



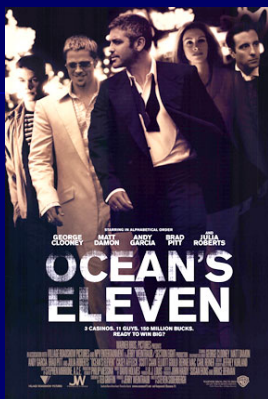
A Taxonomy For The Design, Development And Implementation Of Patient Registries

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ISPOR Taxonomy for Patient Registries Classification, Strategy & Design Working Group

AGENDA

- Background
- Scope and Achievements to-Date
- Design
- Development
- Implementation

2



3

BACKGROUND

4



Patient Registry SIG

Classification, Strategy & Design Working Group

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

5

Classification, Strategy & Design Working Group

Goals:

Determine and define:

- 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.

6

ISPOR Taxonomy of Patient Registries

- Each term includes:
 - brief definition
 - broader explanation (in context of registries)
 - the associated values & uses
 - 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:

1. Characteristics & Classifications of Patient Registries
2. Design, Development & Implementation
3. Analysis
4. Reporting & Publishing

8

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9

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)
- ISPE, Guidelines for good pharmacoepidemiology practices (GPP)
- CONSORT, ICJME, GRACE Initiative, selected journal requirements for authors

10

Registry Definition

Prospective observational study of patients **with certain shared characteristics (e.g., particular disease, risk factor or exposure)** that collects ongoing and supporting data over time on well-defined outcomes of interest for analysis and reporting

- Is it a 'study'? Yes.

11

Focus of Our Taxonomy

Prospective observational study where the primary data elements are collected for the direct purpose of the registry

–Protocol, DMP, SAP yields higher internal validity, quality, completeness

–Not studies (e.g., analyses) of pre-existing data

12

Team 2: Design, Development & Implementation Members

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

13

Achievements Identified 25 categories of terms

- **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.
- **9 in Development section including:**
registry purpose, funding and oversight, stakeholders, scope, ethics and privacy, regulatory considerations, etc.
- **5 in Implementation including:**
pre-launch issues, site support, data capture & management, data lock, close-out

14

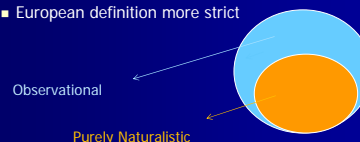
Achievements 160+ terms /definitions completed

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

15

Challenges

- Scope, i.e., keeping the terms in the taxonomy specific to registries and not simply clinical studies, overall
- 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



16

Registry Objectives

- Quality of Care
- Safety Monitoring
 - AEs and SAEs
- Clinical Effectiveness
- Adherence and Persistence
- Economic
 - Resource Utilization
 - Direct and Indirect Costs
- Cost Effectiveness
- Treatment Satisfaction

