1 April 2025

EMA/115125/2025

Joint HTAb-regulatory perspectives on understanding evidence challenges, managing uncertainties and exploring potential solutions

Outcome of a workshop series between HTA bodies and regulators

Introduction

Improving mutual understanding between Health Technology Assessment bodies (HTAbs) and regulators of the assessment challenges each decision maker faces as a result of current approaches to evidence generation, including the management of remaining uncertainties at the time of decision making, was explored in a series of workshops.

Typical methodological challenges faced by regulators and HTAbs were illustrated using three case studies:

- Onasemnogene abeparvovec (Zolgensma), indicated for the treatment of patients with 5q spinal muscular atrophy (either clinically or genetically defined).
- Amivantamab (Rybrevant), indicated as monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations after failure of platinum-based therapy.
- Axicabtagene ciloleucel (Yescarta), indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBCL) that relapses within 12 months from completion of, or is refractory to, first line chemoimmunotherapy.

Participants identified the main challenges during assessment and at fulfilling their respective roles focussing on the evidence available at initial market entry of the three products, discussed learnings and explored potential solutions in terms of alternative evidence generation strategies.

The agreed summarised conclusions and key considerations provide an important framework for future HTAb and regulatory collaboration on both improved evidence generation strategies as well as methodologies for mitigating the identified uncertainties. Such summary should help developers to design development plans that provide relevant evidence for each type of decision making.

Conclusions

The following key areas of remaining uncertainties at time of respective decision making were identified by regulators and HTAbs as relevant from both perspectives:

- lack of (prospectively planned) comparative evidence against relevant comparator(s)
- uncertain relevance of study endpoints for decision-making (e.g., 'surrogate' endpoints, with surrogacy not always established or demonstrated)
- the impact of intercurrent events on the validity and interpretability of treatment effect estimates, in the context of the estimand framework
- maturity of data and duration of follow up (particularly in the context of claims of 'cure')
- small populations and trial recruitment challenges, e.g. paediatric indications, biomarker-directed therapies, or rare diseases
- limited knowledge or experience of certain diseases, e.g., treatment pathways, prognostic factors, effect-modifiers
- challenges arising from parallel development of multiple medicinal products in a disease area
- limitations in the ability to obtain adequate additional evidence when new treatments have become available.

Discussions about potential solutions addressing respective evidence needs to support decision making across the life cycle must acknowledge the difference in scopes between marketing authorisation, including potential orphan maintenance applications as applicable, and HTA decision making. That said, any discussions of the necessary clinical studies must also acknowledge the specific regulatory scope for clinical trial applications and its implications for downstream evidence generation. Overall, there was general agreement between HTAbs and regulatory participants that clear research questions of clinical interest need to be pre-specified, which together with context-specific feasibility concerns then drives the choice of what constitutes adequate evidence generation.

Regulatory-HTAb collaboration early at the design stage and throughout the entire product lifecycle is therefore key. This may include early clinical trials used to support conditional marketing authorisation, 'pivotal' clinical trials, to post-launch studies. In many cases, HTA and regulatory research questions are distinct but overlapping; wherever possible, studies should be designed to meet both decision makers evidence needs simultaneously.

Collaboration can be facilitated through the parallel EMA-HTA Joint Scientific Consultation, but also discussions on finalised EMA and HTA assessments, and other interactions. To further exchange such learnings and anticipate future challenges, medicinal products for HTA-regulatory dialogue outside of the formal JSC process should be identified on the basis of scientific importance e.g., (potentially) disease-modifying therapies, first-in-class treatments, rare or challenging diseases, novel study designs.

In summary, the **following key points** were identified by HTAbs and regulators as potential solutions to address joint evidence needs:

- **There is a strong preference for randomised evidence from both regulators and HTAbs when assessing benefit/risk and comparative effectiveness of medicinal products.**

  Depending on the context, it could be considered (e.g. in oncology or life-threatening rare conditions) that randomisation becomes more challenging once initial (early stage) evidence is

available. Therefore, it was suggested to randomise as early as possible in the clinical development programme. In situations where randomised controlled trials (RCTs) may be challenging to conduct, novel randomised designs present a promising alternative to single-armed trials. Examples may include 'seamless' phase I-II designs in early clinical development, multi-arm 'platform trials' in disease areas with evolving treatment options, and other flexible, adaptive designs that preserve randomisation while potentially reducing sample size requirements and development timeframes. However, both HTAbs and regulators acknowledge that there are methodological, practical and operational challenges associated with complex trial designs. Further reflections on optimising opportunities for improving evidence generation and guidance on such designs is therefore considered to be a priority.

