REAL-WORLD EVIDENCE IN ECONOMIC EVALUATIONS: REALLY REALISTIC?

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Introduction

Real-world (RW) evidence is an emerging worldwide paradigm that claims to join the forces of academia, research institutes and industry to advance in the field of data science, particularly pharmaceuticals [1]. Although appealing, the concept is still controversial so a common, technical definition is currently lacking in the literature. According to the ISPOR task force report published almost ten years ago [2], RW evidence can be defined as that drawn from 'data used for decision making that are not collected in conventional randomized controlled trials (RCTs)'. In practice, while RCTs are the acknowledged 'gold standard' for efficacy, their selected populations, idealized conditions and limited time horizons may be considered intrinsic limits to assess effectiveness and costs.

The sources of RW data can be various [2], the main ones in order of rigor being i) registries (prospective observational cohort studies), ii) electronic health records (mainly e-medical charts), and iii) administrative databases (typically retrospective data). RW evidence is expected to support rational decision-making, especially after market approval of drugs [3]. This has recently encouraged regulatory authorities to fast-track drugs to market as soon as possible, e.g. the European Medicines Agency through its 'adaptive licensing' [4]. Ideally, once preliminary efficacy and safety have been assessed, the evaluation of relative effectiveness and cost-effectiveness is postponed after marketing approval, relying on RW data for evidence. Thus RW sources are potentially vital for economic evaluations (EEs).

To explore the current state of the art of the subject, we first conducted a literature review of European full economic evaluations (EEs) which claimed to be based on RW data, then discussed the policy implications from a third-party payer's perspective.

RW and Economic Evaluations

Literature search

We searched the PubMed international database to select full EEs focused on drugs claimed to be based on RW data, published in English from December 2007 until December 2015. We used 'real-world evidence' and 'costs OR cost' as search terms[1]. The four studies finally

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[1] From the 210 articles initially identified, 189 were immediately discarded, being: epidemiological and clinical studies (103); study protocols (12), studies on methods (12) and of comparative effectiveness research (13); economic reviews (15) and other topics (34). Of the remaining 21 EEs, we further excluded ten studies not conducted in EU settings, three partial EEs and two EEs not focused on drugs.

selected [5,6,7,8] came from three countries (Italy, The Netherlands and The UK) and were all cost-utility analyses focussed on already marketed drugs and based on Markov models conducted from the third-party payer's viewpoint (Table 1).

Study-by-study analysis

In the most recent Dutch study (on follicular lymphoma) [5] the cost-effectiveness of rituximab (the sponsored drug) was assessed in different scenarios to match RCT with RW evidence. While RCT efficacy and volumes of health care services came from the long-term follow-up of a European trial (334 patients), RW effectiveness and resource consumption were mainly sourced from two national haematological registries, from which a sample of 113 patients was selected. To compare two subgroups of patients (treated and untreated with rituximab), the 'propensity score' method was applied and eventually only 86 patients (43 per subgroup) were included in the analysis. Utility values were sourced from a British observational study (cited only as a congress abstract).

The second Dutch study (the only one funded by a public authority) [6] focused on oxaliplatin in therapeutic regimens for treating patients in stage III colon cancer. The authors matched efficacy from a large multicenter international RCT (1,347 patients) with RW effectiveness from a national population-based observational study to obtain different scenarios, by virtually splitting RW patients (391) too as eligible or ineligible according to the RCT inclusion criteria. Utility values were entirely derived from the literature. Resource consumption for estimating costs was taken from the registry mentioned for all scenarios (including that based on RCT efficacy). Retrospective RW data led to two unbalanced arms (281 with oxaliplatin versus 110 without). This was the only study that estimated micro costs in a sample of Dutch hospitals to cost hospital services.

In the Italian study (on HIV infection) [7] the RW data to assess the effectiveness of two alternative antiretroviral regimens was derived from a clinical database of a big hospital in Lombardy region, but the sample size and patients' characteristics were not reported. Mortality rates were based on national statistics, quality of life was sourced from American literature and validated for Italy by an expert panel of ten infectious disease specialists. RW resource consumption was taken from the Lombardy region administrative database (unknown number of patients in this case too), except for two main side effects from national clinical guidelines.

We finally excluded two EEs since the authors explicitly stated they did not refer to RW data. Thus we selected four studies for review and screened them according to a checklist focused on RW sources.

