



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

Team 1: Characteristics & Classification Members

- **Co-chair: Sally Thompson PhD, MSc**
Director, Outcomes Research, Pfizer, Inc
- **Co-chair: Dimitris Polygenis PharmD**
Vice President, Consulting & Clinical Services
McKesson Corp, Phase 4 Solutions
- **Grace Leung MPH**
Health Economist, Genentech
- **Neal Mantick**
Director, Registries, Abt Bio-Pharma Solutions, Inc.

Registry Definition

- Prospective, observational study of patients, **sharing some common characteristics** over time, that collects ongoing and supporting data on well-defined outcomes of interest for analysis and reporting

Essential Characteristics of a Registry

Characteristics	Considerations
Observational	<ul style="list-style-type: none"> Real world assessment
Non-interventional	<ul style="list-style-type: none"> No protocol-defined treatment/management, allocation of patients and patient visits Limited risk; ethics review/consent required → focus on protection of personal health information
Data Collection	<ul style="list-style-type: none"> Dictated by patient and patient experience (i.e., heterogeneous and missing data) Need to define key assessments and outcomes of interest
Outcomes Evaluation	<ul style="list-style-type: none"> Baseline assessment critical Observation period – longer-term 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	<ul style="list-style-type: none"> Prospective Non-interventional Sample-based Collection of information in population that share common exposure (i.e., pregnancy registry) 	<ul style="list-style-type: none"> Clinical outcomes i.e., morbidity, mortality 	<ul style="list-style-type: none"> Pregnancy registry Determine association/correlation between exposure and outcome
Outcomes Epidemiologists Policy makers Governments Public Health Academia	<ul style="list-style-type: none"> Prospective Non-interventional Population-based Collection of information in population 	<ul style="list-style-type: none"> Clinical outcomes i.e., morbidity, mortality 	<ul style="list-style-type: none"> 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 care
Safety Surveillance Manufacturers Regulators Clinicians	<ul style="list-style-type: none"> Prospective Non-interventional Sample-based Collection of information in patients receiving common intervention 	<ul style="list-style-type: none"> Adverse events Unexpected adverse events Serious adverse events 	<ul style="list-style-type: none"> Support product registration Conduct post-marketing surveillance ('real world setting') Identify 'signals'

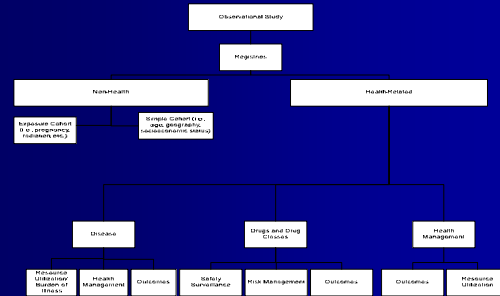
Registry Classification II

Registry Type Sponsors	Design	Measurement	Application/Use
Risk Management Regulators Manufacturers	<ul style="list-style-type: none"> Prospective Interventional Population-based Use one or more tools to meet goal(s) May collect info beyond FDA-approved labelling 	<ul style="list-style-type: none"> Clinical outcomes as compared to clinical studies Safety information and adverse events compared to clinical studies Compliance with prescribing management and prescribing protocols Impact of tools on ensuring compliance an outcomes 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Prospective Non-interventional Population-based Collects information in cohort of patients with common disease 	<ul style="list-style-type: none"> Drug utilization and safety Outcomes – morbidity and mortality Resource utilization Clinical management 	<ul style="list-style-type: none"> Understand natural history of disease Identify, compare and evaluate management patterns Identify 'signals' relating to safety, effectiveness and outcomes Quantify burden of illness, OoL 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	<ul style="list-style-type: none"> Prospective (some retrospective) Sample-based Collects information on patient cohort receiving common treatment 	<ul style="list-style-type: none"> Safety and effectiveness Outcomes – morbidity and mortality Resource utilization Clinical management and add-on therapy 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Prospective/retrospective Collect information on common population Population/sample-based 	<ul style="list-style-type: none"> Treatment and management patterns Resource utilization Outcomes 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Prospective or retrospective Sample-based 	<ul style="list-style-type: none"> Direct costs i.e., medical care, drug use, hospitalization Productivity costs i.e., absenteeism, productivity 	<ul style="list-style-type: none"> Burden of illness Cost of care Reimbursement evaluation Health economic evaluations

