Registry Data – practical considerations for drug development and post approval strategy

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Real World Data (RWD) => Real World Evidence (RWE)

- Real world data (RWD) is patient data collected outside of a randomized controlled trial, often for non-research purposes\(^1,3\)

- Most proponents associate RWE with data that is derived from medical practice among heterogeneous sets of patients in real life practice settings, such as insurance claims data and clinical data from electronic health records\(^2\)

- Real World Evidence (RWE) - using research methods to derive evidence from RWD\(^3\)

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\(^1\) IMS White paper, Why pharma needs to work differently with payors and IDNs on RWE. May 2015

\(^2\) Network for Excellence in Health Innovation brief. RWE: A new era for healthcare innovation. Sep 2015

\(^3\) Public Workshop: A Framework for Regulatory Use of Real-World Evidence, 13 Sep 2017
Type of Registries

- **Disease** – patients with the same diagnosis.
- **Product** – patients that have been exposed to treatments, procedures or medical devices.
- **Pregnancy** - women exposed to treatment of interest during pregnancy, preferably before outcomes can be known.
- Registry is a RWD source
Importance of Rare Disease Registries

- US: <200,000 people
- EU: 5 in 10,000 & life-threatening or chronically debilitating
- Over 6,800 rare diseases identified to date
- Over 50 million people worldwide are affected
- Most without or sub-optimal treatment options
- **Challenge:** early Diagnosis and disease understanding
Rarity significantly complicates Drug Development

- Lack of validated endpoints and biomarkers
- Limited clinical experience
- Experimental complex treatments
- Logistics, expert centers.....
- Methodology and Interpretation
- No alternative RWD
Registries in Drug Development

Disease understanding
- Frequency
- Natural History
- Standard of Care

Context & Comparator
Information for clinical studies

Safety and Effectiveness
Post-marketing commitments

Drug Discovery – Drug Development – Lifecycle management

Unmet Medical Need
ODD

Clinical Trial Planning
RDPP

RMPs
Historical comparison

PASS
REMS/RMMs
Registry data for Natural History

**EXAMPLE from CIBMTR**

- *Jazz Pharmaceuticals recently announced FDA Approval for their treatment of Hepatic Veno-Occlusive Disease (VOD) with Renal or Pulmonary Dysfunction following Hematopoietic Stem-Cell Transplantation (HSCT).*

- **CIBMTR:**
  - Research collaboration between the National Marrow Donor Program® (NMDP)/Be The Match® and the Medical College of Wisconsin (MCW)
  - Unique and extensive clinical outcomes database populated from a large network of transplant centers.
  - Established as part of the Stem Cell Therapeutic and Research Act of 2005 that mandates US transplant centers to submit data from all US allogeneic HSCTs.

- **Data showed that VOD post HSCT is rare and**

  - **Risk of developing condition was higher in children** [0.045 (148/3,316)] **compared to adults** [0.011 (172/16,030)].

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*Center for International Blood and Marrow Transplant Research (CIBMTR) [https://www.cibmtr.org/](https://www.cibmtr.org/); https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208114Orig1s000MedR.pdf*
Historical control data is required to support design and interpretation of a single arm Bayesian design phase 2a clinical trial for the prevention of delayed graft function (DGF) in adults after renal transplantation.

DATA SOURCE

NHSBT Registry* (UK) data will be merged with medical charts data from UK transplant clinics in Newcastle, Cambridge, Glasgow, and Edinburgh.

OBJECTIVE

Study will describe DGF background rates and longitudinal serum creatinine levels and compare results to phase 2a clinical trial.