- Final vs. Intermediate Clinical Outcomes

Mandated vs. Discretionary

17

Registry Objectives

- Scientific
- Commercial

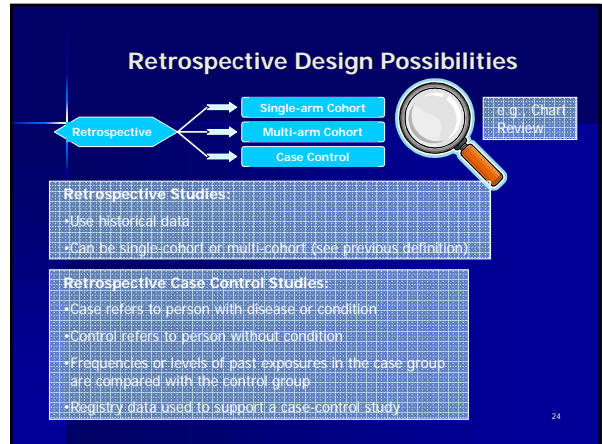
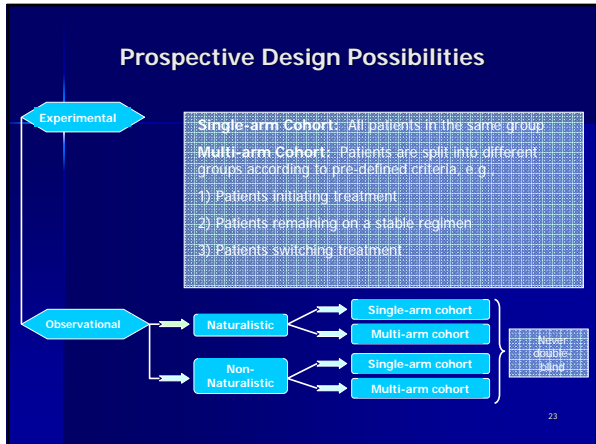
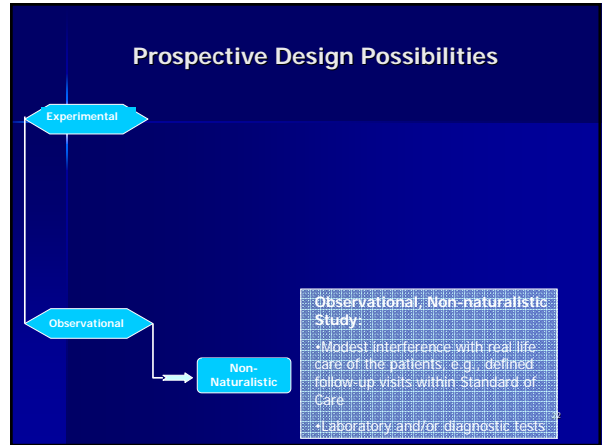
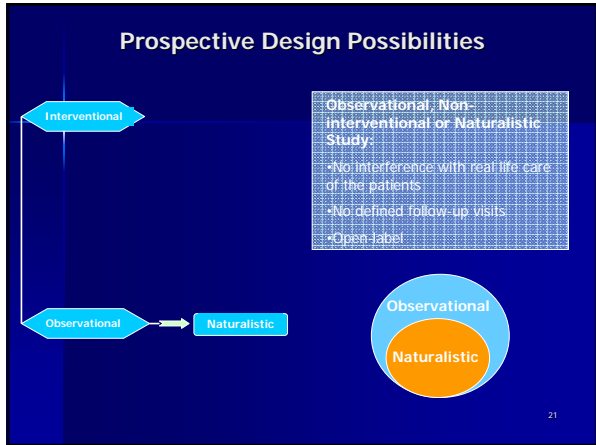
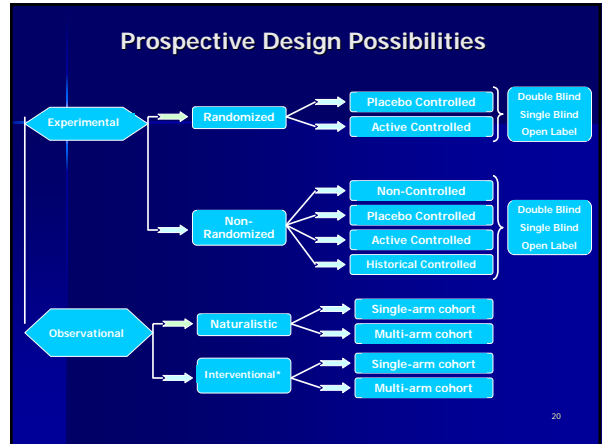
- Clinical
- Clinical Audit

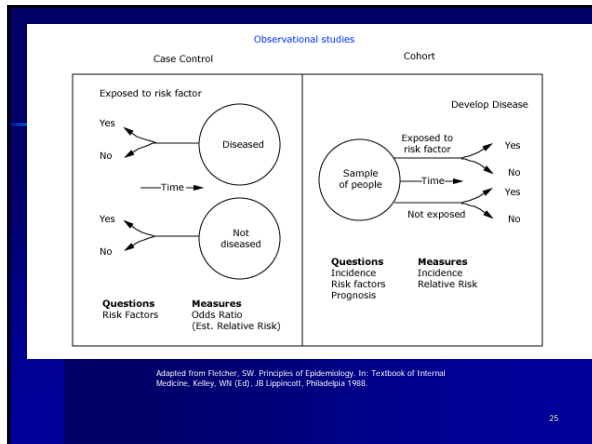
	Clinical	Clinical Audit
Scientific	Safety	Quality Assurance
Commercial	Effectiveness, Communication with Medical Community	Appropriate Use

