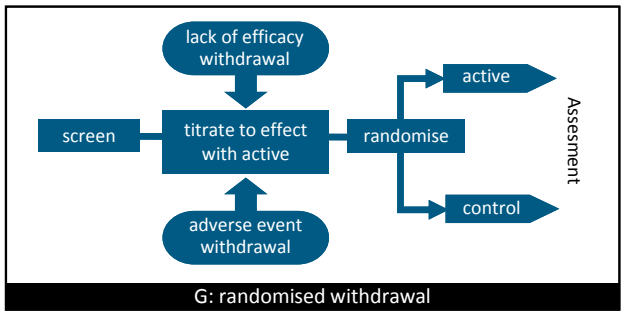
See Cornu et al, 2013; Gagne et al 2014



E: randomised placebo phase



F: stepped wedge



G: randomised withdrawal

- **Minimizing sample**
  - Adaptive randomization
  - Longer trials, more events/ patient
  - Risk stratification
  - Continuous and composite measures, repeated measures
  - "relaxed alpha's" within Bayesian frameworks
- **Maximizing treatment**
  - Parallel groups
  - Crossovers and permutations
  - Factorial
  - "n-of-one"
  - Randomized placebo
  - Stepped wedge and variations
  - Randomized withdrawal

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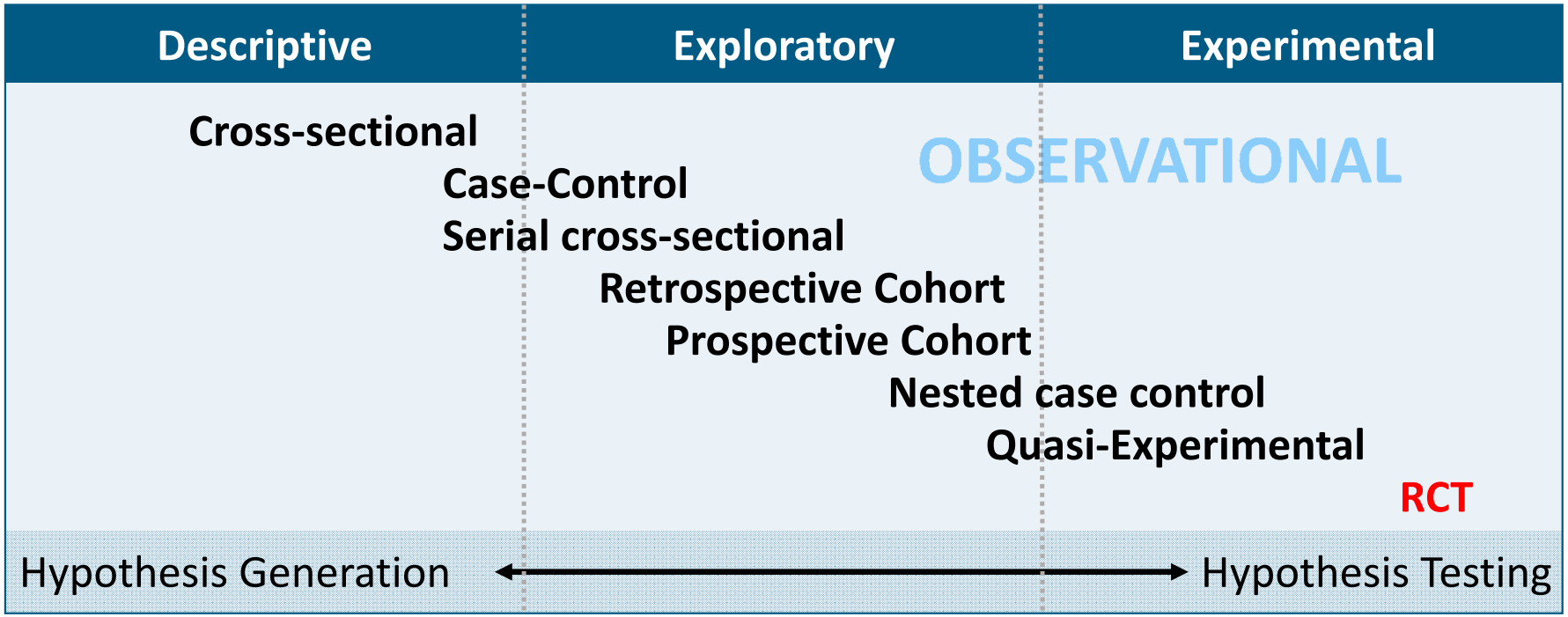
…But Other Arrows in the Quiver



Shah, N. Evidence standards in the era of comparative effectiveness. AHDB.2(1): s41-s48, 2009.

