

Patient Registries as Instruments for HTA Outcomes Research: A European Perspective

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KEY POINTS . . .

Registry data can offer more realistic information on the effectiveness of treatments and supply the major model parameter inputs for epidemiology data in health technology assessment economic modelling, provided that the registries are complete, easily available, and regularly updated.

Currently, there is lack of harmonisation and standardisation in registry data collection and analysis methods, a shortage of methodological guidance, and a number of obstacles concerning data access, privacy and confidentiality, and policies for study approval.

Inclusion of cost and resource use data to patient registries would enable the formation of a representative European population data set, permitting longer follow-up on issues of effectiveness and safety.

Introduction

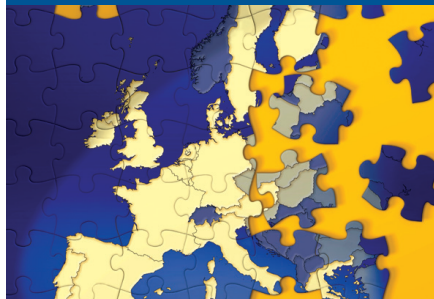
Health Technology Assessment (HTA) analysis of drugs and devices is increasingly in need of real-world data to address aspects of clinical effectiveness and economic evaluation in a health-policy relevant manner, as in the case of Access with Evidence Generation (AEG) or conditional reimbursement models [1,2]. The focus being on proving the benefit of interventions in the usual circumstances of health care practice rather than the ideally controlled environments where intervention efficacy is usually tested in accordance to the definitions adopted by the High Level Pharmaceutical Forum of the European Commission and published in their report on the core principles of relative effectiveness (2008). Repositories holding such valuable real-world data collections are health care provider databases, clinical study databases, and patient registries. The latter are of particular interest for their large size, extended period of follow up, and existing procedures for long-term data curation and maintenance. The introduction of electronic tools for data collection, analysis, and dissemination opens a new host of opportunities for improving both the quality and the utilization of patient registry data alongside other data sources.

health and research. PARENT has grounded its work on the definition of patient registries provided by the US Agency for Healthcare Research and Quality [3], so we understand registries as data collections created through observational study methods, which can be used to evaluate the outcomes of a population that has either had the same disease, condition, or exposure to certain factors. The Joint Action started in the context of the Second Programme of Community Action in the Field of Health—the main EU Health Strategy implementation instrument [4]—which placed emphasis on the use of cross-border e-Health instruments. For PARENT, the e-Health instrument in question is ICT-enabled patient registries. In other words, registries that base and execute their full lifecycle of operations on the use (and with the assistance) of state-of-the-art health information technology (HIT) solutions. Across EU countries, a sustained effort has been ongoing for more than a decade to develop regional and national health information infrastructures based on the use of information systems and electronic health records (EHRs)[5]. PARENT aspires to utilize this effort in order to streamline the process of electronic collection, processing, and use of data not only for health care services provision, which has largely been

A common problem for researchers is locating potentially relevant data collections and subsequently assessing their suitability for answering the questions at hand.

The Patient REGistries iNITIatives (PARENT) Joint Action is a collaborative project of the European Commission and selected EU Member States to advance the cross-border use of patient registries in Europe (www.patientregistries.eu). The Action is a response to the Directive 2011/24 requirement of developing guidance on effective methods for utilizing medical information for the purposes of public

the focus of activities thus far, but also for the secondary use of data [6]. The domain of HTA, particularly as applied in the sectors of drugs and medical devices, has been from the onset of PARENT one of the main focus areas. We have sought to clarify how patient registries can improve as an HTA instrument and what steps and tools are needed in support of the process (from a technical, legal, and policy standpoint).



Use of Patient Registries in European HTA

Due to resource constraints, all new interventions that are effective cannot be introduced into the health care system. A useful tool to illustrate the costs and health outcomes associated with different treatment options and facilitate the necessary prioritization between new interventions are health economic evaluations. In HTA economic modelling analyses, registry data are used as major model parameter inputs for epidemiology data. Overall, registry data may serve as a source of more realistic information on the 'effectiveness' of treatments. The prerequisites for such use are registries that are complete, easily available, and regularly updated.