- **There are substantial opportunities to complement pre-licensing clinical trial data with randomised trials in registries and routine care to inform regulatory and HTA decision making.**

  'Pragmatic' RCTs, defined here as RCTs conducted in routine clinical practice settings, have the potential to generate high-quality evidence on (relative) effectiveness under real-world conditions. They may also offer the opportunity to study the use of the medicine beyond the tightly controlled populations typically seen in pre-approval trials, and provide relative effectiveness evidence against additional relevant comparator treatments not studied previously. Similarly, registry-based RCTs, in which disease registries are used as a platform to design studies, identify and recruit eligible participants, and collect data, offer a promising avenue for efficient evidence generation. Pragmatic and registry-based trials may be particularly relevant for evidence generation in the post-launch phase, where they could be used to address remaining uncertainties identified in regulatory and HTA assessments, if feasible and appropriate for the research question(s). They could also be considered and foreseen at earlier stages of the clinical development programme. Regulatory-HTAb collaboration on the design of these studies can help to ensure that remaining uncertainties are addressed with robust evidence and in a timely manner. Investment in high-quality disease registries at a European level can help to advance the use of these study designs for regulatory and HTA purposes.

- **The estimand framework provides a valuable, shared language for aligning study design with regulatory and HTA objectives.**

  Regulators and HTAbs may require different estimands for decision-making; when this is the case, clinical trials should be designed to allow the estimation of multiple estimands in parallel. Stakeholders should seek advice from regulators and HTAbs on the relevant estimand(s) for their decision making and ensure that these can be estimated from the clinical trials, balancing considerations such as clinical relevance alongside the ability to estimate multiple target estimands with minimal bias. Regardless of the preferred (primary) estimand, comprehensive sensitivity and supplementary analyses are essential to investigate underlying assumptions. The use of appropriately harmonised estimands across different studies within a disease area would be highly valuable to decision makers, both as a means of establishing efficacy in terms of agreed disease-specific measures of benefit, and to allow for reliable direct and indirect comparisons of different treatments. The development of further disease-specific guidance on estimands is therefore regarded as a priority for future collaboration.

- **Improving collection, analysis and reporting of outcomes other than the 'primary' study outcome(s) can substantially reduce uncertainty in decision-making.**

  Regulatory and HTA decision-making relies on evidence covering a range of outcomes beyond the primary endpoint(s) of clinical trials, even where these analyses are not formally 'confirmatory'. In practice however, evidence for these 'non-primary' outcomes can be of poor-quality, or lacking

entirely, leading to uncertainty in decision-making. To address this, relevant 'non-primary' outcomes should be given greater consideration at the time of study design, including during scientific advice procedures. As a particular example, continued collection of data on disease status, symptoms, quality-of-life and safety following the occurrence of events such as progression, discontinuation, or initiation of subsequent therapy, is strongly recommended.

- **The timely availability of individual participant data (IPD) from clinical trials has potential to enhance the quality of evidence synthesis, indirect comparisons, and other cross-study analyses.**

  Access to IPD, including detailed baseline covariate data for both the intervention and comparator arms, is required to apply statistical methods that adjust for confounding (e.g., methods based on propensity scores), an essential requirement for reliable inferences from non-randomised studies. Evidence synthesis based on RCTs can also benefit from availability of IPD, allowing for robust investigation of effect-modification and the application of methods such as IPD (network) meta-regression. For both non-interventional studies and RCTs, IPD access will contribute to the quality and robustness of the indirect comparisons that are fundamentally necessary for HTA assessment and may inform benefit-risk assessment and contextualisation at marketing authorisation. Furthermore, the availability of IPD at the time of assessment can allow for more robust investigation of underlying assumptions, the (re-) alignment of outcome definitions across studies, and the ability to target different estimands of interest. Options to ensure availability of IPD for regulatory and HTA work involving cross-study comparisons should therefore be explored.