…That Can Answer Diverse Questions

To inform protocol design?

As a complement to a submission strategy?

To shape formulary & reimbursement decisions?

With many objectives

- Natural history of disease
- Burden of illness
- Treatment Pathways
- Disease Management
- Usage (on & off label)
- Comparative effectiveness

For Today's Presentation

- What questions are amenable to observational methods, and who is asking?
- How has R&D in orphan diseases shaped patient, family, and payer expectations?
- What are the options and the challenges in implementation?
- What are opportunities and limitations in analysis and interpretation– as a standalone study, or integrated with interventional trials?

Barbara Zupancic, MBA, MSc

Director, Global Patient Recruitment and Retention

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New Perspectives in Patient Centered Recruitment and Care

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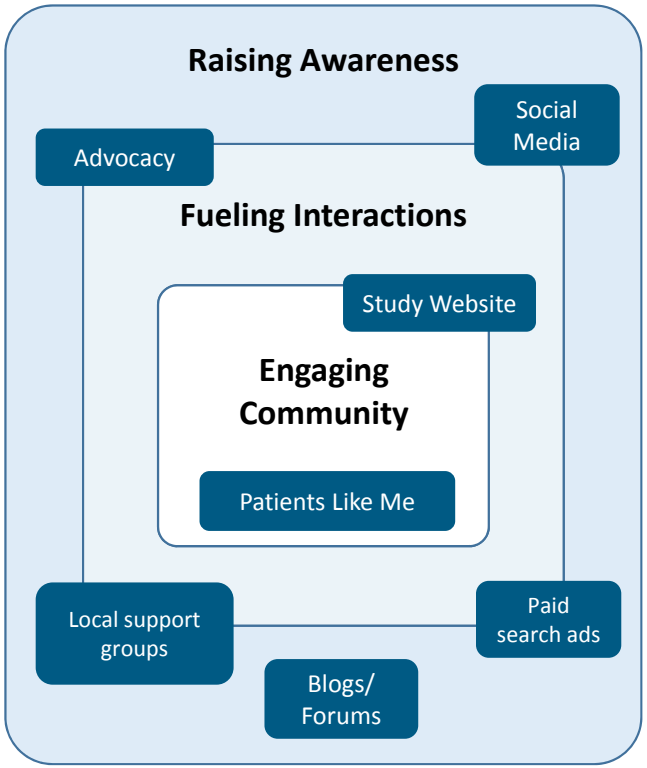
Patient Focused Engagement