Registry Classification Hierarchy



Team 2: Development, Design & Implementation Members

- Yvonne Lis PhD**
 Director, Carter-Lis Associates Limited
- Gabriel Sandblom MD, PhD**
 Ward Physician, Department of Surgery
 University Hospital, Lund, Sweden
- Paula Funk-Orsini PhD**
 President, Areté Medical Outcomes Research, Inc.
- Claudio Faria, PharmD MPH**
 Associate Director of Clinical Research
 University of Massachusetts Medical School
- Kathryn Starzyck MSc**
 Associate Director of Scientific Affairs, Outcome

Development

Pre-protocol activities encompassing:

- Research question or registry purpose
- Stakeholders
- Funding and oversight
- Regulatory and research practice considerations

Design

Activities at protocol development stage:

- Formalizing objectives and hypotheses
- Target population
- Design features
- Endpoints and data elements

Implementation

Activities following a signed protocol:

- Pre-launch issues
- Launch
- Standard operating procedures
- Site initiation
- Patient enrollment
- Site support
- Data collection and validation
- Site close out
- Database lock

Achievements Identified 24 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.
- 4 in Implementation including:
pre-launch issues, site support, data lock, close-out

Achievements 150+ terms /definitions completed

- 76 terms in Development section including:
exposure, feasibility, informed consent, IRB/ethics approval, target population
- 50 terms in Design including:
observational, non-interventional, naturalistic, active/passive surveillance, historical control
- 28 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

Team 3: Analysis Members

- **Co-Chair: Shital Kamble MS**
PhD Candidate, Health Services Research, UNC, Charlotte
- **Co-Chair: Christopher Blanchette PhD**
Director, Center for Pharmacoeconomic and Outcomes Research
Lovelace Respiratory Research Institute
- **Joanna Lis PhD MSc**
Health Economics Manager, Sanofi-Aventis
- **Eric Gemmen MA**
Executive Director, Analytics & Health Outcomes, Quintiles, Inc.
- **Carl Gibbons BSc**
Research Analyst, Schering-Plough Ltd
- **Alex Exuzides PhD**
Director, Ovation Research Group
- **Donatus Ekwueme PhD**
Senior Health Economist, US Centers for Disease Control and Prevention

Statistical Analysis Plan

Describes the statistical techniques that will be used to evaluate the objectives of an observational study that uses registry data

Achievements Identified 13 broad categories of terms

Including...

- Power/Sample Size Calculations
- Statistical Inference and Hypothesis Testing
- Timing of Analyses
- Available Variables for Analyses
- Main Analysis Techniques
- Treatment of Missing Observations
- Multiplicity Adjustments

Achievements 70 analysis terms defined

Including....

- Elixhauser Comorbid Disease Adjustment Method
- Ordinal Logistic/ Logit and Ordinal Probit Models
- Cox Proportional Hazards Regression Models
- Two-part Models
- Propensity Score Methods
- Instrumental Variables
- Clinical Significance
- Statistical Significance
- Standard Errors
- Confidence intervals

Team 4: 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.

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

36 Reporting & Publishing terms defined

Including....

- Internal and external validity
- Selection bias
- Quality domains
- Declaration of Helsinki
- Registry funding
- Authorship
- Transparency
- Study limitations

Challenges for the Taxonomy Teams

- Definition of patient registry
- Similarities/differences and overlap with other study methodologies and types
- Different uses/applications across jurisdictions
- Overlapping terms
- Comprehensiveness
- Number of terms to include



Patient Registries SIG *Design & Operations Working Group*

Chair:

Leanne Larson, MHA

Vice President, Registry Consulting
ICON Lifecycle Sciences

D & O Working Group *Overview*

- **Goal**
 - to establish good research practices on the design, implementation, and analysis of patient registries to meet the registry sponsor's desired goal(s), domestically and internationally.
- **Three Project Teams**
 - 1: Registry Design
 - 2: Registry Operations
 - 3: Registry Data Management and Analysis

Team 3: Data Management & Analysis Members

- **Co-Chair:** Mike Novotny MBA, MA, *Medrio*
- **Co-Chair:** Mia Malmenäs MSc, *Shire HGT*
- Lusine Abrahamyan MD, MPH
University of Toronto
- Rebecca Gruhlkey MBA, *Thomson Healthcare*
- Marg Hux PhD, *i3 Innovus*
- Michelle Turner MS, *ICON Lifecycle Sciences*
- Herve Caspard MD, ScD, *Sanofi-aventis*

Data Management & Analysis Team Work Plan

- Evaluate registry data collection options, and develop a summary report describing:
 - EDC
 - Paper
 - Fax
 - IVRS
 - Other
- Define analyses supporting audience informational needs, including those for publications, internal reports, and regulatory submissions

Team 1: Design Members

- **Chair:** Richard Glicklich MD, President, *Outcome*
- **Susan F. Anton, PhD, BS, MPH, DrPH**
Boehringer-Ingelheim Pharmaceuticals
- **Lusine Abrahamyan MD, MPH, PhD**
University of Toronto
- **Sue Elliot PhD, MBA, Axiom**
- **Matthew Gordon, ICON Lifecycle Sciences**

Design Team: Purpose

- Identify registry design methods, requirements, and case studies of successful registries.
- Develop consensus on design elements to reach specified objectives.
- Evaluate how effectively the design meets the internal and external goals.
- Recommendations into GRP paper on patient registry design.