*https://www.nhsbt.nhs.uk; #https://www.gsk-clinicalstudyregister.com/study/205930
Design Aspects for Historical Comparisons

1. Comparator Selection

Primary study population:
All eligible Registry patients - similar type & severity of disease and similar study sites
(N=763)

Sub-population of historical controls matching subjects to the clinical trial pop.
N depends on the matching criteria and availability of data. (40-60 pts)

Phase 2a clinical trial data (7-14 pts)

2. Relevant Endpoints
- Comparable to trial
- Availability in Medical Practice

3. Appropriate Statistical Methodology for comparison
Risk factor matching – propensity scores – indirect comparisons

Hypothesis
Strength and Challenges

Strengths:

• Existing RWD and experience in clinical practice
• Maximisation of sample size and power
• Less burden on patient and medical community

Challenges:

• Incomplete matching
• Measured and unmeasured confounding
• Limited statistical analysis and unknown assumptions

“In general, studies using historical controls are credible only when the observed effect is large in comparison to variability in disease course (e.g., substantial improvement in outcome is observed with treatment in a disease that does not naturally remit).”

1 https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm423881.htm
Registry Data for Safety and Effectiveness

Post Approval Commitment: Non Interventional Post-Authorisation Safety Study (PASS) Category 1

- **GSK2696273 for ADA-SCID patients without suitable HLA-matched related stem cell donor**
- **Ultra Rare Genetic Disorder**
  - birth rate ~0.3 cases per 100,000 in EU
- **Life-threatening disease, often fatal within the child’s first years of life**
- **Novel Treatment, Complex Procedure**
• **Title:** Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID) Registry for Patients Treated with GSK2696273 Gene Therapy: Long-Term Prospective, Non-Interventional Follow-up of Safety and Effectiveness

• **Objective:** to collect long term safety and effectiveness outcomes for ADA SCID patients that have received GSK2696273

  - 50 patients with at least 15 years of follow up

• **Reporting:** PSURs every 6 months for 2 years; registry reports every 2 years

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Considerations: sample size, outcomes, data source, operationalization

EU PAS Registration Number: EUPAS15795; [https://www.gsk-clinicalstudyregister.com/study/200195](https://www.gsk-clinicalstudyregister.com/study/200195)
• Samples Size in Rare Disease Safety and Effectiveness studies has to be determined on a case by case basis

• Considerations
  – the persuasiveness of the data
  – length of treatment or exposure
  – nature of the benefit
  – patient population that would be treated after marketing approval
  – concern for potential treatment harm

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm423881.htm
### Safety and Effectiveness Outcomes

**Extensive & complex outcome data capture due to novelty of treatment**

<table>
<thead>
<tr>
<th>Observational data and minimal timepoints for their collection</th>
<th>Pre-treatment phase</th>
<th>Treatment phase</th>
<th>Annually Years 1 to 11</th>
<th>Year 13</th>
<th>Year 15</th>
<th>&gt; Year 15</th>
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<td>✓</td>
<td>✓³</td>
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<td>Peripheral lymphocyte counts (absolute and differential)</td>
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<td>✓</td>
<td>✓</td>
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<td>Laboratory blood test results (i.e., biochemistry/haematology/TSH)</td>
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<td>✓</td>
<td>✓</td>
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</tbody>
</table>

**Risk Management Plan:** Risks to be reported
- Autoimmunity
- Unsuccessful response to gene therapy
- Risks related to medical or surgical procedures (e.g. central venous catheter)
- Malignancy due to insertional oncogenesis
- Non-immunologic manifestations of ADA-SCID (e.g. hepatic steatosis, cognitive defects, behavioural abnormalities, hearing impairment)
- Risks related to residuals present in the drug product
- Hypersensitivity to the product
- Replication competent retrovirus
- Lack of data in neonates
- Lack of data in adolescents
- Lack of immunogenicity data
- No reproductive toxicity studies or embryofoetal development studies
- Lack of data in delayed onset or late onset ADA-SCID
Complex Registry Landscape

- EBMT – European Blood & Marrow Transplant
  - NEW Cell & Gene Therapy Registry announced (Mar17)
- ESID – European Society Immune Deficiencies
- SCETIDE – Stem Cell Transplant for Immune Deficiencies in EU
- Country specific Registries
  - UK PID - (2008)
  - CEREDITH - French National PID registry
  - PID Net (German 2009)
  (this is not a comprehensive list)

- Data source or framework for an aligned gene therapy safety and effectiveness study is not (yet) available.
- Only Option: Product Registry
Focus on the Patient