In the context of collaboration between EUnetHTA Joint Action 2, the European Society for Cardiology (ESC) and PARENT Joint Action, the Norwegian Knowledge Center (NOKC) undertook a validation of the ESC's atrial fibrillation registry case report form by utilising NOKC's HTA report on new oral anticoagulants for atrial fibrillation [7]. The PICO (Patient–Intervention–Comparator–Outcome) parameters for this comparison were defined as follows: P: atrial fibrillation patients; I: dabigatran, rivaroxaban, apixaban; C: warfarin, dabigatran, rivaroxaban, apixaban; O: survival, morbidity, safety. The data sets were compared along the following axes: population and risk factors, risk assessment, interventions and comparisons, outcomes, costs, and resource use. Based on the findings, the registry of the ESC can be used to give input for relative effectiveness assessment (real world use) and economic evaluations, as well as for monitoring patient treatment, compliance, and follow-up in Europe (Fig.1). Its present data content, however, does not cover costs and resource use data which are necessary for economic evaluations. Such data categories could be foreseen for future inclusion in registries, thus enabling the formation of a data set from a European population which is representative of the different countries and would permit longer follow-up on issues of effectiveness and safety.

EUnetHTA Joint Action 2 pilots on rapid Relative Effectiveness Assessment (REA) studies have also included real-world data (including registries). For example, one study assesses the use of zostavax for the prevention of herpes zoster and post-herpetic

neuralgia [8] and another study evaluates the use of canagliflozin for the treatment of type 2 diabetes mellitus [9]. Through these studies, as well as through the work undertaken in the framework of the IMI GetReal project (www.imi-getreal.eu), HTA researchers have made some crucial observations [10]. There is lack of harmonisation and standardisation in terms of the data collection and analysis methods employed with real-world data and a shortage of guidance with regard to methodological issues. Additionally, different needs for evidence and differences in standards of care across jurisdictions may affect the possibilities to collect real-world data in a standardized way. A number of obstacles have been identified that could be handled through policy actions. In terms of data controllers' processes, these barriers relate to access to real-world data, matters of data privacy and confidentiality, and policies for study approval. The role of the EU regulatory and legal framework is a largely determining factor with respect to some of the aforementioned topics, both in a positive and in a negative sense.

The EU Legal, Regulatory, and Policy Framework Surrounding the Use of Real-World Data

An extensive amount of policy documentation addresses eHealth, health data, and cross-border provision of health care services (Fig.2). The centerpiece of this legal landscape is undoubtedly the directive on the application of Patient's Rights in Cross-Border Healthcare (Directive 2011/24). In addition to the emphasis placed on the utilization of medical information in support of public health and research, the directive also promotes collaboration between European Member States on both areas of e-Health and HTA, with the purpose of ensuring safety and quality of care. It is against this backdrop of legal and regulatory developments that we strive to clarify what the role of patient registries is and could be, and at the same time, seek to answer the question of how well registries can satisfy the demand for real-world data.

In the area of pharmacovigilance, the current legislation recognizes the possibility of proceeding into post-authorization safety and efficacy studies where the use of real-world data becomes particularly relevant. The medical devices regulatory framework on the other hand, while still being reformed, also clearly points towards placing more emphasis on following devices throughout their lifecycle [11].

Any use of health data in the EU takes place within a specific framework of data protection. EU Member States are currently still operating on the basis of the Data Protection Directive of 1995 (95/46/EC). A long and arduous process, however, has been ongoing for more than two years, to modify and bring that framework up to date. Currently, we are at the stage of trialogue negotiations between the Council of Ministers, European Parliament, and European Commission. The end result will be decisive; since, from the point of view of health data, the situation remains rather unclear [12]. On the positive side, however, the proposed regulation sets up a consistency mechanism at the EU level combining an advisory role for the European Data Protection Board and a role >

Figure 1. Validation Results Outcomes.