Controversies & Challenges in Patient Registry Design

Goal: Case-based manuscript focused on controversies/challenges as a pivot point for broader discussion of practical issues and solutions in registry design.

Examples:

- Hypoactive Sexual Desire Disorder Registry
Case identification
- Juvenile Rheumatoid Arthritis Registries
Sample size determination
- Quality Improvement Registries
Impact of behavior change on registry design / analysis

Controversies & Challenges in Patient Registry Design: Cases/Issues

- **Susan F. Anton DrPH**
Boehringer-Ingelheim Pharmaceuticals
 - Natural History Registry Case: *Hypoactive Sexual Desire Disorder*
 - Issue: Case Identification
 - While a registry for a marketed product will generally have regulatory and professional treatment guidelines to follow, a disease registry is more likely to include development, advancement and assessment of screening and diagnostic tools among its objectives.

Controversies & Challenges in Patient Registry Design: *Cases/Issues*

- Lusine Abrahamyan MD, MPH, PhD(c)
University of Toronto
 - Rare Disease Registry Case: *Juvenile Idiopathic Arthritis*
 - Issue: Sample Size Determination
 - Determining adequate sample size in rare-disease registries presents some unique challenges. Sample size considerations from describing natural history to event rates (post marketing surveillance) will be addressed.

Controversies & Challenges in Patient Registry Design: *Cases/Issues*

- Rich Gliklich, MD
Outcome
 - Quality Improvement Registries Cases
(OPTIMIZE-HF, IMPROVE-HF, Get With the Guidelines, Own the Bone)

Controversies & Challenges in Patient Registry Design: *Cases/Issues*

- Issue: Design and analytic challenges when the *intent* of the registry is to *change behavior*
 - While registries are typically designed to 'observe' practice, it is now well demonstrated that registries can change clinician behavior (such as in quality improvement).
 - What comparators and analyses might need to be made in these scenarios? What implications do registries that intend to change behavior have on those that are not intending to, but may?

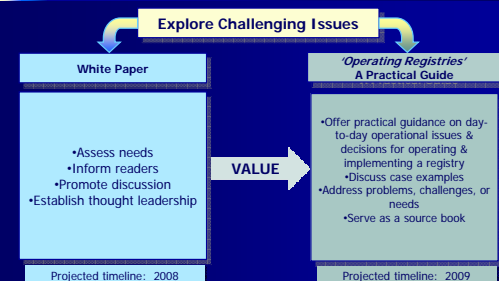
Team 2: Operations *Members*

- **Co-Chair:** Shelley Stanley, MS, RD, *HealthCore*
- **Co-Chair:** Michelle Leavy, BA, *Outcome*
- Elizabeth Hernberg-Stahl, MSc, *Shire HGT AB*
- Sonja Wustrack, MPH, *ICON Lifecycle Sciences*

Key Operational Areas

1 Site Management	1. Describe strategies for site identification, qualification, recruitment, relationship management, communication & retention
2 Patient Management	2. Identify tactics for patient recruitment, incentives & retention
3 Regulatory Management	3. Analyze regulatory & ethical issues
4 Data Management	4. Review methods of data collection, management & quality assurance
5 Safety Management	5. Present options for collecting & reporting adverse events
6 Change Management	6. Recommend strategies for identifying & managing change
7 Feasibility & Logistics	7. Discuss feasibility evaluation & logistical concerns
8 Study Materials	8. Provide examples of effective, relevant study materials
9 Analysis & Publication Plan	9. Examine analysis & publication planning

Milestones





Patient Registries SIG

Communicating Patient Registry for Health Care Decision-Making Working Group

use of registry evidence in disease management and health care decision making

Chair: Annette Stenhagen DrPH
Vice President, Epidemiology & Risk Management
United BioSource Corporation

Establishment of 3 Project Teams to Develop Recommendations on...

