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Value demonstration

Early planning for evidence generation and communication is vital to show the worth of new drugs to payers

Health economics, outcomes research and market access are increasingly becoming key functions in the pharmaceutical industry. However, integration of these functions in drug development and commercialisation remains sub-optimal, meaning lost opportunities to influence clinical research strategically, marketing programmes and pricing. Drug development functions are still focused (and incentivised) on time to regulatory approval, rather than success in achieving reimbursement – even though the evidentiary standards required by payers are higher than ever before. The result is that products are still coming to market without viable value propositions, largely because manufacturers begin planning to generate value evidence too late.

Early planning and initiation of value evidence generating studies should begin during phase II at the latest, but ideally from proof of concept.

What payers want

Payers at all levels, from national agencies such as the National Institute for Health and Clinical Excellence (NICE) and the Scottish Medicines Consortium (SMC) in the UK, through to individual hospitals, face increasing demand for healthcare and dwindling budgets and so are interested in the value for money of new treatments compared with the current standard of care.

What is value? In simple terms, a new treatment may provide benefits by (1) increasing the quantity of life (e.g. improving survival); (2) increasing the quality of life (QoL) (e.g. reducing morbidity); (3) reducing costs (e.g. reducing hospitalisations). The preferred health outcome measure of NICE and SMC is the quality-adjusted life-year (QALY), which combines benefits (1) and (2). Value for money of a new treatment compared with the current standard of care is determined by evaluating the 'incremental cost-effectiveness ratio' (ICER) – i.e. the difference in costs (incorporating benefit 3 above) divided by the difference in effectiveness. This process can be represented graphically in a 'cost-effectiveness plane' (see figure).

Cost effectiveness

The origin of the plane represents the comparator (C), which can be the current standard of care, no treatment or placebo. For the purposes of simplification, it is sufficient to focus on the north-east quadrant (i.e. more effective but costlier), because this is where most innovative new products will be. Point A represents a new alternative that is much more effective and not much more expensive than the current standard of care. A public health programme for smoking cessation is one such example; it clearly provides value for money, and so is likely to be adopted by decision makers. On the other hand, point B represents a new treatment that is marginally more effective but significantly more expensive than the standard of care. The reimbursement decision rests on the 'cost-effectiveness threshold', or how much money the decision maker is willing to pay for health gains (dotted line in figure). For NICE, the generally accepted threshold is £20,000–£30,000 per QALY gained. Treatments with ICERs below this threshold (i.e. points to the right of the dotted line) are considered cost-effective; treatments with ICERs above the threshold are not.

For most new products, a cost-effectiveness argument is built using models of disease progression and treatment effect that extrapolate clinical outcomes and costs beyond the time horizon of phase III clinical trials. Uncertainties in input parameters may have a large impact on predicted outcomes and this is where models are vulnerable to criticism. Perhaps surprisingly, many manufacturer cost-effectiveness models submitted to NICE still incorporate published key inputs (such as costs and utilities) that are either outdated or were determined for a different patient population from the proposed indication. An important aim of early value evidence generation is to minimise uncertainty by maximising the robustness of the clinical, cost and QoL inputs.

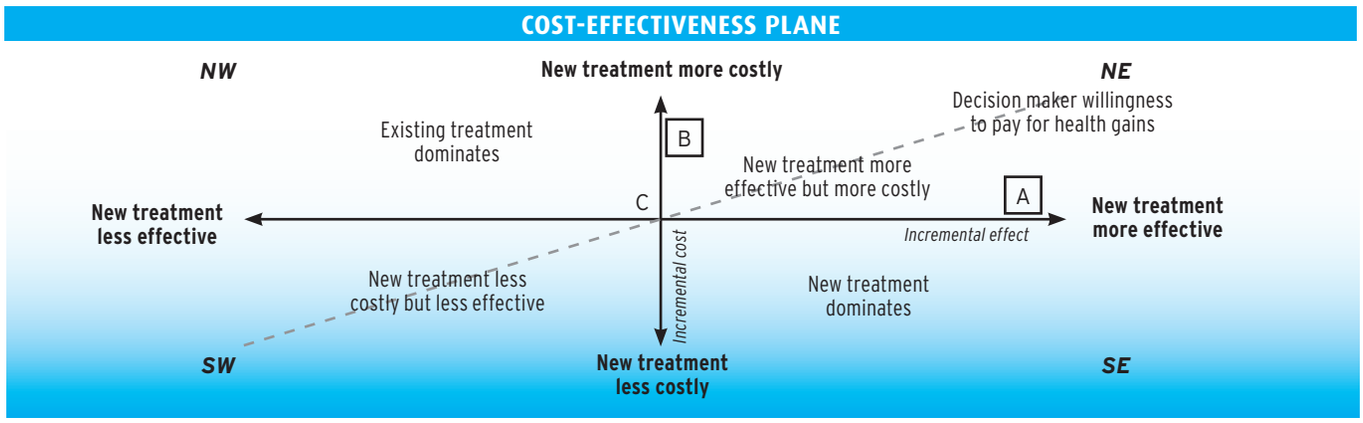
Under the proposed Value-Based Pricing (VBP) framework in the UK, NICE assessments will be based on a variable cost-effectiveness threshold that will be weighted by assessments of burden of disease/unmet need and the level of therapeutic improvement/innovation. Similar criteria are already applied in countries such as France and Italy. This may address some limitations of the current UK system; for example, the relative lack of evaluation of health benefits from a societal perspective (e.g. carers, employers), and the challenge of determining the value of 'end-of-life' drugs. Such a framework provides additional opportunities for pharmaceutical companies to demonstrate product value, if they generate the evidence early enough.

