Comparative and Relative Effectiveness: A Challenge For Health Systems, Regulators, or Pharmaceutical Companies?

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1 Interest in Relative Effectiveness and Relative Efficacy

Looking at how well drugs work in routine clinical practice, rather than only in experimental randomised controlled clinical trials (RCTs), is increasingly seen as essential for a proper assessment of both net benefit (health gain minus harm\(^1\)) and value (net benefit minus net cost). Establishing net benefit involves estimating effects in routine clinical practice, termed comparative effectiveness research (CER) in the US and relative effectiveness (RE) research in the European Union (EU)\(^2\). Yet, assessments for both market authorisation by drug regulatory authorities (DRAs)—such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA)—and ‘at launch’ appraisals by health technology assessment (HTA) bodies acting on behalf of payers—such as France’s HAS and Germany’s IQWiG—typically use efficacy and relative efficacy data\(^3\).

2 Why Relative Effectiveness Results May Vary Across Countries

Bengt Jönsson (2011) identifies three reasons why RE may differ across, and within, health system, reasons that may not be captured in relative efficacy studies:

1. **Different baseline population risks.** Even if we assume relative effectiveness is the same, differences in baseline population risks will produce different absolute gains in health for a given incremental cost. Relative efficacy studies use entry criteria to ensure the population in the RCT is the same and so will not pick this up.

2. **Different comparators.** Existing practice varies, as both small-area variation studies and studies of the extent of variations in the use of new

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\(^1\) We should note whilst HTA bodies regard effectiveness as health gains minus any health losses from side effects or adverse reactions, drug regulatory authorities (DRAs) regard most health losses as safety effects to be assessed separately.

\(^2\) We henceforth use the terms ‘comparative effectiveness research’ (CER) and ‘relative effectiveness’ (RE) research interchangeably. Comparative effectiveness is defined as ‘comparing health outcomes and the clinical effectiveness, risks, and benefits of two or more medical treatments, services and items.’ (PPACA, 2010), which means ‘real world’ settings (Garber and Sox, 2010). Relative effectiveness can be defined as ‘the extent to which an intervention does more good than harm compared to one or more alternative interventions under the usual circumstances of health care practice’ (Pharmaceutical Forum, 2008). For a discussion by Bengt of the relationships of EBM, HTA, CER and CEA see Luce et al. (2010).

\(^3\) For a discussion of the scientific issues that give rise to tensions between DRAs and HTA bodies around relative efficacy data, see Eichler et al., 2011.
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medicines tell us (Wilking, Jönsson and Högberg, 2009); hence the impact of switching to the use of a new treatment will also. Relative efficacy studies can also use different comparators, but part of the variation may come less from the particular comparator than from the comparator is used in practice. Controversy about the relative effectiveness of SSRIs versus tricyclics for depression reflected the lower doses of the latter used in clinical practice to avoid their greater side effects, thus reducing effectiveness. More recently, sustained release dosing of risperidone for psychosis has been found more effective than repeat dosing because it increases compliance (Lambert et al., 2011). Most comparator issues can be dealt with through the use of active comparators in RCTs, or the use of indirect comparisons using efficacy data. On some occasions, however, real world data will be needed.

3. Differences in the efficiency of health systems. This is a key issue for Bengt, and one that is often not recognised by policy makers. Efficiency will be partly captured in the choice of comparator although, as we have noted, health systems may differ in the health gain they achieve for any given comparator. RCT-based studies of relative efficacy will usually eliminate these differences through use of the same clinical protocol, with very occasional exceptions. One exception was a multi-country RCT of novel oral anticoagulants (NOACs) against warfarin, which found large differences in the outcomes achieved for patients on warfarin (and therefore in the relative efficacy gain from use of the NOACs) because of differences in the effectiveness of warfarin management in countries with patients in the trial (Wallentin et al., 2010). National system differences had not been eliminated by the trial protocol.

Bengt points out that the single European market for pharmaceuticals could be seen as being built on the concept of relative efficacy. The EMA licenses on the basis of RCTs of efficacy and relative efficacy\(^4\); HTA bodies use the same RCT evidence in ‘at launch’ assessments to determine use and/or reimbursement price; the EU Directive giving patients the right to cross-border health assumes a drug has the same effect wherever given\(^5\); and the R&D-based pharmaceutical industry puts its efforts into RCT-based clinical development. Using this model, unnecessary duplication occurs between the EMA and HTA bodies and across HTA bodies themselves—all are analysing the same data.