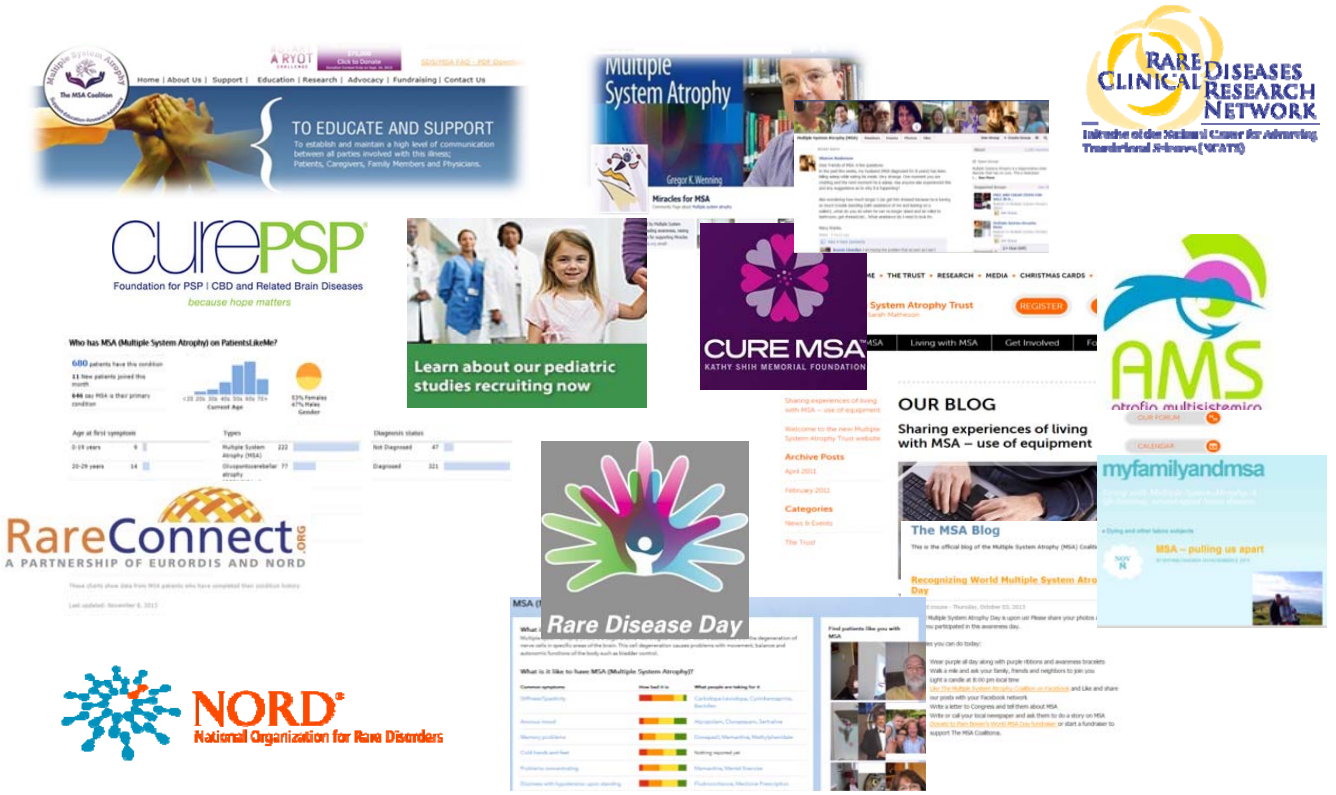
- Rare Disease Patients are a community
- Most Affected are children
- The patient voice is a powerful driver in rare-disease research
- We must truly understand the role of the caregiver
- Engage small investigator community
- Go where the patients are
- Engagement with Patient and Physician organizations
- Local team fosters close contact with national KOLs and referral centers
- Adapted site and patient treatment settings (evaluation vs. treatment sites)
- Expert involvement (KOL) in protocol and trial design (availability of validated endpoints)

Considerations Specific to Rare Disease

- Rare indication and finite number of subjects available for participation
- Recruitment success is highly dependent on site selection
- Feasibility is still driven by sites with the best patient access
- Identify gaps at more research naïve sites; plan mitigation and training
- Often need to address expanded geography - the study goes where the patients are
- Greater emphasis on utilizing advocacy groups, word of mouth through patient community, advertising
- Engagement with specialized resources – rare disease research networks, patient registries, Patients-Like-Me, etc.
- Travel Assistance is crucial. Need to organize a central resource for pre-paid travel arrangements where needed

Outreach, Support and Engagement Tactics





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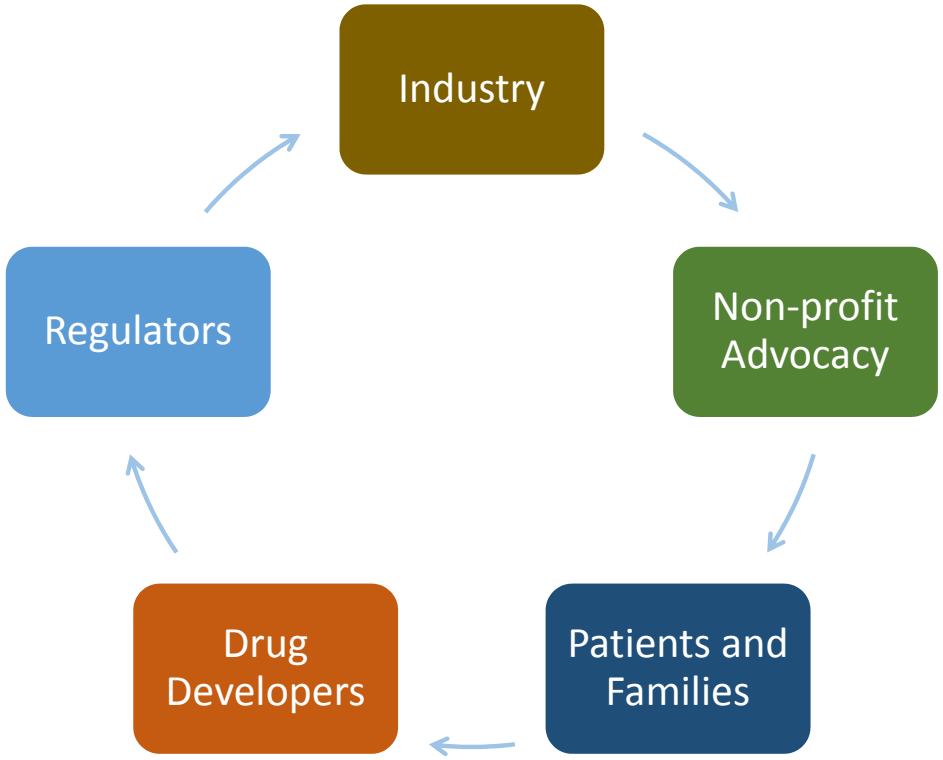
Value of Observational Research in Rare Disease