18

Registry Study Design Characteristics

19





- ## Other Study Models
- Ecologic
 - Population based, rather than individual subject
 - Aggregates patient data at investigational sites, transmitting only a summary of this data for analysis
 - Avoids privacy issues
 - But, loss of variation/power for statistical inference
 - Consider multiple simple studies
 - e.g., Screening for ACE inhibitor tolerability
 - If pass, enter CHF registry that includes ACE inhibitors in one or more arms
 - If fail, enter CHF registry that does not include an ACE inhibitor arm (i.e., make use of screen failures)
- 26

Registry Development Attributes

27

- ## Registry Stakeholders
- Primary
 - responsible for creating and funding the registry or those who require the data or who will use the data to inform decision making, e.g.,
 - manufacturers, health care service providers, payers, policy makers, regulatory authorities, academia.
 - Secondary
 - will benefit from knowledge of the data or would be impacted by the results but who are not instrumental in establishing the registry, e.g.,
 - regulators, reimbursement committees, HTA organizations, treating physicians and their patients, professional or patient societies.
- Registries usually have multiple stakeholders; Building consensus is critical*
- 28

- ## Use of Registry Data for Regulatory and Payer Requirements
- Do regulatory authorities use registry data for procedure or product approval?
 - Yes, but only for conditional approval, i.e., post-approval safety
 - CASES-PMS (Stents), NCGS – Used for conditional FDA approval
 - Needed to be more representative of physicians treating patients
 - Needed to be generalizable to physicians without stenting experience
 - Test training program
 - What conditions are placed on the registry for its data to meet the standards expected by regulatory agencies and payers?
 - Registry has identical inclusion/exclusion criteria to that of the registration trial
 - MACE rate ≤ to that of Phase III trial
 - e.g., Providers must submit data for registry as condition of coverage ²⁹

- ## Funding and Oversight
- Budget
 - Governance
 - Steering Committee
 - Data Ownership
 - Access Rights
- Should be decided prior to start of registry
- 30

Ethics and Privacy

Respect for persons
Beneficence
Justice
CIOMS (WHO)
ICH-GCP
Conflicts of Interest
Common Rule
FDA Regulations
Research participants
Informed Consent
Informed Consent waiver
IRB/Ethics Committee
Data Privacy Committee
De-Identified Information
Privacy Rule/ HIPAA
Belmont Report

31

Ethics and Privacy (cont.)

- Personal IDs removed from any study files that are accessible to non-study personnel in accord with applicable laws and regulations.
 - Study files should be encrypted and stripped of personal IDs, and code keys stored separate from study files.
 - All personnel with access to data containing personal IDs will sign a pledge to maintain the confidentiality of study subjects, and will maintain an ability to verify the origin and integrity of data sets from which personal identifiers will have been removed.
- from ISPE, GPP

32

Registry Scope

- Size
 - Patients/Participants
 - Sites
 - Representative?
- Setting or Context
 - One or multiple?
- Normal vs. Standard of Care
- Study Population vs. Target Population
- Inclusion Criteria
 - Note on 'Naturalistic'
- Geographic Location
- Duration of Observation
 - Episode of care to Lifetime
 - FPI to LPO
- Core Dataset – variables required to achieve primary objectives
- Feasibility

33

Registry Participants

As registries are observational studies and not investigational trials, the observational unit is generally considered to be the 'patient' or the 'participant' rather than a 'subject'.