\(^4\) We do not use an acronym for relative efficacy. One of the problems in the debate about the merits of evidence of relative efficacy versus evidence of relative effectiveness in Europe has been that both have been given the acronym RE, which means that it is often not clear which concept is being discussed.

\(^5\) It could be argued that the cross-border Directive is designed to increase competition in services and so enable patient choice to extend across member state boundaries to improve effectiveness and cost-effectiveness. It is widely seen, however, as a mechanism to drive a uniform approach to coverage—i.e. what is provided to patients—on the assumption that effectiveness is the same when the same care is provided.
Bengt also points out there is a strong scientific case for the EMA to look at relative efficacy, including analysis of indirect comparisons, on behalf of HTA bodies. Such an option was rejected by the HTA bodies themselves, which do, and want to do, this themselves.\footnote{Strictly speaking, no formal proposals were made or rejected; the EMA took informal soundings. HTA bodies were opposed to the EMA entering ‘their’ terrain. The progressive part of the pharmaceutical industry saw that, without buy-in from HTA bodies, this would introduce another hurdle, not eliminate one. The conservative part of the industry has always opposed any extension of the EMA’s remit to HTA.} A prototype of a potential pan-EU process is an undertaking the European Network for Health Technology Assessment (EUnetHTA, 2014). This involves ten pilot Rapid Relative Effectiveness Assessments with two lead HTA bodies sharing the review process. Given these are ‘at launch’ reviews, they inevitably will focus on relative efficacy. However, they also may provide an approach for avoiding duplication and may provide building blocks for both those systems that look at cost-effectiveness using RE, including The Netherlands, England, Scotland and Sweden, and those that focus on relative efficacy to assess therapeutic added-value, notably France and Germany (Towse and Barnsley, 2013).

As Bengt argues (Jönsson, 2011), the challenge for both the EU and the US is realising value in practice. I interpret the challenge Bengt gives us as a seemingly simple one:

> Can we create an EU (and US) environment in which the focus is on relative effectiveness and cost effectiveness with an optimal amount of RE evidence generated and used efficiently?

Efficiency in this context requires (i) static efficiency in maximising the use of cost-effective new drugs and other technologies\footnote{Strictly, this is second best static efficiency, i.e. maximising use subject to prices being above marginal cost during the patent period.} (ii) sending the correct signals to companies about research priorities, to achieve dynamic efficiency, and (iii) putting health care under pressure to move towards their efficiency frontiers to: (a) achieve optimal health gain from use of any given set of technologies and (b) choose the most effective set of technologies given income constraints and patients’ preferences.

## 3 Addressing the Challenge of Realising Value

We seek to address this challenge from two perspectives: where we are now and what needs to happen to move forward.

First, where are we starting from in the EU? The RCT relative efficacy approach increasingly is seen as not being enough. Payers, HTA bodies and regulators are asking for post-launch studies. In response, pharmaceutical companies are investing in ‘real world’ data collection in anticipation of further growth in demand...
for it. Yet, collecting and using such evidence can be resource intensive. As Bengt has pointed out, this carries a great risk of:

1. **Duplication and lack of synergy.** Companies are expected to undertake similar, but different, post-launch studies for DRAs, for multiple HTA bodies based in different jurisdictions; such bodies separately assesses and appraises the same evidence; the studies are in addition to current pre-launch RCTs; and companies are making multiple sequential and duplicative ad hoc investments in research capability in both pragmatic trials and observational studies.

2. **A mismatch of expectations** as to what these studies will reveal. Companies are looking for higher prices and revenues, payers for more targeted use and lower expenditure.

3. **Focusing on drug pricing only**, with results used only to inform drug pricing or approved use, and not to improve health system performance. For Bengt, this would be an important missed opportunity.

The second consideration is what needs to happen to create a better environment. Looking first at RE information and then at cost-effectiveness, three things are needed for a system built around RE to lead to improvements in efficiency:

1. **A new drug development paradigm** in which companies can generate RE evidence in either (i) pre-launch pragmatic trials whilst meeting DRA requirements or (ii) post-launch as part of adaptive licensing\(^8\) combined with coverage with evidence development or some other form of performance-based risk sharing arrangement.