Plan early

Early value evidence generation plans must consider two key aspects:

1) The plan for pre-launch evidence generation, to demonstrate product value at launch and support early reimbursement.
2) The plan for post-launch evidence generation, to address uncertainties in the launch value proposition, demonstrate real-world effectiveness and justify continued reimbursement at future evaluations.

The importance of publishing value evidence in respected peer-reviewed journals cannot be overstated. Most manufacturer reimbursement submissions currently rely extensively on data on file or commercial-in-confidence information. However, such data can be criticised more readily than work that has been through the rigour of the peer-review process. Articles published in advance of reimbursement negotiations will be identified in systematic literature reviews conducted by health technology assessment agencies such as NICE (or their proxies, e.g. NICE-commissioned Evidence Review Groups) and must therefore be considered in



their clinical and economic evaluations. Even if the new VBP assessments of burden of disease and therapeutic improvement/innovation are determined in a non-transparent fashion by an expert committee, early publication of relevant evidence will be essential to inform this process.

A key strategic aim of initiating plans for value evidence generation as early as possible is to inform the design of the phase III programme. Expert input is needed here, because controlled clinical trials may not be the most appropriate study design for generation of many value endpoints. Some aspects worthy of consideration are:

Economic burden of disease – assessments of healthcare resource utilisation, costs and societal burden (e.g. productivity losses and informal care) may be built into clinical trials. Trial designs may need to be adapted to gather data beyond the point at which patients would normally leave, for example, to capture information on resource usage and costs associated with clinical events or disease progression.

Quality of life and utilities – in the UK, robust data on health-related QoL and preferences for health states (utilities) are essential. Clinical trials may incorporate instruments to estimate utility (e.g. EQ-5D questionnaire) in addition to disease-specific QoL questionnaires. Utility estimates can drive cost-effectiveness model inputs (essential in the UK) and provide the basis for mapping algorithms from accepted disease-specific QoL measures into generic instruments such as the EQ-5D.

Anticipating patient segmentation – phase III trials are designed primarily to achieve regulatory approval, but the population in which a product is ultimately reimbursed may be a subset of patients where value is easier to demonstrate (e.g. patients with more severe disease, or non-responders to the current standard of care). Pre-specifying selected subgroup analyses may provide robust evidence of efficacy in identified key patient groups.

Preparing for comparative evaluation – the comparator in most phase III clinical trials is still placebo, rather than the current standard of care. However, payers want comparative evidence; in the absence of head-to-head trials, they use indirect or mixed-treatment comparisons. It may therefore be of benefit to design phase III trials in a way that facilitates subsequent indirect comparisons (e.g. similar inclusion criteria, duration and endpoints to trials using the standard of care).

It is not possible to build all of the required value evidence generating activities into a clinical trial programme, so complementary studies will be required (e.g. additional phase IIIb or phase IV trials to satisfy specific local requirements). Early value evidence planning must also consider the two other key aspects of VBP:

Burden of disease/unmet need – assessments should be made of current treatment algorithms, providing up-to-date evidence of unmet need by identifying the proportion of patients that are not effectively treated with current standards of care, and the consequent burden in both economic (costs, resource utilisation) and human (QoL) terms. Systematic reviews of the literature, retrospective analysis of healthcare databases and pre-launch prospective observational studies are methods used to generate this evidence.

Level of therapeutic improvement and innovation – although this may be the most subjective of the criteria used to assess value, the opportunity nevertheless exists to generate supportive evidence. Convening a clinical expert panel and utilising a robust methodology (e.g. Delphi process) to generate agreed statements based on disease burden, patient needs and the impact of treatment can form the basis of a published consensus report and influence subsequent guidelines.

Evidence of effectiveness in the real world

Uncertainties in the clinical evidence base for a product at launch are inevitable; manufacturers cannot realistically conduct clinical trials of sufficient size and duration to provide at launch all of the clinical outcomes evidence that payers would ideally want to have. That does not, however, negate the value of formulating a plan in the pre-launch phase to demonstrate long-term, real-world effectiveness post-launch. Observational studies and pragmatic clinical trials can provide comparative effectiveness evidence (improved patient outcomes, reduced costs) against current standards of care over a longer duration and more representative patient population than phase III clinical trials. It is likely that plans to generate real-world evidence of product value post-launch will soon be a mandatory part of reimbursement submissions, providing for 'access with evidence development' and taking into account future changes such as new indications and competitor launches.

Ultimately, early plans for post-launch value evidence generation should aim to build robust cost-effectiveness arguments based on real-world data, to support post-launch reimbursement negotiations. If the VBP framework in the UK proceeds as originally planned, then at launch pharmaceutical companies should be able to develop scenarios based on the results of their planned post-launch studies (e.g. base/best/worst-case) and negotiate based on the potential reimbursement/pricing implications. Theoretically, this could allow for a potential increase in price should the real-world data be more positive than the launch evidence. Whether this will come to fruition remains to be seen.

The Authors

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