- **There remain significant unresolved challenges with the use of observational real-world data (RWD) to inform effect estimation by indirect comparisons.**

  At present, observational RWD (i.e., observational data that describe patient characteristics including treatment utilisation and outcomes in routine clinical practice) are often introduced to construct an external comparator group for an indirect comparison with a single-armed trial. These comparisons are often done in *post-hoc* manner that was not foreseen in trial protocols or pre-planned in another way, and without adequate adjustment for confounding and other sources of bias. Such approaches cannot in general be considered to provide confirmatory evidence for regulators or robust estimates of relative treatment effects for HTAbs. Key challenges identified include lack of sufficiently granular data in RW sources to allow appropriate measuring of baseline confounders (e.g., composite disease scores) and replication of trial inclusion/exclusion criteria; poor data quality; the lack of a well-defined study baseline; and inherent differences between clinical trials and routine practice in terms of monitoring, supportive care, outcome measurement and other factors. Thoughtful planning, appropriate study design, and the existence of a suitable comparator data source are essential requirements for reliable integration of RWD in evidence generation.

- **There are however also substantial opportunities to complement clinical trial data with real-world data to inform regulatory and HTA decision making.**

  The value of RWD to inform e.g., natural history studies, disease epidemiology, identification of relevant comparators and mapping of current clinical practice, is widely recognised. However, other applications of these data are less well-developed. For example, early non-interventional studies can help inform the design of clinical trials, addressing considerations such as feasibility, the prognostic effects of biomarkers, appropriate inclusion/exclusion criteria and stratification factors, and duration of follow-up, as well being used to better anticipate or inform both regulatory and HTA considerations around target estimands. Furthermore, throughout the stages of evidence generation, there is also potential to enhance learnings from clinical trials by linking trial data and

real word data, for example to facilitate long-term survival follow-up, to investigate potential surrogate outcomes, or to assess the durability of treatment effects.

- **Regulators and HTAbs have common interest in understanding and developing frameworks to support structured, informed decision making under uncertainty.**

  Such frameworks could facilitate the identification, assessment, and balancing of remaining uncertainties, particularly in the context of regulatory decision making. A key challenge in regulatory decision-making lies in evaluating the clinical importance of favourable and unfavourable effects, where the use of health utilities, as commonly applied by Health Technology Assessment (HTA) bodies, may provide a bridge to the regulator's assessment. Furthermore, more reliable estimation of the overall effects of treatments on health utility in clinical trials would help to address evidence needs for cost-utility analyses conducted by many HTAbs. Exchanging knowledge and best practices between regulators and HTAbs in this regard is considered a valuable opportunity.

Acknowledgements

This workshop series was organised by a team of experts consisting of assessors, statisticians, health economists and scientists from HTA and regulatory agencies around Europe, under the coordination of David McConnell (Senior Statistician, NCPE, Ireland) and Dominik Karres (Senior Scientific Officer, EMA). We would like to thank colleagues from the participating agencies for their hard work and valuable contributions to the workshops.

HTA agencies:

National Centre for Pharmacoeconomics (NCPE), Ireland

Institute for Quality and Efficiency in Healthcare (IQWiG), Germany

Norwegian Medical Products Agency (NoMA/DMP), Norway

Belgian Health Care Knowledge Centre (KCE), Belgium

National Institute for Health and Disability Insurance (RIZIV-INAMI), Belgium

National Authority of Medicines and Health Products (INFARMED), Portugal

Spanish Agency of Medicines and Medical Products (AEMPS), Spain

Regulatory agencies:

European Medicines Agency (EMA), Netherlands

Swedish Medical Products Agency (MPA), Sweden

Medicines Evaluation Board (CEG/MEB), Netherlands

Federal Agency for Medicines and Health Products (FAMHP), Belgium

Federal Institute for Drugs and Medical Devices (BfArM), Germany

French National Agency for the Safety of Medicines and Health Products (ANSM), France

Austrian Medicines and Medical Devices Agency (AGES), Austria

Health Products Regulatory Authority (HPRA), Ireland

The organisers would also like to thank the Heads of HTA Agencies Group and the Chairs of the EU HTA Coordination Group and MPG Subgroup, as well as the Chairs of the CHMP, CAT, COMP, SAWP and MWP for their support, and the Irish Department of Health and National Centre for Pharmacoeconomics for hosting the hybrid workshop in Dublin in November 2024.