   This change requires, among other things, two major changes to the parallel scientific advice given by DRAs and by HTA bodies acting on behalf of payers. First, there needs to be a conscious effort to achieve a consensus as between both the DRA and HTA bodies and as between the various HTA bodies about end points and study design.

   Second, this should not only cover pre-launch evidence collection, but also post-launch evidence collection with a potential trade off between them. In other words, the DRA and HTA bodies might be willing to accept more uncertainty around at-launch evidence if this uncertainty is to be addressed post-launch and, conversely, they may accept that no

\(^8\) Adaptive licensing has been defined as ‘a prospectively planned, flexible approach to the regulation of drugs and biologics…iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation.’ (Eichler et al., 2012)
substantial post-launch studies are required if particular plans for extensive pre-launch data collection are put in place. Such a mechanism would make a reality of the need for manufacturers to trade pre- and post-launch studies to keep development costs under control.

2. **A major elimination of the duplication of infrastructure and assessment effort** to drive costs out of the system. This requires that:

   a. Health systems introduce information systems that track patients, in particular using electronic health records (EHRs). This will enable them to improve system efficiency, but which as a by-product offers companies the opportunity (for a fee) to ‘piggy back’ on this effort in order to conduct observational studies of the RE of drugs, identify patients for RCT or pragmatic trial recruitment, and conduct pragmatic clinical trials at low cost by tracking patients through routine data sources (i.e. their EHRs) after the intitial randomisation;

   b. Health systems and governments to put in place research infrastructure for pragmatic clinical trials, including ‘Large Simple Trials’, which companies pay to use, but would be required replicate on each occasion when they wished to, or were asked to, conduct a study;

   c. EUnetHTA achieves the goal of a single pan-EU HTA submission for at-launch rapid assessment of RE, with mutually recognition of rapid-RE assessments of that submission (i.e. as with the EMA rapporteur system, only two agencies conduct the review), thereby reducing HTA/payer and manufacturer duplication of effort. Effective use of the EMA’s assessment of the RCTs as part of its licensing role should be part of this, whether through a further revised European Public Assessment Report (EPAR) or other means. Such other means could include HTA bodies paying the EMA for additional analysis or reporting, if that is a more efficient way of achieving the goal of a high quality RE assessment, rather than HTA bodies conducting their own reviews. Such an RE assessment then would be used by all national and regional HTA bodies and payers in the EU as input to their appraisal and reimbursement decisions.

3. **An understanding of the efficiency of health systems** in which new drugs are to be delivered—or not, as the case may be. This requires the use of

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9 A Large Simple Trial is a prospective, pragmatic controlled trial that combines randomisation with large numbers of patients, broad inclusion criteria, multiple study sites, minimal data requirements, and electronic registries.
techniques such as data envelop analysis, including the calculation of Malmquist indices, and stochastic frontier analysis to understand how well health systems are using particular technologies or more generally performing inputs into health gain outputs. Such analysis can then be put to two uses.

a. Providing a basis for understanding whether post launch studies of drugs are likely to produce different results in different health systems. Whilst Eichler et al. (2011), in their analysis of efficacy–effectiveness differences, argued that population differences were likely to be minimal within the EU, they did acknowledge other health system differences might exist—a key aspect of Bengt’s approach. The use of analytical techniques offers a route to identifying where efficiency differences may require separate studies.

b. Providing a basis for identifying poorly performing health systems, i.e. those that appear to be delivering health care treatments and health outcomes well below the maximum available given the resources they choose to deploy.

Changing the environment that determines the generation and use of RE will move us towards an EU-wide model for efficient health systems, achieving elements (i) and (iii)(a) of our efficiency requirements set out on page 3.