The British study [8] compared indacaterol (the sponsored drug) with tiotropium and salmeterol in patients with COPD. Efficacy and utility were derived from multi-center international RCTs on indacaterol, COPD-related mortality rates from a Spanish EE. RW data were limited to the resource use of the main health care services and taken from a large national survey of 20,001 subjects. One clinical expert validated all resource consumption, including that from foreign literature and assumptions for COPD exacerbations. Despite the short time horizon (three years), efficacy and costs were both discounted.

Policy Implications

RW is a fashionable term that still finds scant application in European EEs according to our review. A few recent studies claimed to refer to RW evidence, mostly based on mixed data sources and small RW samples. The major apparent contradiction was that, despite RW claims, models (mainly long-term) populated by a mix of sources (including expert opinions and authors' assumptions) underpinned all studies reviewed -real 'patchworks' like many other published EEs [9].

In theory, it is obvious to insist that RCTs (especially those for market approval) cannot prove effectiveness so EEs based on them should be called cost-efficacy rather than cost-effectiveness analyses [6]. In practice, however, it is hard to demonstrate effectiveness in RW by other means than RCTs, because of the many potential biases mainly generated by lack of randomization [3]. Health policy makers have relied on the RCT design for information on efficacy with good reason since allocating patients by chance to alternative treatment conditions permits an unbiased comparison of treatment differences. In a properly designed RCT, any difference observed between the randomised conditions at the end of the trial must be due to either the treatment itself or the play of chance, and statistics can assess the extent to which the differences have arisen by chance or not. As a consequence, RW evidence-based effectiveness is still scant in literature. For instance, an attempt to replicate the findings of landmark RCTs in heart failure, using a sophisticated propensity score approach in RW data, ended in failure with a massively biased estimate providing a qualitatively opposite (and incorrect) result to that found in the RCTs [10].

For costs, i.e. the real 'added value' of EEs, it is worth recalling that the estimate of each cost item is made up of both resource use and unit cost. RW data can only contribute to assessing the former, while the latter require different sources by definition [11]. In addition, volumes of all cost items are hardly ever available from a single source so more than one is usually necessary and models populated with RW data can hardly be an exception.

Unit costs are the second cost component, as influential as resource consumption in estimating real costs and far from realistic in many EEs, starting from drug prices, which are becoming increasingly uncertain for both new drugs under confidential agreements [12] and mature drugs purchased through tenders [13]. Then too, drastic price reductions thanks to generics and biosimilars after patent expiry are hardly ever assumed for already marketed drugs, even in long-term models. Besides drugs, the unit costs of hospital services (by far the main cost from a third-party payer's perspective) are usually sourced from (DRG-like) tariffs - not from micro costs- which are often rough proxies of real costs in many settings, although their use provides consistency and comparability of models at a system level. This is particularly true in European countries like Italy, where national tariffs are seldom updated (twice during the last decade).

Comment

To conclude, we are afraid that expectations raised by RW evidence will be unlikely fulfilled in the short run for effectiveness and are even compromised in the longer run for costs. European regulatory authorities must be aware of these limits and should reconsider the present tendency to rely on preliminary efficacy and safety for market approval and on cost-effectiveness for pricing and reimbursement after launch. We believe they would do better to push the pharmaceutical industry from the very start of the approval procedure for new drugs to produce evidence on comparative efficacy with those already marketed and therapeutically overlapping, then setting prices according to their incremental efficacy (if shown) [14]. Otherwise, it is easy to predict that pharmaceutical expenses will become more and more unsustainable in most EU countries (wealthy Western ones included) during this (never-ending) period of economic crisis.

Table 1. Main characteristics of the selected studies and RW data sources

Variables	Blommestein et al, 2014 [5] The NL	van Gils et al, 2013 [6] The NL	Foglia et al, 2013 [7] Italy	Price et al, 2013 [8] The UK
Main characteristics				
Disease	Follicular lymphoma	Colon cancer	HIV infection	COPD
Alternatives	Rituximab mantainance vs. second-line chemotherapy	Oxaliplatin + FPs vs. FPs	Lopinavir + ritonavir vs. atazanavir + ritonavir	Indacaterol vs. tiotropium/salmeterol
Type of study	CUA	CUA	CUA	CUA
Perspective	TPP	TPP	TPP	TPP
Time horizon	20 years	lifetime	lifetime	3 years
Modelling	Markov	Markov	Markov	Markov
Conclusion	RW data showed that rituximab is cost-effective	Oxaliplatin is cost-effective in the adjuvant treatment	Lopinavir+ritonavir dominated atazanavir+ritonavir	Indacaterol dominated tiotropium and salmeterol
Sponsorship	Yes	No	Yes	Yes
RW data				

