Health Technology Assessment: Assessing relative effectiveness

Relative effectiveness assessment is a new area for many regulatory professionals, but understanding the considerations required for this during clinical development, especially in the pricing and reimbursement phase, is important and requires closer collaboration with colleagues in market access roles as Dr Mira Pavlovic-Ganascia, Advisory Board member, NDA Group, explains in this CPD article.

KEYWORDS: Relative effectiveness assessment (REA); Clinical endpoints; Patient-relevant endpoints; Health-related quality of life (HRQoL); EUnetHTA; Multi-criteria decision analysis (MCDA).

Health technology assessment (HTA) is becoming increasingly important for the pharmaceutical industry and is often seen as the “fourth hurdle” that companies need to “jump” to get their products on the market. The industry has always considered the quality, safety, and efficacy of its products but now – after successfully negotiating those hurdles – it must consider the “value” of its new drugs or devices by comparing new therapies with usual clinical practice, evaluating the likely benefit to patients and assessing the impact of the new therapy on healthcare budgets and spending. While regulators require the evaluation of quality, safety, efficacy and benefit-risk in the controlled environment of a clinical trial, HTA bodies want to measure cost-effectiveness, relative effectiveness and a cost–benefit ratio in a real-world setting, which includes:

• Comparative clinical effectiveness – how do the health outcomes of the technology compare with available treatment alternatives?
• Comparative costs and budget impact – how do the costs of adopting the technology compare with current available treatment alternatives? These costs extend beyond the acquisition costs of the medicines but usually are restricted to costs incurred or saved in healthcare.

A smaller, but increasing, number of countries also consider comparative cost-effectiveness, ie, whether these improvements in health outcomes are commensurate with the additional costs of the technology compared with current established practice. The structure of an HTA report is similar whatever the country and is based on so-called PICO structure that drives the whole evaluation:

• Population/patients with the disease of interest
• Intervention(s), ie, the technology under assessment
• Comparison(s) that should serve as reference
• Outcome(s)/endpoints for assessing effectiveness and safety.

However, not all HTAs require the same information or carry out their assessments in the same manner. In order to get adequate data for relative effectiveness and cost effectiveness assessment, several HTA bodies have put in place scientific advices with product developers in order to express data requirements early enough in the product development pathway. Of particular interest are multi-HTA scientific advices, where a developer

KEY LEARNING POINTS

• The efficacy and safety of a pharmaceutical is demonstrated by assessing its relative efficacy – the extent to which a pharmaceutical does more good than harm under ideal circumstances, compared with one or more alternative interventions (placebo and/or an appropriate comparator) using disease-specific clinically relevant endpoint(s) in pre-marketing clinical trials. Subsequently its reimbursement status, access to market and pricing are generally based on the assessment of its relative effectiveness.

• Relative effectiveness can be defined as the extent to which a pharmaceutical does more good than harm in a target population compared with one or more alternative interventions for achieving the desired results when provided under the usual circumstances of healthcare practice. Relative effectiveness assessment (REA) is always a comparative one; it evaluates if a new treatment has an added benefit (ie, more benefit or less harm than a standard of care) or is equivalent to existing therapeutic alternatives.

• REA is a component of HTA, which is the systematic evaluation of properties, effects, and/or consequences, both intended and unintended, of a health technology (HT) on healthcare. HTA contributes to answering questions from decision makers related to health policy and/or practice by summarising information about the medical, economic, social and ethical issues related to the use of a HT in a given context.

• REA is based both on trials performed under ideal conditions (ie, efficacy trials) and trials under conditions of everyday healthcare practice (ie, effectiveness trials).

• Endpoints relevant for REA are defined as patient-relevant endpoints – valid measures of clinical benefit or harm due to treatment, that describe the impact of treatment on how a patient feels, functions, and survives. REA preference is for long-term or final endpoints whenever possible. Choice of endpoints and the manner in which they are reported have a major impact on REA.

• Patient-relevant clinical endpoints include mortality, morbidity (due to disease or treatment) and health-related quality of life (HRQoL). HRQoL represents a specific type of a patient-reported outcome (PRO), distinguished by its multi-dimensionality.

• A clinical endpoint is a main symptom or sign of a disease that should be clinically relevant, valid, reproducible and responsive to change.

• Surrogate endpoints may be used when there is compelling evidence of a clear and consistent correlation of treatment effects on the surrogate with effects on the relevant final outcome. The relevance and hierarchy of the different types of clinical endpoints depend on the research question, disease, and the treatment investigated. Not only the primary endpoint of a study, but also other relevant endpoints are assessed in comparison to (an) adequate comparator(s). This simultaneous assessment of all relevant endpoints is a hallmark of REA.

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has the possibility to have the development plan reviewed by several HTA bodies in different European countries.

The EMA has been involved in a number of these combined scientific advice procedures for medicines in a variety of diseases. The outcome is a Scientific Advice (SA) letter from the Committee for Human Medicinal Products (CHMP); with regard to the HTA input, either the minutes are circulated by the company for individual written HTA agreements on the views expressed during the meeting or HTA bodies send their written answers to the questions raised by product developers at the end of the procedure. The choice of HTAs for a combined regulatory and HTA scientific advice is up to the applicant company. Before the face-to-face meeting there may be a closed session between the EMA and HTAs (which are equal partners in the process) to review their respective positions and identify critical divergences.

