Joint EBE-EuropaBio Task Force on Rare Diseases and Orphan Medicines

Position Paper for Rare Diseases and Orphan Drugs Registries and Databases

BACKGROUND AND PURPOSE OF THE POSITION PAPER

Registries are well-established & commonly-used methods for tracking and reporting clinical outcome, safety, effectiveness and epidemiological endpoints for rare disease patients and treatments. The health information from such databases assists families affected by rare diseases, patient organisations, healthcare professionals, scientists, national and European authorities / regulators, the pharmaceutical industry and payers; to make informed decisions at all stages of research, development and delivery of treatment.

This paper favours the term “patient registry” defined as “an organised system that use observational study methods to collect epidemiological uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical or policy purposes.”

Registries are acknowledged and described in the Commission Communication on Rare Diseases: Europe’s Challenges (2008), the Council Recommendation on an action in the field of rare diseases (2009/C 151/02) adopted on 8 June 2009 and in the Cross-Border Healthcare Directive 2011/24/EU.

On 4th October 2011 the European Committee of Experts on Rare Diseases (EUCERD) organised a meeting in collaboration with the EMA “towards a public-private partnership for registries in the field of rare diseases” in which several critical points for successful registries were identified, including the avoidance of fragmentation of data, the establishment of technical and methodological support and a favourable legislative and regulatory framework. The International Rare Disease Research Consortium (IRDiRC) puts an emphasis on the need for global registries.

This paper represents the pharmaceutical industry perspective on the main challenges and recommendations for rare disease multi-stakeholder, multipurpose registries. Registries are important to the pharmaceutical industry, for collecting natural history data and in developing therapeutics and/or diagnostics. They are frequently required by the regulatory agencies for post authorisation safety surveillance. They will become increasingly important in assessing clinical effectiveness, because of the necessity to improve informed decision-making on access to orphan medicinal products.

1 Adapted from “Registries for evaluation patient outcomes: a user’s guide, AHRQ”

2 http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html
Any registry providing data to the pharmaceutical industry and, ultimately, to the authorities must have the following guarantees:

a) Clearly defined objectives, study duration and appropriate epidemiological and statistical methods to meet objectives;


c) A representative patient population with relevant geographical coverage (including broad demographics, genotype/phenotype, or generalisable data, where/when feasible);

d) Flexibility over time to accommodate changing requirements; and

e) Predictable timeliness and accuracy of data entry, analysis and reporting (with means for source data verification where/when feasible).

Whilst recognising that different orphan medicinal products and rare diseases in varying populations will pose different problems for registries, it is hoped that describing the challenges and producing recommendations will provide guidance to stakeholders in developing strategies for the advancement of rare disease registries and policy, with the objective of building knowledge on a collaborative basis, to improve informed decision-making.

GENERAL RECOMMENDATIONS

1. The EBE EuropaBio Joint Task Force registry survey from September 2012 shows that most industry-led registries are set up to respond to regulatory requests for post authorisation safety studies. Most of the diseases mentioned in the registry survey are very rare (<1 in 10 000 individuals), reflecting the fact that less is known about very rare diseases at the time of marketing authorisation. The average number of patients entered into the registry per centre is very low, from 21 registries studied the median number of patients per centre was 3 (range 2.3-30), probably reflecting the fact that registries are a well-suited tool to increase knowledge in very rare diseases.

2. There are a number of ongoing activities and initiatives at a European and international level concerning registries such as EPIRARE, PARENT, the use of observational data (BURQOL-RD and EUenetHTA, EncePP) or the link with other research and meta-level infrastructures (RD-Connect, RD Hub, IRDIRC). The pharmaceutical industry is working across borders and across therapeutic areas, and will have to comply with various stakeholder norms for registries and data analysis, while meeting their own internal quality standard, therefore industry should be represented in these initiatives, in order to ensure linkages and that a consistent framework for registries is implemented among the different stakeholder groups.
3. Since registries are excellent tools for improving knowledge of rare diseases and care of patients, they are a priority area for patients and families affected by a rare disease, patient organisations, healthcare professionals, scientists, national and European authorities, the pharmaceutical industry and payers. The pharmaceutical stakeholder group agrees that registries should avoid fragmentation and that the centralisation of data should be established or, at the very least, the harmonisation of data, so that databases and registries can be linked to each other. Public-private partnerships with already well-established registries should be encouraged, when possible.

4. Observational data, mirroring the real-life situation and providing generalisable results are increasingly important to support various healthcare decisions. Multiple stakeholders with specific requirements rely on observational data for decision-making. However, registry data are often more complex to analyse than clinical trials data and its existence per se is no guarantee that relevant information will be made available to the community. Involving all stakeholders in the design, the analysis and the governance of the registry should ensure a realistic alignment between expectations and deliverables and the adjustments needed over time.

5. A registry governance board, including representation from all partners, should be established, ideally, before starting the registry. Their role will be to determine the registry purpose, objectives, duration, publications and oversight.

6. When feasible, patient registries should be designed around a disease and not an orphan medicinal product and should start, as early as possible, before treatments are made available. This should allow for the description of the disease heterogeneity, natural history and to improve standards of care. The development of a treatment might represent a milestone that will trigger the expansion of the registry or a shift in priority for data collection to accommodate regulatory requirements. HTA and payers’ interest in the registry will also surge at that moment. It is critical for registries to have this understanding and flexibility to avoid duplications of efforts. Clear methods and strategies should be considered in the design and expansion to avoid ascertainment and reporting bias.