- Value of Observational studies
- Observational studies as comparative research- simply filling the gap or adding value to randomized clinical trials
- Real world practice

Stronger Partnerships



21st Century Cures

Lorna Graham, BSc, MSc

Associate Director, Project Management, Evidence

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Observational Research: An Operational Approach

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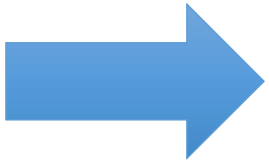
Real World Evidence- Data Generation

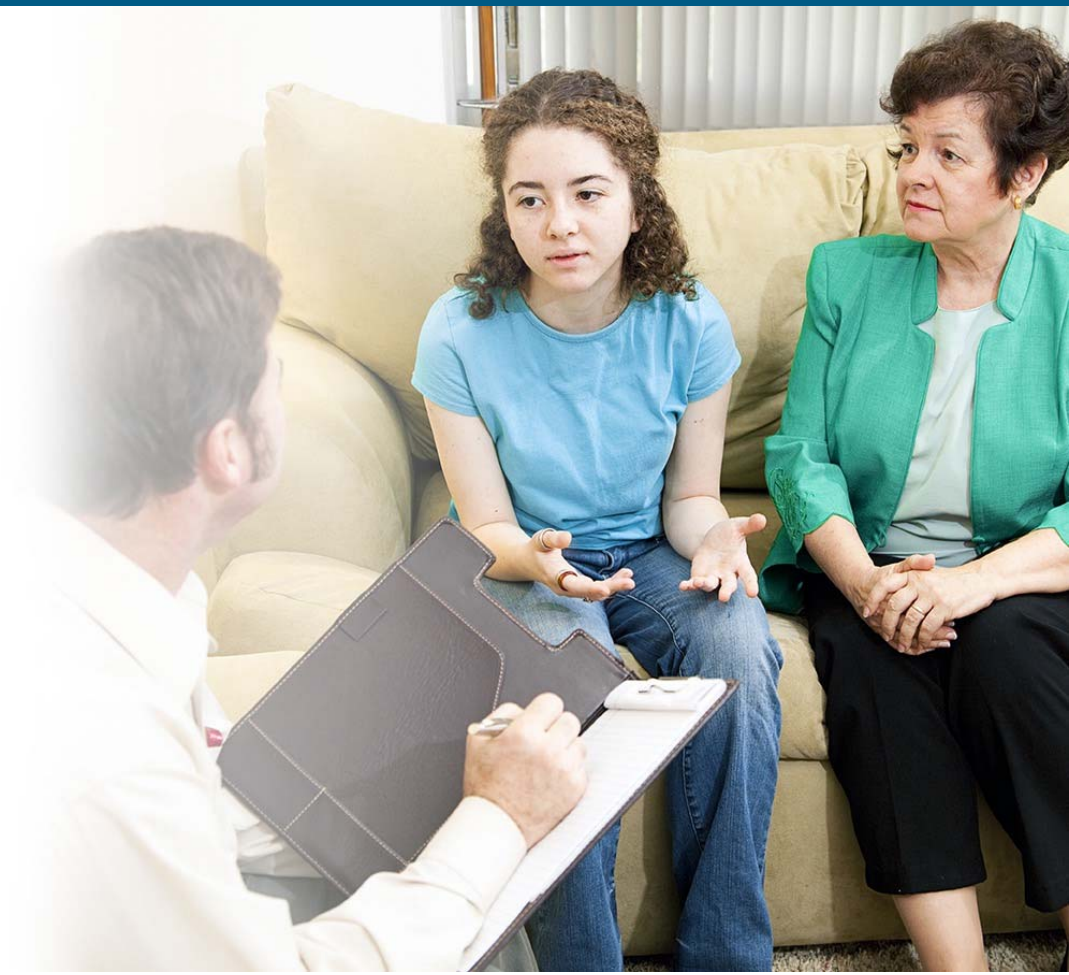
- **Real World Evidence/ Observational Research**
  - PASS
  - PAES
  - Outcome research
  - Prospective Registries (Disease or Drug)
  - Observational
  - Case-control / Retrospective chart review
  - Pragmatic trials
  - Pharmacoepidemiology
  - Health Economics