Both HTA and combined EMA-HTA advice aim at improving evidence to support product effectiveness. A pharmaceutical may not be accepted for reimbursement if the evidence is considered inadequate by HTA agencies. In addition to national healthcare priorities, available resources, utility of the technology to the healthcare system, the quality and adequacy of evidence is essential to support coverage decisions. In many cases, inadequate evidence regarding the benefits and harms of a pharmaceutical assessed is related to the inadequate choice of endpoints and comparator(s) used to demonstrate its benefits and harms.

Clinical endpoints

Clinical endpoints to use for REA are “patient-relevant” endpoints, ie, they reflect how a patient feels, functions, or survives. They broadly measure mortality, morbidity (due to disease or its treatment) and health-related quality of life (HRQoL). Clinical endpoints for REA are valid measures of clinical benefit due to treatment. More specifically, they are expected to be well defined and justified for a given context, relevant, and responsive to change while on treatment. They should reflect evolution of a disease, be reproducible, free of measurement or assessment error, and unbiased.

Clinical or patient-relevant endpoints may be reported by a patient, a clinician, a caregiver or an observer (eg, paediatrics). Patient-relevant endpoints should not be confused with patient-reported outcomes, even if some patient-relevant endpoints are reported by patients themselves. In general, trial endpoints can be symptoms (such as pain, dyspnea or anxiety), final endpoints (such as mortality, MI, stroke), surrogate endpoints (such as HIV viral load, blood pressure, HbA1c), or intermediate endpoints (such as progression-free survival, or angina frequency). All may be used either as single endpoints or as composite endpoints (ie, two or more endpoints combined into one endpoint) if adequate to measure clinical benefit.

The acceptability of a surrogate endpoint as a measure of patient benefit is based on its biological plausibility and when there is compelling evidence of a clear and consistent correlation between the effect of treatment on the surrogate and the effect on the final outcome of interest (validation). Whenever possible, REA is based on final patient-relevant clinical endpoints (eg, morbidity, overall mortality). However, surrogate endpoints can be accepted in the initial assessment if the validity of the surrogate/final clinical endpoint relationship has been clearly established a priori.1-4 It is important at this stage that there are sufficient safety data. For the reassessment of a pharmaceutical, however, effectiveness is recommended to be demonstrated on final morbidity (eg, stroke, myocardial infarction, fracture) and mortality endpoints. Absence of data on final endpoints might be acceptable when a clinical endpoint is difficult or impossible to study (eg, very rare or delayed event) or the target population is too small to obtain meaningful results even after very long follow-up (eg, very slowly progressing and/or rare diseases).

Composite endpoints

Use of composite endpoints should be avoided if suitable single endpoints are available.5 If a composite endpoint is used for REA, components of a composite endpoint should be of similar clinical importance and be limited to three or four. Prior empirical evidence of the value of each component endpoint must be provided. The contribution of each component to the result within the composite endpoint should be reported. All components should also be reported separately as secondary endpoints according to the endpoint hierarchy. Assessors need to be able to discern the effect of the intervention on all components of a composite endpoint. If a significant difference is obtained on the composite endpoint, but the effect is not homogeneous across components, it cannot be concluded that the treatment has an effect on the composite endpoint as a whole.

The impact of an intervention on HRQoL is systematically assessed in REA if appropriate and sufficient data are available. Along with mortality and morbidity, HRQoL is one of the major REA endpoints.6 Improvement in HRQoL alone (for equivalent effectiveness and/or harms) may be the basis for “added benefit” of a new drug compared with an adequate comparator. HRQoL is typically measured using a validated instrument. The appropriateness of the HRQoL measure used depends on the purpose of the REA. If it is used to inform healthcare policy makers about the relative value of a product, the decision-making context plays a crucial role. In a context where drug reimbursement decisions take into account cost-effectiveness data as well as priority setting values across indications, generic HRQoL measures that translate into utility values are preferred to disease-specific HRQoL measures in order to maximise the comparability of REAs across indications. Disease-specific measures may be added as complementary information.

When cost-effectiveness is considered within indications only, disease-specific HRQoL is in principle sufficient, although adding a generic utility measure is useful for coherence across decisions.

EUnetHTA guidelines recommend that the choice of endpoints depends on the target population studied, the characteristics of the disease and its core symptoms and signs, as well as the intended purpose of treatment (ie, diagnostic, preventive, curative, symptomatic, palliative), the unintended side-effects7 and the decision-making context (eg, whether or not cost-effectiveness information is used for deciding on reimbursement). In the context of REA of pharmaceuticals, preference is given to long-term or final endpoints whenever possible (eg, overall survival), as opposed to short-term endpoints that may be acceptable for acute symptomatic conditions with no long-term consequences.

