Designing Clinical Trials to Support Pharmaceutical Reimbursement

The use of health technology assessments (HTAs) to determine whether a healthcare technology should be paid for and at what price is well established in most countries. The evidence requirements of HTA authorities go beyond those of regulatory authorities.

Whilst methods for HTAs vary across jurisdictions, assessments of comparative effectiveness of the new technology vs. the standard of care are common and utilise data from clinical trials that are being used for regulatory submissions.

HTA considerations in the design of regulatory clinical trials are gaining importance in companies developing healthcare technologies. However, the application of these considerations varies and if insufficient attention is given to HTA needs, could significantly increase the risk of a technology not getting reimbursed and / or not achieving a desirable return of investment.

In this article, we present a framework on what to consider during the design of clinical trials intended for regulatory purposes in order to address the evidence requirements for HTAs.

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Reimbursement, clinical trial, HTA, scientific advice

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Introduction

Concerns regarding the growing gap between demand for health services and technologies and available resources has long created the need to regulate healthcare expenditure, and governments have increasingly introduced formal systems to assess the value for money of healthcare technologies coming to market. The predominant processes to do so are health technology assessments (HTAs).

The introduction of the National Institute for Health and Care Excellence (NICE) in 1999 in England significantly contributed to the globalisation of HTAs. Nearly every country now has an HTA organisation in place to help payers determine the value of new medical interventions.

Value assessments conducted by these authorities consist of compiling and analysing the evidence to show the health and economic benefits of a product, compared to the standard of care, are sufficient to justify the price desired beyond the requirements of the regulatory authorities.

Delays in reimbursement decision-making can lead to substantial delays in a new product gaining market access. Negative reimbursement decisions by payers hinder market access substantially, and in turn delays or can impact adversely on sales and return on investment

Historically, HTAs were performed after regulatory marketing authorisation had been granted. Due to the resulting gap between marketing authorisation and reimbursement, HTAs tend now to start much earlier – often in parallel with regulatory approval processes.

Given the central role played by pharmaceutical clinical trials in generating evidence for use in HTAs, those involved in designing clinical trials need to be aware of the methods and procedures required to generate evidence required for HTAs beyond the evidence requirements for regulatory approval.

Furthermore, for a company developing a new health technology, e.g. a new medicine, an understanding of the evidence requirements of HTA decision-makers can help in investment decisions, clinical development plan design and commercial strategy development.

In this article, we present a framework on what to consider during the design of clinical trials to address the evidence requirements for HTAs.

The Role of Clinical Trials in HTAs

Whilst there are differences between countries regarding defining the value of a new health technology, certain central requirements are common and can be addressed in clinical trials.

HTAs appraise a new health technology or indication in comparing a set of product attributes relating to its efficacy, safety, impact on quality of life (QoL) and functional status and pricing compared to the current standard of care.

Evidence used in HTAs for assessing the relative clinical and cost-effectiveness of new pharmaceuticals comes from a variety of sources, such as systematic literature reviews, indirect treatment comparisons and economic modelling. However, clinical trials conducted during the drug development process provide the most important source of treatment effect data for HTAs.

When and What to Consider when Designing Clinical Trials

The when

Traditionally most medicines receive marketing authorisation after completion of large Phase III clinical trials. Increasingly medicines with novel or breakthrough status are receiving regulatory approval based on much smaller Phase II trials and / or non-comparative single-arm trials.

Therefore, it is important to consider the specific evidence requirements for HTAs (i.e. initially when designing phase II trials, but certainly when designing phase III trials) much earlier in clinical development programmes, i.e. when designing Phase II trials but also still be considered when designing Phase III trials.

The what
For the 'what', we consider five critical areas for pharma companies to consider in designing clinical trials to be HTA ready as well as regulatory ready.

Choice of Comparator
The first key consideration concerns the choice of comparator. Non-comparative / single-arm trials create issues when HTA decision-makers try to compare the new technology vs. the standard of care. Placebo-controlled trials result in similar issues, if the placebo arm of the trial differs substantially from clinical practice. Both result in the need for extensive indirect treatment comparisons (ITC), which potentially reduces the robustness of the clinical evidence used in HTAs

We recommend, wherever possible, to use the standard of care as the comparator. This may be difficult where there is no gold standard and clinical practice across or within countries involved in the trial varies. In such cases we recommend consideration of the use of an active comparator based on physician choice, to enable treatment comparisons relevant to HTA decision-makers in their respective jurisdictions. It is, however, still useful and prudent in some cases, such as when there are many possible comparators to include placebo to increase the capacity for ITC and network meta-analysis to be performed, using placebo as the reference comparator. This, for example, is important in psoriasis where a new biologic entrant would face numerous existing biologic therapy comparators with too many to be able to perform head-to-head clinical trials against.

Measurement of Clinical Effectiveness
The second key consideration is the measurement of clinical effectiveness (efficacy and safety). HTA requires outcomes to be patient-relevant, and there is a growing interest in the use of patient-reported outcome measures (PROMs) in clinical trials[1]. In some disease areas, e.g. cancer, it may not be possible to power a trial to capture the treatment effect on hard outcomes, such as mortality / overall survival, and surrogate endpoints are used, such as progression free survival, which is an issue for ensuring the trial results are relevant to patient outcomes. However, surrogate endpoints can be useful when a clear and robust link can be established with patient-relevant outcomes, e.g. as for the link between HbA1c in type 2 diabetes and cardiovascular events. However, this is only when those links have been or can be validated by studies, so that HTA decision-makers can accept them.