Patient focused registries can improve health, care, and science
Eugene Nelson and colleagues call for registries of care data to be transformed into patient centered interactive learning systems

Eugene C Nelson professor¹, Mary Dixon-Woods professor², Paul B Batalden professor¹, Karen Homa researcher³, Aricca D Van Citters researcher³, Tamara S Morgan researcher¹, Elena Ettimovska professor⁴, Elliott S Fisher professor¹, John Ovreteit professor⁴, Wade Harrison researcher⁴, Cristin Lind professor⁵, Staffan Lindblad professor⁴ ⁵

¹Dartmouth Institute for Health Policy and Clin, New Hampshire, USA; ²Institute of Public Health, University of Cambridge, Cambridge, UK, ³Medical Management Centre, Karolinska Institute, Stockholm, Sweden

Large scale collection and analysis of data has become a health systems worldwide. The systems include registries, quality registries, databases, clinical audits, and quality improvement programmes. - but all collect data on patients' diagnoses, care processes, and outcomes. The systematic comparison and analysis across the decades of data will, for example, reveal the United Kingdom.

- Rare Disease Patient Registries should include data directly reported by patients along with data reported by healthcare professionals. By complementing clinician-reported data in Rare Disease Patient Registries, patients can contribute to improving their contribution to the analysis of data. Continued creation of easily accessible and validated standards, platforms and scientific guidance to ensure the high quality collection of patient-entered data should be encouraged and guaranteed.
Patient Centric Model

LOCAL PHYSICIAN

Clinic letters, medical notes

Medical notes

OSR PHYSICIAN

GENE THERAPY REGISTRY CENTRE

Discharge summaries, blood test reports, patient questionnaires

PATIENT & FAMILY

Usual follow-up and emergency care
Electronic Data Capture – Example Patient

- Registry uses a patient-facing mobile application to collect data
Future Opportunities: From Product to Disease Registry

- One Stop Shop for academia, regulators, industry & patients
- Standardized framework across diseases & treatments
- Comprehensive database – Fit For Purpose
- Patient centric & EHR data collection approach facilitating data collection from patients and reporting outcomes to investigators

Urgent Need for Collaboration across Medical & Patient Community, Industry and Regulator
Moving from rare to common diseases

• **Similar Opportunities and Challenges**
  - Public-Private Collaborations
  - Complex Registry Frameworks
  - Patient Centric Approach
  - Utility for Regulatory Decision Making

• **Common Diseases**
  - RWD beyond Registries
  - Complex Statistical Methodology
Putting the approach into context

Pregnancy Registries

- Common approach to generating data on medication/vaccine safety in pregnancy post launch
- Accepted by regulators (published guidance).
- Is it the optimal approach for all medicines and diseases?

<table>
<thead>
<tr>
<th>Registry</th>
<th>Time period</th>
<th>Total 1st trimester exposures</th>
<th>Risk of major birth defects (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral</td>
<td>1989-now</td>
<td>16,699</td>
<td>2.8% (2.6%-3.1%)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1992-2010</td>
<td>1558</td>
<td>2.2% (1.6%-3.1%)</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>1996-2012</td>
<td>478</td>
<td>4.2% (2.6%-6.5%)</td>
</tr>
<tr>
<td>Menveo</td>
<td>2014-now</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Summary: Registries in Drug Development

• Supplement or Alternatives to Clinical Studies

• Data is complete but not perfect

• Accepted approach for Rare Diseases
  ● Often only RWD available
  ● Challenges: small number of patients, complex endpoints & environment
  ● Urgent Need for Collaboration across Academia, Industry and Regulator

• Common Diseases: similar opportunities & challenges & more

• Registries only useful if appropriate design, analysis and maintenance is warranted
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  ● Andrew Roddam (Vice President, Head of Department)
  ● Marianne Cunnington (Senior Director, TA head)

• **Product Registry**
  ● Jonathan Appleby, Pauline Ng, Nadia Garman, GSK study team
  ● TIGET/OSR study team

• **Renal Transplant Study**
  ● Luke Devey, GSK study team
  ● NHSBT and participating transplant centers