QUALITY ASSURANCE AND STANDARD OPERATING PROCEDURES

7. Any registry collecting data on the use of OMPs should also be required to follow the same standard operating procedures in terms of quality control, reporting mechanisms and pharmacovigilance as would be the case for therapies used in the treatment of non-rare diseases. In particular, any activity should comply with the requirements resulting from the Pharmacovigilance Risk Assessment Committee and the EU Pharmacovigilance legislation from July 2012 covering non interventional studies. Furthermore it should comply with the ENCEPP guidance documents on post authorisation safety surveillance.

8. Registry structures and processes should check for the quality (validity, accuracy, completeness) of the data and decrease the risk of potential bias. If a single registry seems to be the most desirable way to achieve this, the amount and diversity of data that will need to be collected to satisfy the data needs of all stakeholders might jeopardize the quality of the registry output over time. Data management solutions e.g., reasonable routine on-site or remote monitoring, audits, to ensure data quality and standards and structural solutions to manage registry growth, should be envisaged as much as possible at the design phase and their appropriateness reconsidered regularly e.g., set up of sub-registries or technical solutions to combine separate data sets.
Epidemiologists should be used to help with the study design, collection, statistical analysis of data and interpretation of results.

9. It is expected that Centres of Expertise and European Reference Networks will be the most important contributors to the registries. However not all patients treated with an OMP will be seen at the centre of expertise involved in the registry. Therefore, the data captured in the registry may not reflect the true heterogeneity and geographical spread of the affected population. Industry will have an important role, together with other stakeholders, including patient groups, in identifying the clinicians managing these patients and encouraging their enrolment in the registry. Trying to enrol all patients in all centres increases the cost of registries and may decrease the quality of data as patient follow up is less standardised. A satisfactory balance between representativeness of the patient sample and quality and costs of the collected data should be sought.

LONG-TERM DATA COLLECTION AND FUNDING

10. The nature of rare diseases, their heterogeneity and their often chronic nature requires that data should be collected on a long-term basis. Often the RD patient population is initially underestimated and milder cases or insidious complications might only be recognised after several years as disease knowledge develops.

11. In chronic, lifelong disorders with small populations, cross-sectional data are often of little help and a cohort of patients followed over their life span is the most informative. The ideal duration of a registry and the ideal number of patients is dependent on the registry objective and vary from disease to disease. Therefore registries need to take into account long-term funding mechanisms and potential additional resource requirements at specific moments in time i.e. start-up phase, additional data requirements, audits or the renewal of the IT platform. Public-Private-Partnerships will support the long-term sustainability of many registries (where there is the development or availability of an OMP) that may have been funded on the basis of inherently precarious, short-term project funding from public funding bodies, such as the European Commission or NIH.

12. Industry can be a valuable partner in funding the additional data collection required for its own purposes (often mandated into existence due to risk management plans) and funding an access to the clinical and laboratory data already collected in the registry. The financial agreement should be fair, reasonable and transparent to the network.

13. In public private partnerships with disease registries, access rights and exclusive rights to OMP data should be agreed between the different parties. The protocol should clearly define mechanisms and timelines for the reporting of adverse events.

14. Financial support could consider the ENcePP code of conduct and guidance documents.

DATA PROTECTION, ETHICS AND PATIENT CONSENT

15. Achieving data protection and ethical approval for a registry is one of the most time-consuming and complex tasks, whether the registry is academically led or led by a pharmaceutical company. The first is delay in gaining approval by ethical committees. The second is the limitations that may
be placed upon the registry. The third difficulty is the variability of processes for obtaining approval in different countries. The data protection and ethical approval needs to accommodate direct gathering of data, indirect gathering and further processing of data for unforeseen purposes. The possibility of the pharmaceutical company accessing an academic registry for drug development and post-marketing surveillance, in an aggregated form needs to be foreseen and transparent to patients and their carers in the consent forms.

16. In consenting that their details be included in a clinical database, patients are making a conditional gift. The gift is their personal information. This is accompanied by conditions that are stipulated in the consent form, including: confidentiality, secure storage, restricted access to data, and use of data. The patients' views on symptoms, side-effects of medication, quality of life and research priorities are critical to the registry added value. Indeed, patient-reported outcomes are included in the EU Pharmacovigilance legislation among important endpoints that can help support descriptions of risks and these should be captured alongside the clinicians supervised data on the benefit of treatments.

GLOSSARY OF TERMS

BURQOL-RD : Social Economic Burden And Health-Related Quality Of Life In Patients With Rare Diseases In Europe

EBE: European Biopharmaceutical Enterprises

EMA: European Medicines Agency

ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EUCERD: European Committee of Experts on Rare Disease

EUnetHTA: European Network On Health Technology Assessment

GPP: Good Pharmacoepidemiology Practices

GVP: Good Pharmacovigilance Practices

HTA: Health Technology Assessment

IRDiRC: International Rare Disease Research Committee

NIH: National Institutes of Health

OMP: Orphan Medicinal Product