- **Pre-market launch, providing real-world data on:**
  - Natural history of disease
  - Burden of illness
  - Treatment Patterns
  - Competitor products
  - Disease Management
  - Historical control to support clinical trial
- **Post-launch, providing real-world data on:**
  - Brand usage (on and off label)
    - Safety, efficacy, compliance, adherence, persistence, treatment satisfaction
  - Competitor brand
    - Comparative effectiveness
  - Disease Management

Data Collection Challenges

- Rare disease – limited patient population and hard to find
- Caregivers involvement and consent: Patients are often children or young adults
- Rare sub-groups within rare disease
- Lack of research data sharing and transparency



Data Collection Methods

- Call Centres (WCT direct-to-patient Contact Research Centre)
- ePRO and eCOA (smartphones, tablets, computer, smart TV)
- Direct data Smart devices
- Global registries
- Data gathering via data abstractions from electronic record databases and/or directly from hospital (patient consent is not always needed depends on data collected)
- Patient, advocacy groups and caregivers being involved in the design of research programmes and patient recruitment planning/execution

Data Collection Process

- Only necessary data should be collected — eliminate data 'padding'
- Observational studies: Data points need to be in-line with routine care
- Real World Data: Visit schedule windows are usually based on standard of care guidelines in each country
- Data cleaning process designed for observational research
  - Data is usually monitored remotely
  - PRO information can not be queried, must be accepted as it is. Accepting missing data. Heavy PRO component, patient experience and compliance.
- Multiple PRO scales in eCRFs, linguistic validation needed for scales (timeline impact)
- The right statistical approach analysis and critical item collection. Knowing from the start collection point to reduce CRF and data changes later on.

Josie Measures

Vice President, Biostatistical Operations

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Statistical Considerations in Observational Studies

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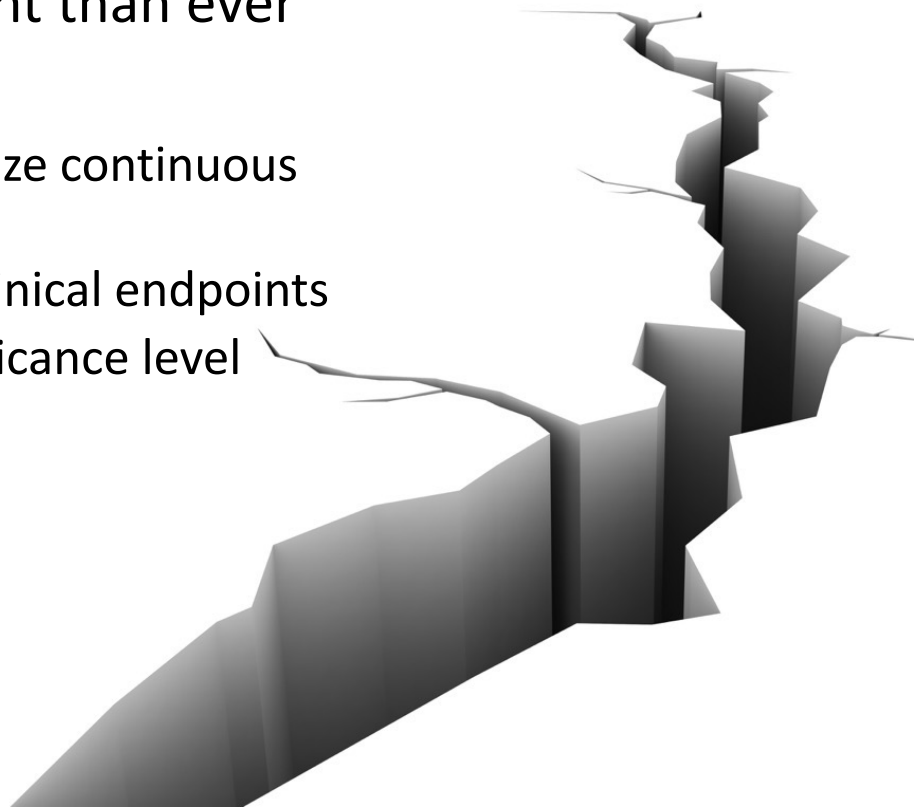
Sample Size