Achieving all the elements of efficiency will require adding cost effectiveness to the use of RE evidence. Pharmaceutical prices, whether set by companies or negotiated in some way, need to be linked to use in each health system according to the value (net benefit minus cost) the products deliver. Bengt has long argued (Drummond et al., 1997) that reference pricing is inefficient and prices should reflect local incremental value. This will be essential to achieving elements (ii) and (iii)(b) of our efficiency requirements. Although the EU has no political responsibility for pharmaceutical pricing10, it can support efficient local value assessment and use through its support for a pan-EU RE process and for adaptive licensing11. It is also, importantly, supporting comparisons of health system

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10 The European Commission currently appears to believe that efficiency in pharmaceutical use will be encouraged by having a single price for drugs throughout the EU, and is encouraging pricing disclosure and transparency to achieve this. As a report for the Belgian Presidency of the EU (Annemans et al., 2010) pointed out, however, such a policy will lead to substantial unnecessary inequality in access to drugs within the EU as patients in poorer countries are denied access to new medicines because their governments cannot afford to pay the European price. It fails element (1) of our efficiency criteria in a rather spectacular way. Not unsurprisingly, low income countries and manufacturers are opposed to the policy, whilst some richer countries support it as a mechanism to obtain lower prices for their health systems.

11 The European Commission seems reluctant to actively support adaptive licensing, presumably because of fears that it may lead to more product withdrawals. However, it is
efficiency and the Innovative Medicines Initiative to promote more efficient drug development.

Both pharmaceutical companies and payers may experience a mismatch of expectations about what RE studies will reveal. Companies are looking for higher prices and revenues, payers for more targeted use and therefore lower expenditure. Appraisal of RE evidence should edge both parties towards efficient pricing and use of a new drug on the assumption that pricing and use will reflect value and, as evidence of value changes, so will price and use. In some cases, study results will mean that companies will end up with lower prices and/or less use than they had expected; in other cases, payers may end with higher prices and/or greater volume-generated expenditure than they had expected.

Member state health systems decisions about the efficient use and pricing of medicines will continue to differ because of variations in: (1) clinical practice (2) willingness to pay for health care treatments (3) health system efficiency and (4) patient demographics. Some of these will converge over time, and achieving the efficiency objective we have ascribed to Bengt does require movement on clinical practice and health system efficiency.

Finally, it is important to ask how Bengt’s approach might be translated into a US setting, not least because drug development is a global activity. Duplication of evidence generation, gathering and review in the US and the EU is not efficient unless there are genuine differences in RE on each side of the Atlantic such that separate evidence is required.

The US hitherto has been built around the efficacy approach. The FDA issues market authorisation; payers manage drug budgets by a combination of tiered copayments and discounts from suppliers of competing therapies – often linked to tier placement; the variation in outcomes can be substantial. However, the focus is increasingly on achieving health outcomes, and achieving them more efficiently. Interest in real world data is growing and payers and manufacturers are already using observational data generated from claims databases. Investments in EHRs are taking place. Payers are looking for RCT evidence from pragmatic trials. If the Accountable Care Organisations (ACOs), now being established under the Patient Protection and Affordable Care Act, take on capitation-based contracts that link risk to patient outcomes, they will have a strong incentive to cost-effectively manage patients over time. As a consequence, the importance of collecting routine outcome data will increase substantially. Whilst it is very unlikely that the FDA would introduce adaptive licensing, use of its’ Accelerated Approval option is achieving the same effect of making new drugs

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supporting pan-EU discussions on coverage with evidence development by payers and HTA bodies acting on their behalf, and has commissioned research. This is a necessary corollary to adaptive licensing; payers will need tools to help them deal with greater uncertainty about net benefit and value at launch.
available earlier, with greater uncertainty for payers about their net benefit and value in routine clinical practice. PCORI and NIH are making investments in pragmatic clinical trial research infrastructure capability. All of this increasing the potential for the US to move towards a model based on generating and using CER evidence.

Could we improve trans-Atlantic efficiency? It is possible that PCTs and observational studies carried out in the US or EU would provide relevant evidence on the other continent, albeit with some adjustments. This is a scientific issue to be explored. Could there be mutual recognition by the FDA and EMA of each others’ assessment reports—recognising that decision criteria differ—and a shared view of relevant trial design and, so, in the nature of scientific advice offered? That may be more difficult to achieve due to differences in legal frameworks and regulatory approaches. It would be ironic, however, if trans-Atlantic convergence on efficient approaches to assessing CER/RE evidence, together with local use of cost-effectiveness analysis (achieving Bengt’s efficiency objectives) occurred before convergence of FDA and EMA approaches to efficacy and relative efficacy assessment.

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