Outcomes	HTA (Health Technology Assessment)	ESC (European Society for Cardiology)
Mortality	Overall survival	Death
Morbidity	Systemic embolism Ischemic stroke Intracranial bleeding AMI (acute myocardial infection) Major extracranial bleeding	Heart failure Tromboembolic events Hemorrhagic events Acute coronary syndrome Other cardiovascular events
Safety	Major gastro-intestinal (GI) bleeding Serious adverse events Other adverse events	Non-cardiovascular events Complications
HRQoL	European Quality-of-Life-5 Dimensions (EQ-5D-5L) Questionnaire	EQ-5D-5L Questionnaire

for the Commission to ensure coherent application of the rules for cases with an EU-wide impact. Thus, it attempts to address the long-known problem of variation across national implementations and interpretations of the Data Protection Directive. The proposed regulation strengthens Data Protection Authorities by making sure they act in concert.



Tools and Solutions Developed by PARENT Joint Action

Throughout its course, PARENT has delivered materials and tools targeted at known weaknesses in the area of patient registries. We have created a broad overview of the current state of patient registries in Europe, which complements earlier clinical domain-specific mapping efforts (EPIRARE survey, ORPHANET). We have created mechanisms to coordinate with other projects that work on the European level with registries and electronic medical record data, and thus acted as a bridge between eHealth and Public Health. We have collaborated closely with partners of the EUnetHTA Joint Action 2 and focused specifically on the HTA needs of patient registry data, not only at the phase-of-market access, but also for surveillance purposes, as well as reassessment of health technologies.

A common problem for researchers is locating potentially relevant data collections and subsequently assessing their suitability for answering the questions at hand. The PARENT Registry of Registries (RoR, available online at: www.parent-RoR.eu) has collected descriptive information on nearly 250 registries that currently operate at the national level in European Member States. As a next step, there are plans to incorporate the registries of the ECS and actively encourage more registries to join.

There are questions about the quality of observational data, as well as the publication of studies based on registries' sources, since HTA often utilizes as a methodology the meta-analysis of published studies rather than primary research. Both of these issues—and many more—are being addressed in the PARENT Guidelines and Recommendations for efficient and rational governance of patient registries. The Guidelines have been developed as a collaborative process, engaging more than 40 authors across Europe, and

have been the subject of iterative discussions with experts and stakeholder representatives. They aspire to provide registry holders—either new ones that are just starting to create a registry, or existing ones that want to maintain and update their registry—with clear guidance and reference to best practices. The Guidelines were released to the public in early fall 2015, and also in online (Wiki) format (parent-wiki.nijzs).

Moreover, we are also specifically targeting issues of sustainability and horizontal coordination between scientific disciplines and related policy action areas, so that the tools and collaborative environments developed by PARENT will continue to exist and develop further in the future. There are clear barriers in the way that the patient registry community currently operates versus the needs of HTA practices, (i.e., in terms of transparency, operational processes and accessibility of data). Even if we manage to improve the quality of the data that resides in registries, health technologies evolve fast, new elements appear, and the speed of input and modification of registry data is too slow to keep up with this process. A means of giving early warning to registry holders on the type of data soon to be needed, indicating corresponding updates in registry data content which may become necessary, can increase the likelihood that relevant data will be available when HTA researchers start investigating new or emerging technologies. Moreover, at present there is no fast and agile way to ensure prompt access to relevant patient registry data at the timelines imposed by rapid HTA assessment or alerting mechanisms, even when the existence of a data collection is known. One way of resolving the problem could be the development of a dedicated and preferential process to support such registry data use purposes.

PARENT has identified a number of complementary areas with other real-world data initiatives (such as the IMI GetReal project and others), and we are seeking ways to align our activities to the fullest extent possible. The significance of the Guidelines and PARENT work in general, as well as its relevance specifically for HTA, has been underlined in the latest Work Plan of the 3rd Health Community Programme [13], where piloting of PARENT deliverables in the forthcoming EUnetHTA Joint Action 3 has been indicated. Before the end of the Joint Action in November 2015, we also achieved the express support of two important EU bodies established through the directive: the e-Health Network and the Health Technology Assessment Network. The aim is to improve visibility and dissemination of the tools and services available to EU registry holders who would like to bring their registries forward to the level of quality and operations demanded by modern research and health care policy making.