- Patients/participants are not subjected to any treatment or intervention on account of the study

34

Operational Considerations

- Timelines
- SOPs
- Monitoring
- Quality Assurance
- Reporting Requirements
- Scientific Advisory Panel
- Pilot
- Closure

35

Regulations/Guidelines/ Good Research Practices

- ICH-GCP
- EFPIA Code
- EMEA Clinical Trial Directive
- DHHS Guidance for Industry:
 - Good PV Practices & Pharmacoepidemiologic Assessment (March 2005)
 - Establishing Pregnancy Exposure Registries (August 2002)
- ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP) (2004)
- Guidelines for Evaluating Public Health Surveillance Systems
- Quality of reporting of observational longitudinal research
- Registries for Evaluating Patient Outcomes (AHRQ; April 2007)
- Swedish Association of the Pharmaceutical Industry (LIF) Rules for Non-Interventional Studies (2006)

36

Interventional or Non-Interventional

Observational

Non-Interventional – by U.S. definition
(may be) Interventional – by EU Clinical Trials Directive

PROs, Diagnostics (labs), Procedures
implications for ethics, privacy

As there are no generally accepted criteria for determining when additional diagnostic and monitoring procedures should be considered as an intervention, this remains an issue that has to be decided on an individual basis.

37

Normal Care vs. Standard of Care

Normal Care

- Health care delivery as it is exercised by the average professional in a particular healthcare environment.
 - Normal care, sometimes referred to as “real-world care”, is the result of a study being observational—and, in particular, naturalistic—in design. Patients are observed without undue interference by protocol demands.

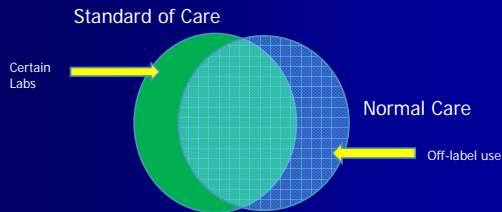
Most guidelines address ‘standard of care’:

Standard of care

- International, national or local treatment guideline/protocol, which specifies the most appropriate treatment
 - Not all treatment guidelines or protocols are evidence based.
 - Patients receiving standard of care do not constitute all patients receiving normal care.
 - Normal or real-world care includes some treatments that may not be considered standard of care.

38

Standard of Care vs. Normal Care



39

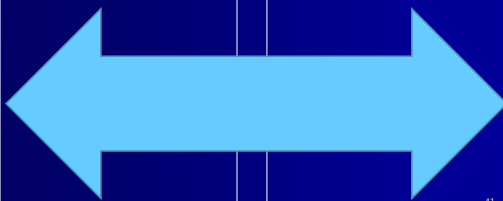
Registry Implementation

40

Where Design Meets Execution

Optimize Registry Design to Meet Objectives

Operational Realities / Practicality

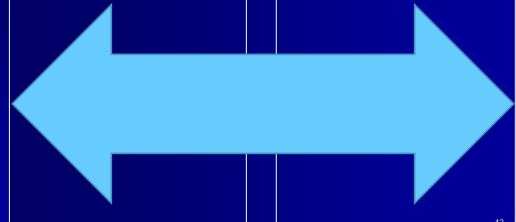


41

Continuum of Degree of “Real-Worldliness”

Protocol-Driven

Naturalistic



42

Data Collection Materials and Methods

- CRFs
- Solicited reporting
- Spontaneous reporting
- Measurement precision
 - Weight scales; laboratory normal vs. abnormal ranges
 - Random error vs. Systematic error

43

Site Support

- Site identification
- Site start-up
- Regulatory Documents
- Site initiation and Training
- Investigator Meetings
- Patient Recruitment
 - Tools
 - Screening/Enrollment Logs
- Helpdesk
- CRA
- Clinical Monitoring
- Study Performance Measures
- Site Motivation Tools
- Site Reimbursement
- Patient Honoraria
- Patient Retention
- Loss to Follow-up
- SDV

44

Research Experience of Principle Investigators and Site Resources



- | | | | |
|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| <p>Professional research sites
(rely on clinical trials income)</p> | <p>Research experienced sites
(have study co-ordinators appropriately set up to perform studies)</p> | <p>Research aware sites
(have performed a few studies, study co-ordinator investigator spouse)</p> | <p>Research naive sites
(never performed study)</p> |
|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|

- The demands of many observational studies and registries require moving research into the community practice environment of private physicians and group practices that have little to no prior experience in clinical research
- Centralized support of these sites can play a large role in their motivation, compliance with data collection and ability to meet enrollment targets

