Patient Registry SIG

Classification, Strategy & Design Working Group

Chair: Chris L. Pashos PhD
Vice President and Executive Director, HERQuLES
Abt Bio-Pharma Solutions, Inc.

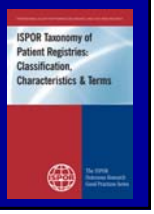
Classification, Strategy & Design Working Group

Goals:

- determine and define the most appropriate language for patient registry standardization, a patient registry terminology (common language), universal patient registry characteristics and a globally harmonized patient registry classification system.
- to establish good research practices related to choices of registry strategy and consequent design.

ISPOR Taxonomy of Patient Registries

- Each term will include a brief definition, a broader explanation, the associated values & uses, and conclude with a discussion of issues or conflicts related to the term.
- The issues/conflicts will be the basis of the Working Group's Good Research Practices papers.



Classification, Strategy & Design Working Group

Establishment of 4 Project Teams:

- Characteristics & Classifications of Patient Registries
- Design, Development & Implementation
- Analysis
- Reporting & Publishing

The Taxonomy Teams' Methodology

Identification of terms: hand-searched existing sources for terms:

- Berger et al, ISPOR Book of Terms (2003)
- AHRQ, Registries for Evaluating Patient Outcomes: A User's Guide (2007)
- CONSORT, ICJME, selected journal requirements for authors

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Classification, Strategy & Design Working Group

Team 1: Characteristics & Classifications

Co-Chair: Dimitris Polygenis PharmD
Co-Chair: Sally Thompson PhD, MSc

Characteristics & Classification Members

- Co-chair: Sally Thompson PhD, MSc
  Director, Outcomes Research, Pfizer, Inc
- Co-chair: Dimitris Polygenis PharmD
  Vice President, McKesson Specialty
  McKesson Corporation
- Grace Leung MPH
  Health Economist, Genentech
- Neal Mantick
  Director, Registries, Abt Bio-Pharma Solutions, Inc.

Achievements

- Developed working definition
- Identified common elements and considerations
- Agreement as to what is NOT a registry
- Identified commonly used registry designs and applications
- Set the stage for further discussion/clarification (to follow in subsequent sections)

Registry Definition

- Prospective observational study of subjects, **with certain shared characteristics**, that collects ongoing and supporting data over time on well-defined outcomes of interest for analysis and reporting

Essential Characteristics of a Registry

Characteristics	Considerations
Observational	• Real world assessment
Non-interventional	• No protocol-defined treatment/management, allocation of patients and patient visits • Limited risk; ethics review/consent required however focus is on protection of personal health information
Data Collection	• Dictated by patient and patient experience (i.e., heterogeneous and missing data) • Need to define key assessments and outcomes of interest
Outcomes Evaluation	• Baseline assessment critical • Longer-term observation period • Hypothesis generating versus hypothesis testing

Key Differences versus other Study Designs I

	Characteristic	Registry versus Traditional RCT
1	Treatment	Evaluate care in real-world setting
2	Time period/Duration	Long-term outcomes collected
3	Patients	Can involve large numbers of patients; 'typical' patients seen in real-world setting Limited inclusion/exclusion criteria
4	Methods	Do not require comparator/placebo; 'typical' care Open-label; no defined/mandated interventions or data collection No random allocation of patients

Key Differences versus Other Study Designs II

	Characteristic	Registry versus Traditional RCT
5	Statistical Analysis and Data Collection	Hypothesis generating; no sample size calculation; focus on 'generalizability' Heterogeneous patients
6	Patient Consent & Ethics Review	Focus on handling of personal health information and not risk
7	Safety	Voluntary reporting of adverse events Unsolicited (vs. solicited) adverse event collection