References

- [1] Garrison LP Jr, Neumann PJ, Erickson P, et al. Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. *Value Health* 2007;10:326-35.
- [2] Parmenter L, van Engen A. HTA and market insights: Real-world evidence generation for evolving stakeholder needs. *Quintiles, White Paper*. Available at: <http://www.quintiles.com/~media/library/white%2Opapers/hta%20and%20market%20insights.pdf>. [Accessed July 21, 2015].
- [3] Gliklich R, Dreyer N, Leavy M, eds. *Registries for Evaluating Patient Outcomes: A User's Guide*. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center [Outcome Sciences, Inc., a Quintiles company] under Contract No. 290 2005 00351 T07.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014.
- [4] Third Health Programme (2014-2020), European Commission. Available at <http://ec.europa.eu/>

health/programme/policy/2008-2013/index_en.htm. [Accessed July 24, 2015]. [5] European countries on their journey towards national eHealth infrastructures. eHealth Strategies study Report, January 2011. Available at: http://ehealth-strategies.eu/report/eHealth_Strategies_Final_Report_Web.pdf. [Accessed June 25, 2015]. [6] Safran C, Bloomrosen M, Hammond WE, et al. Toward a National Framework for the Secondary Use of Health Data, An American Medical Informatics Association White Paper. *Am Med Inform Assoc* 2007;14:1-9. [7] Efficacy and cost-effectiveness of new oral anticoagulants compared to warfarin for the prevention of stroke in patients with atrial fibrillation. Report from Kunnskapssenteret (Norwegian Knowledge Centre for the Health Services) No 5–2013, Health Technology Assessment. [8] Zostavax For The Prevention Of Herpes Zoster And Postherpetic Neuralgia. Pilot assessment using the draft HTA Core Model for Rapid Relative Effectiveness Assessment Pilot ID: WP-SA-1 V4.0 Final version, September 2013 - EUnetHTA WP5 Joint Action 2 Strand A, Rapid Relative Effectiveness Assessment of pharmaceuticals. [9] CANAGLIFLOZIN FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS, Version 1.3, February 2014. EUnetHTA WP5 Joint Action 2 Strand A, Rapid Relative Effectiveness Assessment of pharmaceuticals Pilot assessment using the HTA Core Model® for Rapid Relative Effectiveness Assessment. Available at: https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/WP5_SA-2_canagliflozin_for_the_treatment_of_diabetes_mellitus.pdf. [Accessed July 24, 2015]. [10] IMI GetReal project WP1: Deliverable D1.2 – Review of Policies and Perspectives on Real-World Data (RWD). April 2015. Available at: <http://www.imi-getreal.eu/Portals/1/Documents/Publications/D1.2%20Review%20of%20Policies%20of%20Perspectives%20on%20Real-World%20Data.pdf>. [Accessed September 12, 2015]. [11] Press Release June 2015. Available at: http://www.consilium.europa.eu/press-releases-pdf/2015/6/40802199534_en.pdf. [Accessed June 17, 2015]. [12] Ensuring a healthy future for scientific research through the Data Protection Regulation 2012/0011(COD). Position of academic, patient and non-commercial research organisations – July 2015. Available at: http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtp059364.pdf. [Accessed July 24, 2015]. [13] European Commission, DG Health and Food Safety Health Programme - Annual work plan for 2015. Available at: http://ec.europa.eu/health/programme/events/adoption_workplan_2015_en.htm. [Accessed July 15, 2015]. ■

Additional information:

The preceding article was based on the workshop, “Patient Registries as HTA Tools in Economic Outcomes Research: Requirements, Barriers, and the Way Forward,” presented at the ISPOR 17 Annual European Congress, 8-12 November 2014 Amsterdam, The Netherlands. The presentation can be found at: <http://www.ispor.org/Event/ReleasedPresentations/2014Amsterdam#workshoppresentations>

For an overview on Directive 2012/26/EU, Regulation (EU) No 1027/2012, Delegated Regulation (EU) No 357/2014, see: http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm

For an overview on The European Medical Devices regulatory framework, see: http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/revision/index_en.htm.

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