- Small number of eligible subjects
- Minimizing sample size is more important than ever
- Considerations
  - Using continuous endpoints, don't categorize continuous endpoints into responder/non-responder
  - Surrogate endpoints, e.g. biomarkers for clinical endpoints
  - Change assumptions about power or significance level
  - Novel study designs



Methods for Observational Studies

- Lack of comparison group
- Data are confounded
- Risk factors are not well understood → dealing with confounding difficult

Example of confounding

CRIME A BLOG ABOUT MURDER, THEFT, AND OTHER WICKEDNESS. JULY 9 2013 2:59 PM

When Ice Cream Sales Rise, So Do Homicides. Coincidence, or Will Your Next Cone Murder You?

By Justin Peters

895 0

Selling a boy an ice cream cone, or a murder magnet?

Photo by Andrew Burton/Getty Images

Crime is Slate's crime blog. Like us on Facebook, and follow us on Twitter @slatecrime.

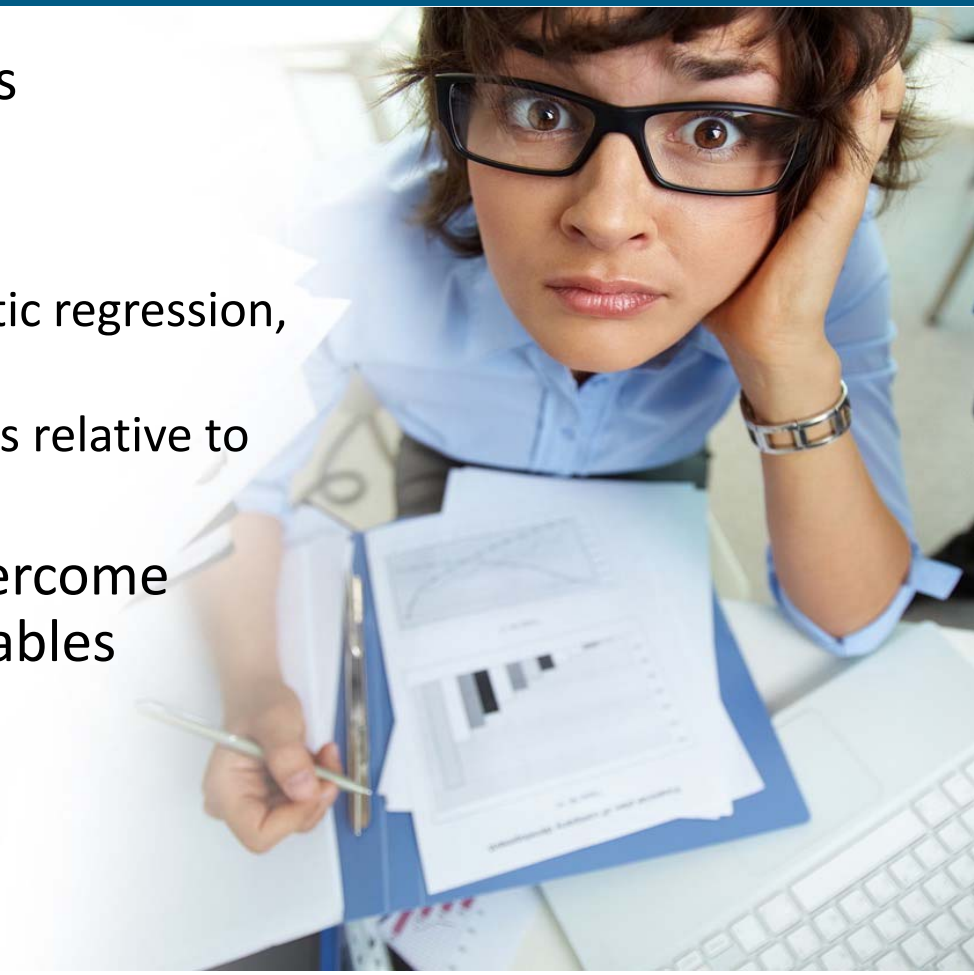
JUSTIN PETERS

Justin Peters is a Slate correspondent and the author of The Idealist: Aaron Swartz and the Rise of Free Culture on the Internet.