Registry Classification I

Registry Type Sponsors	Design	Measurement	Application/Use
Simple Cohort Epidemiologists Public Health Clinicians	• Prospective • Non-interventional • Sample-based • Collection of information in population that share common exposure (i.e., pregnancy registry)	• Clinical outcomes i.e., morbidity, mortality	• Pregnancy registry • Determine association/correlation between exposure and outcome
Outcomes Epidemiologists Policy makers Governments Public Health Academia	• Prospective • Non-interventional • Population-based • Collection of information in population	• Clinical outcomes i.e., morbidity, mortality	• Understand natural history of patient cohort that share common characteristic i.e., social science research, population-based research, epidemiological research • Examples: mortality, literacy, access to medical
Safety Surveillance Manufacturers Regulators Clinicians	• Prospective • Non-interventional • Sample-based • Collection of information in patients receiving common intervention	• Adverse events • Unexpected adverse events • Serious adverse events	• Support product registration • Conduct post-marketing surveillance ('real world setting') • Identify 'signals'

Registry Classification II

Registry Type Sponsors	Design	Measurement	Application/Use
Risk Management Regulators Manufacturers	• Prospective • Interventional • Population-based • Use one or more tools to meet goal(s) • May collect info beyond FDA-approved labelling	• Clinical outcomes as compared to clinical studies • Safety information and adverse events compared to clinical studies • Compliance with prescribed management and prescribing protocols • Impact of tools on ensuring compliance an outcomes	• Mandated by regulators to meet specific goals and objectives in minimizing known risks while preserving benefits • Assessing product's risk-benefit balance • Developing and evaluating tools to minimize risks while preserving benefits • Making adjustments to risk management tools to further improve risk-benefit balance
Disease Regulators Manufacturers	• Prospective • Non-interventional • Population-based • Collects information in cohort of patients with common disease	• Drug utilization and safety • Outcomes – morbidity and mortality • Resource utilization • Clinical management	• Understand natural history of disease • Identify, compare and evaluate management patterns • Identify 'signals' relating to safety, effectiveness and outcomes • Quantify burden of illness, QoL • May be iterative in establishing and benchmarking best practices • Assess screening, identification and monitoring practices • Cost-effectiveness

Registry Classification III

Registry Type Sponsors	Design	Measurement	Application/Use
Drug and Drug Class Clinicians Manufacturers Regulators Payers	• Prospective (some retrospective) • Sample-based • Collects information on patient cohort receiving common treatment	• Safety and effectiveness • Outcomes – morbidity and mortality • Resource utilization • Clinical management and add-on therapy	• Post-marketing surveillance • Compare effectiveness to efficacy • Study non-approved uses • Identify drug-related 'signals' • Cost effectiveness • Willingness to pay • Reimbursement evaluation
Management Payers Clinicians Health policy makers Health administrators Academia	• Prospective/retrospective • Collect information on common population • Population/sample-based	• Treatment and management patterns • Resource utilization • Outcomes	• Care mapping • Continuous quality improvement • Resource utilization and costing • Burden of illness • Quality of care • Provider performance • Health economic evaluation • Reimbursement evaluation
Resource Utilization Payers Policy makers Clinicians Health administrators	• Prospective or retrospective • Sample-based	• Direct costs i.e., medical care, drug use, hospitalization • Productivity costs i.e., absenteeism, productivity	• Burden of illness • Cost of care • Reimbursement evaluation • Health economic evaluations

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Classification, Strategy & Design Working Group

Team 2: Design, Development & Implementation

Chair: **Eric Gemmen, MA**
Senior Director, Medical Affairs, Epidemiology & Outcomes Research, Quintiles Late Phase & Safety Services