We recommend, where possible, to select endpoints relevant to patient outcomes, e.g. survival, PROMs (see more below). Where this is not possible, we recommend establishing robust links between surrogate endpoints and patient outcomes and to validate them in separate studies or with external databases.

When considering the selection of endpoints for a clinical trial, it is also important to keep in mind how the data will be used in HTAs where the new technology will be compared with other technologies used in clinical practice via an ITC. Therefore, it is important to review which endpoints have been collected in trials of most relevant comparator technologies to enable such treatment comparisons.

We recommend reviewing the comparator trials and consider endpoints used in those trials as the endpoints in the trial for the new technology, or to supplement those already planned for use.

Qol, PROMS and Cost-Effectiveness
The third key consideration concerns quality of life (QoL) and patient-reported outcomes (PROMs). HTA organisations use QoL and functional status data, either for use in cost-effectiveness evaluations or as individual value attributes of additional benefit a new technology offers. A separate economic model needs to be developed (typically in Excel) to utilise input data from the clinical studies and other sources.

To support the economic value case for a new pharmaceutical, the instruments used in the trial need to allow the generation of utilities (QALYs). Utility measurement data from generic health status measures, like the EQ-5D, tend to be preferred by HTA organisations. In some cases, it is also possible to use condition specific instruments with a validated mapping function to utilities, such as mapping the EORTC QLQ-C30 questionnaire for cancer patients to the EQ-5D[2].

Besides their use in cost-effectiveness evaluations, the use of generic and condition specific instruments will generate data to inform HTA decision-maker's assessments of the additional benefit of the new technology compared to the standard of care as individual value attributes.

QoL and functional status data should be collected at baseline and throughout the trial and follow-up period.

We recommend collecting QoL and functional status data using generic health status measures which allow the generation of utilities (such as the EQ-5D), as well as including a condition-specific instrument. In selecting which PROMs to choose, it is important to review the trials of the most relevant comparators to enable better comparison between technologies during HTAs.

Resource Use and Cost Data
The fourth key consideration concerns the collection of resource use data, such as hospitalisations, outpatient/GP appointments and tests/investigations to inform the cost-effectiveness analysis. There is no universally recognised method for economic data collection in clinical trials and a variety of techniques are used. The methods and instruments used should reflect the health condition the new technology addresses. The researcher planning the trial should again review the trials of the most relevant comparators to identify potential methods and instruments.

Resource use data should be collected at baseline and throughout the trial and follow-up period. However, resource use data collection from a multinational clinical trial should be performed with caution due to the concerns over the generalisability of the data for country-specific HTA submissions. Hence, there is a key role for local validation of resource use estimates from a trial and/or observational data collection.

Follow-up Time in Trials, and Data Analysis Plans
The fifth key consideration is the follow-up time of the trial. Studies should have an appropriately long enough follow-up time to enable the collection of sufficient and robust data relevant to HTA decision-makers.

In addition, a plan detailing how and when individual endpoints will be collected is essential. This should include the frequency, methods, sources and time horizon within which the data is needed. Besides the data collection plan, the researcher planning the trial should also consider the development of a specific health economics / HTA statistical analyses plan (SAP) covering such aspects as to

how PROM and resource use data will be analysed for HTA and use in economic models. This would complement the regular clinical study SAP.

HTA Scientific Advice

The official procedures

NICE in the UK provides HTA scientific advice as a fee-for-service consultation to developers of health technologies advising companies on how to generate evidence relevant for future HTA submissions to NICE and other HTA authorities. Advice can be requested on medicinal products, devices and diagnostics. Also, the EMA and EUNetHTA (EU body responsible for co-ordinating HTA methods and policies in Europe) offer a joint scientific advice programme to companies with up to three HTA organisations involved.

All of those processes come with varying requirements for preparation and company input and varying levels of opportunities for engagement with the involved parties.

Unofficial Procedures

There are several options, including:

1. Advisory board meetings with health economists with clinical trial experience for selected key territories, HTA experts and clinicians to review and input into clinical trials.
2. One-to-one meetings with payer / HTA experts to review and gain input for clinical trial programmes from specific experts for specific regions and / or countries.
3. Working with specialist health economics consultants with clinical trial, HTA scientific advice and HTA experience to review plans and gain input into clinical trials, to develop a whole HTA scientific advice programme tailored to the individual company requirements and to provide wider market access and HTA advice, also supporting and / or conducting individual projects.

For all of the above we recommend working with health economics/outcomes experts with clinical trial and HTA experience to review plans and gain input into clinical trials, to develop a whole HTA scientific advice programme tailored to the individual company requirements and to provide wider market access and HTA advice. Also to support and / or conduct individual HTA relevant projects. This can also include the consultants helping the company to navigate the official procedures.

Conclusion

In summary, we would like to emphasise that for a product to be able to get a positive HTA recommendation leading to reimbursement by payers, companies need to carefully consider the evidence needs of HTA authorities when planning clinical trials for all new medicines these can and will differ from regulatory evidence needs.

For each new product this should start early, i.e. when planning Phase II trials, in and throughout the clinical development process, in order to optimise the chances of gaining reimbursement and consequently return of investment.

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