PRO EVALUATION Team

Use of patient registry data in evaluating patient-reported outcomes

REAL WORLD HEALTH CARE COSTS Team

Use of patient registry data in the development of 'real world' economic information on health care costs

PR & RCT Team

Recommendations for the Use of Patient Registry Data as a Complement for Randomized Clinical Trials

PRO EVAL Team Members

- **Chair: Carl Asche PhD, MSc, MBA**
University of Utah
- Tao Fan MS, Merck
- Mark Jewell PhD, EPI-Q, Inc.
- Matthew Reaney MSc, AHP Research
- Wendy Toler PharmD, JazzPharma
- Kathi Weis PhD, Pfizer

PRO EVAL Team

Issues to Address

- Growing use of patient registries to generate "real world" data on specific diseases or interventions.
- Types of PROs to generate evidence for health care decision making.
- Health care resource utilization.

PRO EVAL Work Plan

- Literature review based on MESH terms chosen by the team on: the **use of patient registries to evaluate PROs**, including a review of specific instances where this **PRO data has been used in health care decision-making**.
* 200 plus articles in final selection. Under review.
- A review of the current guidance for the use of patient registries to generate PRO data.
Glikich RE, Dreyer NA, eds. *Registries for Evaluating Patient Outcomes: A User's Guide*. AHRQ Publication No. 07-EHC001-1. April 2007.
- Next step: identify current gaps in research methodology and guidance, including trade-offs between validity or relevance and lack of data control.

REAL WORLD HC COSTS Team Members

- **Chair: Lynn Okamoto PharmD**, United BioSource Corporation
- Sue Gao PhD, MPH, Amgen
- Scott McKenzie MD, Ortho Biotech
- Jacqui Miot PhD, Discovery Health
- Krista Payne MEd, United BioSource Corporation
- Susan Shiff PhD, Pfizer
- Alicia Shillington PhD, MPH, EPI-Q, Inc
- Valerie Hutchins BA, United BioSource Corporation

RW HC COSTS Work Plan

- Identify patient registries from published literature which captured real-time healthcare utilization & costs
- Identify resources & types of economic and financial data to be included in patient registries.
- Develop consensus on resource utilization & economic information to be used in registries
- Develop recommendations into GRP paper on how:
 - to capture real-world economic data within a patient registry
 - health care decision-makers can use economic data from registries.

Literature Review Results

2 review teams with double consensus

MESH terms used

- Patient registry AND healthcare utilization
39 papers; 10 for full review
- Registry OR registries AND cost OR cost effective
56 abstracts returned; 24 for full review

Economic Data: Types & Sources

- Variable consideration based on type of registry and stated objective
 - Eg. registry focused on disease, safety, pregnancy, intervention
 - Single site/country vs multiple countries
- Types of health care utilizations/economic data
 - Eg. hospitalization, emergency room, pharmacy, procedures, long term care, provider visits, etc.
- Data sources
 - Eg. Patient/provider recall, integrated claims analyses, drug/device utilization
- Economic evaluations
 - Eg. Unit cost, charges, patient co-payments

PR & RCT DATA Team Members

- **Chair:** Steven Takemoto PhD, Saint Louis University
- Nancy Dreyer, Outcome
- Claudio Faria, University of Massachusetts
- Trisha Hutzal, Johnson and Johnson
- Gerlinde Kaempf, Merck
- Pat McCollam, Eli Lilly
- Steve Takemoto, Saint Louis University
- Fang Wang, GlaxoSmithKline
- Jaroslaw Wechowski, Pharmarchitecture Limited
- Jasmanda Wu, Ortho McNeil

PR & RCT DATA Work Plan

- Establish patient registry in the hierarchy of medical evidence
 - Definition of terms
 - Strengths of randomized trials
 - Hierarchy of evidence
 - Strengths of outcomes research
 - Characteristics of quality trials
- Identify unmet needs
- Develop survey to assess usefulness of observational and registry data for healthcare coverage and reimbursement decisions
- Develop recommendations into GRP paper

SURVEY: Assessing the usefulness of observational & registry data for healthcare coverage & reimbursement decisions

Survey Results to Date:

- As of April 29, 2008, 28 survey responses
- 5 point Likert scale
- 1-strongly disagree; 5-strongly agree
- T-test used to test for significance

**Communicating PR Information for
HC Decision-Making Workshop**

Tuesday 2:30 – 3:30 PM
GRAND Ballroom East (Lower Concourse)

W5: Expansion of the Forum material presented today with an extended discussion of 'Recommendations for the Use of Patient Registry Data as a Complement for Randomized Clinical Trials'