Design, Development & Implementation Members

- Murtuza Bharmal PhD
  Associate Director, Quintiles Late Phase & Safety Services
- Maznah Dahlui MD, MPH
  Department of Social and Preventive Medicine, University of Malaya
- Nancy Dreyer PhD, MPH
  Outcome
- Donatus Ekwueme PhD
  Senior Health Economist, U.S. Centers for Disease Control & Prevention (CDC)
- Claudio Faria, PharmD MPH
  Associate Director of Clinical Research, UMass Medical School
- Huan Huang PhD, MS
  Senior Analyst, Boston Health Economics
- Joanna Lis PhD, MBA
  Manager of Health Economics Department, sanofi-aventis, Warsaw, Poland
- Yvonne Lis PhD
  Director, Carter-Lis Associates Limited
- Anuprita D Patkar, PhD
  Associate Director, Health Economics & Reimbursement, ETHICON
- Gabriel Sandblom MD, PhD
  Department of Surgery, University Hospital, Lund, Sweden
- Kathryn Starzyck MSc
  Associate Director of Scientific Affairs, Outcome

Achievements
Identified 25 categories of terms

9 in Development section including:
registry purpose, funding and oversight, stakeholders, scope, ethics and privacy, regulatory considerations, etc.

11 in Design including:
research question(s), design characteristics, study population, data elements, data sources, data collection materials & methods, guidelines & standards, registry size and duration, etc.

5 in Implementation including:
pre-launch issues, site support, data capture & management, data lock, close-out

Achievements
160+ terms / definitions completed

76 terms in Development section including:
exposure, feasibility, informed consent, IRB/ethics approval, target population, etc.

50 terms in Design including:
observational, non-interventional, naturalistic, active/passive surveillance, historical control, etc.

37 terms in Implementation including:
site identification, regulatory documents, ICF-GCP, database build, clinical research associate, query resolution, loss to follow-up, source document verification (SDV), site close-out, etc.

Challenges

- The terms 'registry' and 'observational study' are often used interchangeably, although registries are a *subset of observational studies*
  - Moreover, the term 'observational' may differ in meaning between Europe and the US
    - European definition more strict
- Scope - keeping the terms specific to registries and not simply clinical studies, overall

Example: Patient Recruitment

Patient Recruitment

- Brief Definition: The process of enrolling patients into the registry.
- Explanation: Registry participants are recruited on a disease basis or exposure/treatment basis
  - Only after treatment/prescribing decision has been made by treating physician
- Issues:
  - Can the existence of a product registry impact the physician's treatment/prescribing decision?
  - Is the enrolled sample representative of the target population?
  - Are enrollment caps/limits at given sites appropriate?

Achievements & Next Steps

2009 ISPOR 14th Annual International Meeting in Orlando Workshop Presentation

W12: A TAXONOMY FOR THE DESIGN, DEVELOPMENT AND IMPLEMENTATION OF PATIENT REGISTRIES

Available on the ISPOR website via the *Research Digest* or on the *Patient Registry Classification, Strategy & Design Working Group webpage*

Draft an article based on our findings and submit to *ISPOR CONNECTIONS* for September/October 2009 issue.

Patient Registry SIG

Classification, Strategy & Design Working Group

Team 3: Analysis

Co-Chair: Shital Kamble MS
Co-Chair: Chris Blanchette PhD

Team 3: Analysis Members

- Co-Chair: Shital Kamble MS
  PhD Candidate, Health Services Research, University of North Carolina at Charlotte
- Co-Chair: Christopher Blanchette PhD
  Director, Center for Pharmacoeconomic and Outcomes Research
  Lovelace Respiratory Research Institute
- Maznah Dahlui MD, MPH
  Lecturer, Department of Social and Preventive Medicine
  University of Malaya
- Donatus Ekwueme PhD
  Senior Health Economist, US Centers for Disease Control and Prevention
- Alex Exuzides PhD
  Director, ICON Clinical Research
- Eric Gemmen MA
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- Carl Gibbons BSc
  Research Analyst, Schering-Plough Ltd
- Joanna Lis PhD MSc
  Health Economics Manager, Sanofi-Aventis
- Anuprita Patkar PhD
  Associate Director, Health Economics & Reimbursement, ETHICON, J&J
- Matt Reaney MSc
  Health Outcomes Scientist, Endocrine, EuOR, Lilly UK

