Conclusions RSNN Expert Meeting - The interface between authorisation and reimbursement (HTA), 28 November 2019

The RSNN expert meeting on 28 November 2019 discussed and elaborated potential research questions on the theme of 'The interface between authorisation and reimbursement (HTA)'. Sixteen experts and stakeholders were invited in a personal capacity to discuss this theme in an informal setting. They all work – or have worked – in government, industry, clinical practice, universities or industry associations, where they have developed knowledge and experience of the theme under discussion. The meeting was held under the Chatham House Rule. The results of this exchange of ideas, provided in summary here, are relevant to the regulatory science knowledge agenda of the RSNN.

1. GAP BETWEEN AUTHORISATION AND HTA

The discussion made clear that there is a gap between authorisation and HTA, both in the formal legal sense (differing mandates, benefit-risks balance in regulation, relative effectiveness, and price and budget impacts of HTA) and in working practice (methods and requirements for providing clinical evidence). These differences are sometimes very specific to a context or country, with consequences for the predictability of the decision-making, which appears to be particularly important for small businesses who only market one product. The gap seems to be widening, partly due to initiatives to gain earlier approval of medicines and with less or alternative forms of clinical evidence. A factor that also contributes to this gap is the variation in assessment capacity and expertise, which manifests in the activities of both authorisation and HTA authorities.

Research questions:

- Does this gap really threaten the effective delivery of new drugs to the patient, or is it more a question of perception and/or framing?
- The gap seems to be caused by different scientific perspectives, different cultures, a focus on risk-benefit as opposed to budget impact, etc. Can we bridge the gap by providing more clarity and insight?

- Can scientific advice (and combinations of advisory practices and procedures) effectively be deployed to bring authorisation and HTA closer together?

2. DIALOGUE AND TRANSPARENCY

Society must be able to depend on the sector's ability to make well-considered choices, based on scientific data and analyses, within the domains of and at the interface between authorisation and HTA (obviously within the bounds of their legal roles and responsibilities). The increasing complexity of the drug development process makes it all the more important to foster dialogue, share knowledge and form public-private partnerships. At the same time, the shift in focus of regulatory authorities towards a greater influence on the development of drugs raises questions about independence, improper influence and transparency.

Research questions:

- Which forms of dialogue and/or advice can contribute to more reliable and productive interactions between the domains of drug development, authorisation and HTA? What are the relevant success factors (scientific quality, timing, file and data sharing)?
- To what extent are authorisation and HTAs influenced by the relationships with stakeholders (industry, government, patients, insurers)? Are these relationships too close? How can the decision-making of authorisation and HTA authorities be made more transparent?
- Are the end users (patients, prescribers, pharmacists, clinical guidelines) sufficiently integrated in the authorisation and HTA processes? Are these processes sufficiently harmonised to the end users?

3. EVIDENCE AND MANAGING UNCERTAINTY

Scientific data and analysis form the basis for any authorisation or HTA decision. The question of what evidence is needed and feasible, is the subject of considerable debate, both within and outside the formal pharmaceutical system. Questions such as: Which clinical endpoints? Which study design? How many patients? and What to compare? are all continuously under scrutiny and give rise to differences of opinion. Are these questions and the answers to them helping to remove the uncertainty, or are they just adding to it? At the same time, new methods for generating evidence have become available, such as real-world data (RWD) and artificial intelligence (AI). All this is taking place against a backdrop of trials that are becoming increasingly complex – including in terms of regulation – and expensive.

Research questions:

- What considerations affect the industry's clinical development programme (study design, endpoints, comparisons)? Are these considerations primarily focussed on authorisation and to what extent are HTA preferences considered?
- How can the generation and fine-tuning of the evidence for relative efficacy, clinical added value and safety be more streamlined?
- What explains why the same scientific data can lead to different conclusions by the authorisation and HTA authorities? To what extent is this related to other contexts (formal mandate, relative cost-effectiveness, risk-benefit balance, managing uncertainties, political preferences, ethical dilemmas, etc.)?
- To what extent is it feasible and productive for authorisation and HTA authorities to share data (mock files) early in the development process?
- There is much debate about the use of RWD. Which questions can RWD answer? Which not? Who owns the data? Who are the publishers? Who has access to the data?

4. DRUG LIFE CYCLES

The life cycle of a drug is usually many decades. Although the interface between authorisation and HTA is primarily relevant for initial market approval and reimbursement decision-making, other questions continue to play a role later on in the life cycle of a drug, such as its continued clinical value, comparisons with newer products, economic arguments for keeping (old) medicinal products on the market, incentives to continue investing in post-innovation innovation (*repurposing*) and unmet medical needs for which no adequate treatment exists (or no longer exists). The factor time places an important role in this life cycle; time is relentless, time changes perspectives (new insights, patent expiry) and research takes time too.

Research questions:

- To what extent are new data and the experiences of clinical practice effectively implemented in authorisation and HTA processes during the life cycle of a drug? How can we learn more from periodic reassessments of drugs?
- How can a more fertile ground be developed at the interface between authorisation and HTA, to ensure the continuous investment in and perpetuation of existing drugs (generic and non-generic), repurposing and the development of necessary antibiotics?
- The interface between authorisation and HTA is not static; much preparatory work precedes it, and much follow-up is involved afterwards. How can the interactions between authorisation and HTA be more effectively embedded in horizon scanning, disease monitoring and the dynamics of innovation?

5. THE FUTURE

The participants in the discussion pointed to many future uncertainties and challenges at the interface between authorisation and HTA. Three of these were particularly salient; not exhaustive nor complete, but they were at the top of the list.

Research questions:

- Are the authorisation and HTA authorities sufficiently prepared and ready to respond (in terms of clinical practice, patient perspectives and strategic objectives) to future developments in medical technology (e.g. imaging and biomarkers)?
- Will the label as we know it today still be viable in the future? Will it remain substantially accurate, legally defendable, economically feasible, technically implementable and customizable? And what about ownership?
- Authorisation and HTA are international domains by definition. Differences and agreements are and will be determined by international treaties, global developments and political influences in the sector. What will the situation be in 10 to 15 years?

The results of this meeting will be processed by the RSNN in future research agendas that should contribute to informing policy discussions.