45

Site Identification and Recruitment

- Physicians
- Hospitals
- Access existing mailing lists/electronic databases to
 - profile the providers treating the patients necessary for the registry
 - Understand the profile of the target population
- Gauge site interest in participating in registry (feasibility)
 - Clearly state the purpose and objectives of the registry,
 - how the data will be used,
 - and assurances of the protection of identities of individual institutions, providers and patients
 - From this population, invite a composition of sites who...
 1. ...collectively represent a sample of providers representative
 - Geography, specialty, practice setting, patient volume, training, EDC
 2. ...you project will, collectively, recruit and enroll a sample representative of the target population

46

Site Start-up

- Regulatory Documents
 - CV, Medical License
- Contracts
- Site Initiation and Training

47

Patient Recruitment and Retention

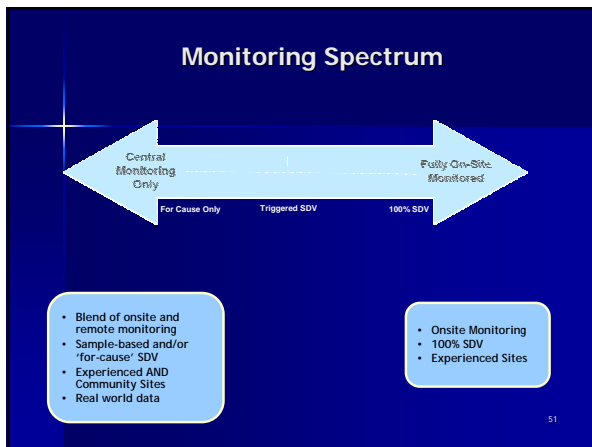
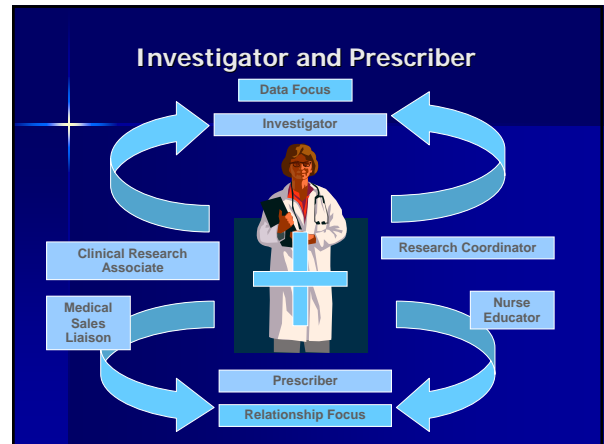
- Tools
 - Web sites / patient on-line communities
 - Newsletters
 - Physician referral
- Screening / Enrollment Logs
- Physician involvement
 - Steering Committee clinical membership
- Incentives
 - Sites
 - Patients
- When does retention compromise validity of outcomes?
 - e.g., adherence, persistence
- Incentives

48

Site Support and Retention

- Helpdesk
- Clinical Monitoring
- CRA
- Study Performance Measures / Reports
- Site Motivation Tools
 - Branding
 - Consistent Data Reports
 - Publication Opportunities
 - Hypothesis/Standard Form
- Site Reimbursement
 - Commensurate with effort involved

49



Data Capture and Management

- Data Capture
 - EDC vs. Paper
 - ePRO
- Database Build
- Edit check specifications
- Edit checks
- Data Protection
- Query Resolution
- Data Cleaning
 - DCFs
- Data Cleaning
 - Primary Variables
 - Missing/Error Rates

52

Data Capture and Management

- Security of the data should be maintained at all times. Access should be limited to authorized individuals.
- Controls, such as document encryption, should be used to ensure the authenticity, integrity, and confidentiality of electronic records when transmitted over open systems (e.g., the internet).
- Adequate back up of the data should be maintained throughout the course of the study.

– From ISPE GPP

53

Close Out

- Site Close-out
- Data Transfer
- Record Retention
- Database Archiving

54

Archiving

1. Study protocol and all approved modifications;
2. Final study report;
3. All source data and, where feasible, any biologic specimens.
4. Copies of electronic versions of analytic data sets and programs
4. SOPs followed
5. Copies of signed informed consents
6. Copies of signed IRB approvals
7. Copies of training documents

55



56