sources (sample size)				
Qol	-	-	-	-
Effectiveness	Two registries (113)	Observational study (391)	Hospital records[1]	-
Resource consumption	Two registries (113)	Observational study (391)	Regional administrative database[1]	Survey (20,001)

COPD, chronic obustrictive pulmonary disease; CUA, cost-utility analysis; FP, fluoropyrimidine; HIV, human immunodeficiency virus; Qol, quality of life; RW, real world; TPP, third-party payer.

[1] Unknown sample size.

1 http://ec.europa.eu/health/files/committee/stamp/2016-03_stamp4/4_real_world_evidence_background_paper.pdf

2 Garrison Jr. LP, Neumann PJ, Erickson P, Marshall D, PhD and Mullins DC. Using real-world data for coverage and payment decisions: The ISPOR real-world data task force report. Value Health 2007;10:326-35.

3 Calvert M, Wood J and Freemantle N. Designing "Real-World" trials to meet the needs of health policy makers at marketing authorization. J Clin Epidemiol 2011;64(7):711-7.

4 Eichler HG, Baird LG, Barker R, Bloechl-Daum B, Børlum-Kristensen F, Brown J et al. From adaptive licensing to adaptive pathways: delivering a flexible lifespan approach to bring new drugs to patients. Clin Pharmacol Ther 2015; 97: 234-46.

5 Blommestein HM, Issa DE, Pompen M, Ten Hoor G, Hogendoorn M, Joosten P et al. Cost-effectiveness of rituximab as maintenance treatment for relapsed follicular lymphoma: results of a population-based study. European Journal of Haematology 2014; 92:398–406.

6 van Gils CW, de Groot S, Redekop WK, Koopman M, Punt CJ and Uyl-de Groot CA. Real-World Cost-Effectiveness of Oxaliplatin in Stage III Colon Cancer: A Synthesis of Clinical Trial and Daily Practice Evidence. Pharmacoeconomics 2013; 31:703–718. Appl Health Econ Health Policy. 2013; 11:259–274.

7 Foglia M, Bonfanti P, Rizzardini G, Bonizzoni E, Restelli U, Ricci E et al. Cost-Utility Analysis of Lopinavir/Ritonavir versus Atazanavir + Ritonavir Administered as First-Line Therapy for the Treatment of HIV Infection in Italy: From Randomised Trial to Real World. PLOS ONE 2013;8(2)e57777.

8 Price D, Asukai Y, Ananthapavan J, Malcolm B, Radwan A and Keyzor I. A UK-Based Cost-Utility Analysis of Indacaterol, A Once-Daily Maintenance Bronchodilator for Patients with COPD, Using Real World Evidence on Resource Use. Appl Health Econ Health Policy (2013) 11:259–274.

9 Garattini L, Koleva D and Casadei G Modeling in pharmacoeconomic studies: funding sources and outcomes..Int J Technol Assess Health Care 2010;26(3):330-3.

10 Freemantle N, Marston L, Walters K, Wood J, Reynolds MR and Petersen I. Making inferences on treatment effects from real world data: propensity scores, confounding by indication, and other perils for the unwary in observational research. BMJ 2013;347:f6409.

11 Garattini L, Grilli R, Scopelliti D and Mantovani L. A proposal for Italian guidelines in pharmacoeconomics. Pharmacoeconomics 1995;7(1):1-6.

12 van de Vooren K, Curto A, Freemantle N and Garattini L. Market-access agreements for anti-cancer drugs. J R Soc Med 2015;108(5):166-70.

13 Curto S, Ghislandi S, van de Vooren K, Duranti S and Garattini L. Regional tenders on biosimilars in Italy: an empirical analysis of awarded prices. Health Policy 2014;116(2-3):182-7.

14 Garattini L, Curto A and Freemantle N. Pharmaceutical Price Schemes in Europe: Time for a 'Continental' One?. Pharmacoeconomics 2016; 34(5): 423-6.