Achievements

Identified 13 broad categories of terms

- Power/Sample Size Calculations
- Statistical Inference and Hypothesis Testing
- Main Analysis Techniques
- Treatment of Selection Bias
- Treatment of Missing Observations
- Multiplicity Adjustments
- Systematic Reviews/ Meta-Analysis

Achievements

70 analysis terms definitions completed

- Charlson Comorbidity Index, Elixhauser Comorbid Disease Adjustment Method, etc.
- Regression- Ordinal Logit/Probit Models, Cox Proportional Hazards Models, Two-part Models, Multilevel Models, etc.
- Propensity Score Methods, Instrumental Variables
- Clinical Significance, Statistical Significance, etc.
- Missing Completely at Random (MCAR), Missing at Random (MAR), etc.

Achievements

2008 ISPOR 11th European Congress in Athens Workshop

W20: Use of Real World Data: Challenges in the Use of Patient Registry Data

Available on the ISPOR website via the *Research Digest* or on the *Patient Registry Classification, Strategy & Design Working Group webpage*

Example: Multiplicity Adjustments

Brief Definition: The process of adjusting for multiple statistical tests to correct for occurrence of false positives (i.e., Type I Error) that could emerge from investigators looking at many additional endpoints and treatment group comparisons.

Explanation: different methods of correcting for multiple testing procedures in clinical trials or observational studies

- Bonferroni method,
- Hochberg false discovery rate (FDR) method,
- Holm correction method,
- Westfall and Young Permutation (Hierarchical Testing),
- Bootstrap method

Example: Multiplicity Adjustments

Issues:

- Is multiplicity adjustment necessary?
  - currently a trend to discount the multiplicity problem and its effects
- very few studies have described specific conditions that demand the use of multiplicity adjustment as a control measure

Patient Registry SIG

Classification, Strategy & Design Working Group

Team 4: Reporting & Publishing

Co-Chair: Kirsten Hall Long PhD
Co-Chair: Diana Frame

Reporting & Publishing Members

Co-Chair: Kirsten Hall Long PhD
Senior Health Economist, Division of Health Care Policy & Research, College of Medicine, Mayo Clinic

Co-Chair: Diana Frame
Independent Consultant, Frame Research LLC

John Ellison
Senior Manager, Scientific Publications, Clinical Research Department, LifeScan, Inc.

Huan Huang PhD, MS
Senior Analyst, Boston Health Economics

Siva Narayanan MS, MHS
Vice President and Practice Leader, Treatment Performance Optimization – Global Portfolio, TNS Healthcare

Achievements

Identified 3 broad categories of terms

- Validity & Quality
- Ethical Considerations
- Public Reporting of Registry Data

Achievements

26 Reporting & Publishing terms defined
Including….

- Internal and external validity
- Bias (selection, response, recall, attrition)
- Quality domains
- IRB / Ethics Committee (reporting considerations)
- Registry funding
- Authorship
- Publication bias
- Transparency

Achievements

26 Reporting & Publishing terms

- Full draft of all terms completed
- Brief Definition, Explanation, Value and Use, Issues, and Bibliography sections for each term
- Beginning to identify cross-indexing with other sections
- Looking ahead to Best Practices work ("preview" of this especially in Issues sections)

Reporting and Publishing Example

Transparency

- Brief Definition: A characteristic of the report defined by the presence and clarity of key information on the rationale, methodology, and support (including funding) used to collect, analyze, and publish registry data.
- Explanation: Transparency in reporting facilitates interpretation of the study by other researchers as well as health care decision-makers, and may lead to faster adoption of results.

Reporting and Publishing Example

Transparency

- Issues: Observational studies have received less attention than clinical trials in the quest for complete and timely reporting of study results. Postmarketing and registry studies play an important role in evidence development, however, and efforts to increase transparency should encompass these observational studies as well. Given limitations on manuscript length in print journals and the frequent complexity of study design and analytic models in observational research, some authors have called for availability of the detailed protocol, coding definitions, and other methodologic detail on the journal's or researcher's web site.