The relevance and hierarchy of the different clinical endpoints will depend on the research question, the disease, and on the treatment investigated. However, even if a trial is powered on a primary endpoint, the added clinical benefit of a new pharmaceutical will be assessed in comparison to an adequate comparator on all endpoints relevant for a disease or its treatment.8 This simultaneous assessment of all relevant endpoints is a hallmark of REA.

In addition, a generic endpoint such as life years gained or quality-adjusted life years gained is often considered to enhance the relevance of the REA for the decision making process in its broad context.9 Adjustment for multiple hypothesis testing may be appropriate.

References

Evaluating cancer treatments

Case study:

Overall survival (OS) data coming from comparative Phase III trials are generally requested by HTA bodies in Europe to demonstrate the benefit of an anticancer drug; globally, a survival gain of at least 2–3 months or more would be considered appropriate for a new drug versus an adequate comparator, even if there is no officially defined threshold. In cancers with low mortality, progression-free survival (PFS) and (exceptionally) response rates might be acceptable as intermediate endpoints.

The PFS role is double in this respect: as a substitution endpoint or as an endpoint with an intrinsic value in relation to quality of life and other clinical benefits (symptoms, reduction) and as an intermediate clinical endpoint more or less correlated to overall survival when the latter is not available. The problem with using PFS as an intermediate and/or substitution endpoint is not specific to oncology but it has a particular importance in cancers with long survivals. As intermediate endpoints tend to overestimate the medical benefit; even if validated for a particular tumour and stage of disease, OS is clearly preferred by reimbursement agencies.

Assessment of added clinical benefit of a new drug is always a comparative one, evaluated against an adequate comparator, in the relevant patient population, by using appropriate clinical endpoints, relevant to the main characteristics of the disease and the aim of treatment. Therefore, in the case of an irrelevant comparator, and/or a wrong choice of endpoints, or clinically irrelevant difference in OS, added benefit may not be granted. In the absence of OS data, lower-added benefit may be granted if it is based on PFS data only. As mature data are requested whenever possible, interim analysis is generally not recommended, especially on PFS, but also on OS data if too premature.

The recent arrival of new treatments that target identified functional genetic mutations (“targeted therapies”) or PD-1/PD-L1,2 axis (“immunotherapies”) and their combinations have profoundly changed treatment strategies as they considerably improve patient survival, but raise new challenges in REA and decision-making processes in Europe as compared with REA of “classical” chemotherapies. Indeed, the evidence provided by developers raises challenges at each step of REA of recently approved immunotherapies: choice of adequate population (overall population or only PD-1 positive patients), choice of adequate dose (absence of a clear relationship between the dose and anti-tumour activity and toxicity), and assessment of response to treatment (pseudo-progressions).

Low response rates, long duration of response and long OS in some patients, all improved with combination immunotherapies but with much higher toxicity and high costs, render decision-making rather difficult.

To optimise accelerated assessment, the EMA has launched the PRIME (PRIority MEdicines) scheme to support the development of innovative medicinal products (such as cancer immunotherapies and/or targeted therapies), supposed to have a major public health interest in conditions where there is unmet medical need. A major therapeutic advantage to patients should be demonstrated through a clinically meaningful improvement of efficacy, and/or or an impact on the prevention, onset or duration of the condition.

**PRIME assessment**

Access to PRIME depends on both the magnitude of the treatment effect, which could include its duration, and the relevance of the observed clinical outcome. Early interaction between the applicant and multiple stakeholders, involving the EMA, HTA bodies and patients, on key decision points/issues for the preparation of marketing AUTHORITATION approval application and reimbursement dossiers, is foreseen to ensure the generation of a robust data package and to facilitate timely access to patients. Existing SA procedures (independent or integrated regulatory and HTA advice, either on the national or European level) may be used for this purpose.

With the current HTA mindset, limited development programmes that might be sufficient for an accelerated assessment and regulatory approval might not be sufficient to support reimbursement, as HTA decisions remain independent of the regulatory route of approval and consider only data available to support REA and not the regulatory approval pathway. However, it is supposed that better understanding of relationships between responses to treatment, durations of response, toxicities and survival, might allow for earlier access to market based on non-final endpoints.

Despite divergences in regulatory and pricing/reimbursement requests for data generation, it is expected that these can be integrated within global product development and outcomes for benefit-risk and REA, standardised in order to be able to “file the same and propose the same”, both for regulatory and reimbursement purposes. This does not guarantee that a drug will be reimbursed – its reimbursement status will probably vary from one country to another. However, there is a hope that decreasing uncertainty of assessment will ultimately facilitate market access and patient care.

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The content of this supplement is drawn from:

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1. PICO is an acronym for which of the following?
   a) Patients Interventions Comparators Outputs
   b) Patients Intelligence Comparisons Outcomes
   c) Population Interventions Comparisons Outcomes
   d) Population Interventions Comparators Outputs

2. The preferred endpoint for REA of oncology drugs is
   a) Tumour response rate
   b) PFS (progression-free survival)
   c) OS (overall survival)
   d) DFS (disease-free survival)

3. Relative effectiveness assessment is not performed in which type of trial?
   a) Versus placebo
   b) Versus active comparator
   c) In open label trials
   d) In comparative trials

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