The New Orleans *Times-Picayune* ran a piece last Friday attempting to answer a

Statistical Methods to Deal with Confounding

- Collect data on all known confounders
- At analysis stage
  - Stratification – few confounders
  - Multivariate methods - regression, logistic regression, analysis of covariance
  - Propensity scoring – few outcome events relative to many confounders
- None of the analysis methods can overcome confounding due to unmeasured variables



Study Designs

- Self controlled observational designs
  - Patients act as there own controls reducing variability and sample size
  - Case-cross over design
  - Immune to confounding by factors that do not change with time
- Case control studies
  - Compares subjects who have that condition/disease (the "cases") with patients who do not have the condition/disease but are otherwise similar (the "controls").[1]
  - Controls are sampled
- Nested Case control study - nested within another study
- Prospective inception cohorts
  - New user design
  - Cohort inception defined by start of some medical treatment
  - Important for outcomes related to interventions that maybe immediately effected

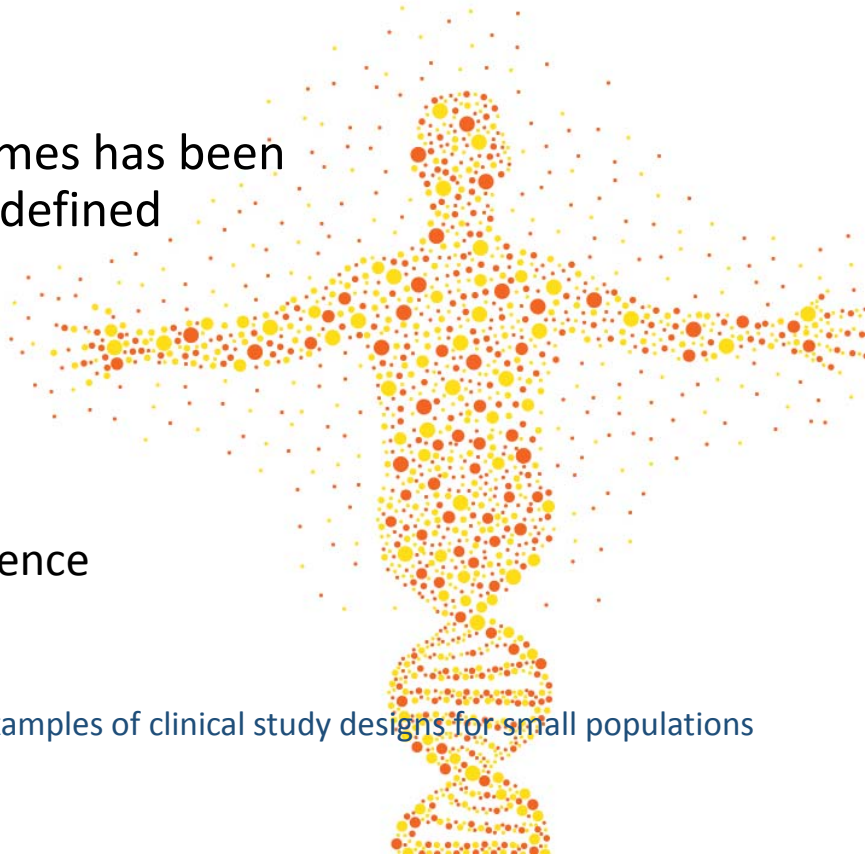
Historical Controls

Two critical reasons for trying to define the natural history of an orphan disease:

1. A single arm historical controlled study sometimes has been basis for approval, if the natural history is well defined
2. Understand natural history

   BUT:

   - Randomized CT is always less favorable
   - Reason is selection bias
   - Not always possible to “adjust” the difference



RJ Temple: The regulatory pathway for rare diseases lessons learned from examples of clinical study designs for small populations