Patient Registries SIG

Analysis & Data Management Working Group

Chair: Leanne Larson MHA
Vice President, Sg2 Healthcare Intelligence

Analysis & Data Management Working Group

Establishment of 3 Project Teams:

- Cost-effectiveness Analysis of Patient Registry Data Tea
- Analysis of Effectiveness in Registry Data Team
- Reporting Results from Registry Data for Publications Team

Co-Chair: Mia Malmenäs MSc, *Shire HGT*
Co-Chair: Mike Novotny MBA, MA, *Medrio*

Analysis & Data Managment Members

- Lusine Abrahamyan MD, MPH, *University of Toronto*
- Marg Hux, MSc, *i3 Innovus*
- Michelle Pritchard Turner MS, *ICON Lifecycle Sciences*
- Rebecca Gruhlkey MBA, *Thomson Healthcare*
- Isabelle Morin MSc, *Shire HGT*
- Nancy Dreyer PhD, MPH, *Outcome*
- Claudio Faria PharmD, MPH, *University of Massachusetts*
- Nandan Kenkeremath JD, BS, *Leading Edge Policy & Strategy*
- Peggy Schrammel, *University of British Columbia*
- Steven Takemoto PhD, *University of California*
- Fang Wang MD, PhD, *GlaxoSmithKline*
- Jaro Wex PhD, MD, BA, *Pharmarchitecture Limited*

Analysis Issues for Patient Registries

Our Focus – guidance & recommendations for analysis within registries:

- Cost-effectiveness
- Effectiveness
- Reporting of registry data for publication

Analysis Issues for Registries

- Existing guidelines lack practical analysis guidance
  - AHRQ Registry guidelines
  - GRACE initiative
- Analysis issues differ by registry GOALS:
  - Natural history of disease
  - Treatment practice and effectiveness
  - Burden of illness and cost-effectiveness of treatments
  - Monitor treatment safety / harm
  - Quality of care

Analysis of Registries

- Registries well suited to collect 'real-world' data
- Incremental Effectiveness – issues identified
- Disease-related cost over fixed time frame
  - Identify relevant resources to include in cost
  - Treatments, administration, safety and effectiveness
    - e.g. management of adverse events, long term complications of progressing disease

Good Research Practices for Cost Effectiveness Analysis of Patient Registry Data

Provide recommendations on:

- Dealing with missing data
  - Variable Follow-up - balance long timeframe with need to impute
  - Missing assessments, incomplete information
- Dealing with potential bias – effect on cost
  - Selection bias, ascertainment and measurement bias
- Cultural and country differences

Good Research Practices for Analysis of Effectiveness in Registry Data

Provide recommendations on suitable statistical approaches to registry data with a particular focus on estimating the effectiveness of treatment methods:

- covariate adjustments
- matching
- propensity scoring
- missing data handling
- etc

Good Research Practices for Reporting Results from Registry Data for Publications

Develop recommendations for reporting results from registry data for publications and evaluate the STROBE guideline for its appropriateness for patient registries

- Develop a checklist for best practices
- A point by point list analyzing the STROBE guideline for relevance to registries

Achievements

2009 ISPOR 14th Annual International Meeting in Orlando Workshop Presentation

W9: ANALYSIS OF EFFECTIVENESS AND COST-EFFECTIVENESS IN PATIENT REGISTRIES

Available on the ISPOR website via the *Research Digest* or on the *Patient Registry Analysis Working Group webpage*

Achievements

2009 ISPOR CONNECTIONS Article

May – June issue

Analysis of Effectiveness in Patient Registry Data

By Mia Malmenäs MSc, Keith Lowton MSc, Isabelle Morin MSc, Shire Human Genetic Therapies, Stockholm, Sweden; Margaret Hux, MSc, i3 Innovus Burlington, ON, Canada, Lusine Abrahamyan MD, MPH, University of Toronto Mike Novotny MBA, MA, Medrio