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Clinical expert opinion to inform Health Technology Assessment

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Abstract

Clinical expert opinion is a valuable source of information for Health Technology Assessments (HTAs). We conducted a retrospective review of HTA submissions made to the National Centre for Pharmacoeconomics (NCPE) from July 2019 to June 2020 inclusive (n=18). We found that clinical expert opinion, obtained by methods such as interviews and Advisory Boards, were used by Applicant Pharmaceutical Companies to support all 18 HTA submissions. Clinical expert opinion was used to inform HTA domains relating to the population, use of drugs in clinical practice, treatment effectiveness, healthcare resources used and health-related quality of life (HRQoL). We also present examples where clinical expert opinion, obtained by the NCPE, was used to inform NCPE assessments. By providing opinion for HTA, clinicians make an important contribution to the decision-making process on drug reimbursement. This supports the availability of effective, safe and value for money drugs for patients in Ireland.

Background

The National Centre for Pharmacoeconomics (NCPE) conducts HTAs of drugs under consideration, by the Health Services Executive (HSE), for reimbursement[1]. The NCPE assessment process aligns with national guidance and international best practice[2,3]. It includes evaluations of the clinical effectiveness, clinical safety, cost effectiveness and budget impact of the drug under consideration. On the basis of the assessment, the NCPE makes a drug-reimbursement recommendation. This recommendation, along with other criteria outlined in Irish legislation[4], are considered by the HSE when making a decision on reimbursement[1]. Healthcare professionals are important stakeholders in HTA; clinical expert opinion forms a key component of NCPE assessments. An Applicant Pharmaceutical Company seeking drug reimbursement (herein referred to as the Applicant) submits a HTA dossier to the NCPE. This dossier includes computational economic models (i.e. cost-effectiveness models and budget impact models). A cost-effectiveness model is an analytic framework used to synthesise information on the natural history of the disease, clinical efficacy of

treatments, HRQoL, resource use and costs associated with the disease and its management in order to estimate the lifetime costs and outcomes associated with drugs[5]. The budget impact model predicts the potential financial impact, to the HSE, of the adoption of a drug into the healthcare system over a five-year period[1].

In general, economic models should be primarily informed by data from high quality, methodologically rigorous clinical trials which are designed to minimise the effects of bias. Other sources of data also used to inform economic models include registry data, national and international treatment guidelines, HRQoL data along with health-care resource use and cost data. Clinical expert opinion is often required to supplement or support this data[6]. This opinion from healthcare providers is a valuable source of information for HTA and its use is advised in national and international guidelines[2, 3]. Clinical expert opinion is obtained by Applicants to inform their HTA submissions (see Table 1) and by the NCPE to inform the NCPE assessment and validate Applicant assumptions. Clinical expert opinion can be a qualitative expression of judgement[7], for example opinion on the target population and the current standard of care. Qualitative opinion may be used to validate the healthcare pathways simulated in a cost-effectiveness model. Clinical expert opinion may also be a quantitative expression of judgement[7]. In these cases, opinion can be used to provide estimates for key parameters in the economic model and to describe the uncertainty associated with these. Clinical expert opinion also helps to ensure that HTAs, assessed by the NCPE, are generalizable to Ireland.

Use of clinical expert opinion by Applicant Pharmaceutical Companies

We conducted a retrospective review of all Applicant HTA submissions made to the NCPE in the 12 months prior to 30th June 2020 (n=18). We investigated if Applicants had used clinical expert opinion to inform these HTA submissions. The review found that clinical expert opinion was sought, by Applicants, to support all 18. The median number of clinical experts, who informed each individual HTA submission, was seven (range 1 to 33); the majority were hospital consultants. The methods, used by Applicants, to collect clinical expert opinion were generally unstructured and included interviews (n=13 (72%)), questionnaires (n=11 (61%)) and Advisory Boards (n=6 (33%)). As shown in Table 1, opinion was used to inform a wide variety of domains and/or parameter estimates in the economic models. Clinical experts were asked to identify or validate “standard-of-care” in the Irish healthcare setting in 13 (72%) of the 18 HTAs. In addition, opinion was frequently used to inform estimates of the number of eligible patients in Ireland (n=14, 78%). Clinical expert opinion was also used directly to inform estimates of treatment benefit, most commonly for cancer drugs, where opinion was used to support the plausibility of long-term survival predictions where long-term survival data were not available (n=6, 33%).

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Use of clinical expert opinion in NCPE assessments

The NCPE also seeks clinical expert opinion as part of the HTA assessment. Clinical experts are identified on the basis of their expertise in the disease area under consideration. Opinion is obtained via one-to-one interviews (conducted face-to-face or remotely) or through written responses to specific questions. Examples of how clinical expert opinion has been previously used to inform NCPE assessments include:

In the HTA of atezolizumab (Tecentriq®), in combination with bevacizumab, for the treatment of adults with advanced or unresectable hepatocellular carcinoma, clinical expert opinion on expected market share estimates of standard of care (sorafenib and lenvatinib) was used to inform the potential net-budget impact[8]. In the HTA of amikacin (Arikayce®) liposomal nebuliser dispersion for the treatment of non-tuberculous mycobacterial lung infections caused by *Mycobacterium avium* Complex, clinical expert opinion suggested that, in Irish clinical practice, guideline-based therapy would be discontinued after six months if patients did not have sputum culture conversion. This informed the duration and costs of guideline-based therapy[9]. In the HTA of gilteritinib (Xospata®) for relapsed or refractory acute myeloid leukaemia with FLT3 mutation, clinical expert opinion indicated that patients alive two years after haematopoietic stem cell transplant are considered 'cured' in line with the literature. This informed HRQoL, resource use and cost parameters[10]. Clinical trial follow-up for pembrolizumab, in combination with axitinib, as a first-line treatment for advanced renal cell carcinoma, was short at the time of HTA submission (median of 27 months). Plausible, long-term overall survival predictions were provided by clinical experts[11].

Challenges

Clinical expert opinion is valuable in HTA. However, clinical expert opinion may be subjective and consequently methods used to obtain opinion should be as objective and rigorous as possible[12]. All those who seek clinical expert opinion should endeavour to have strategies in place to minimise potential biases, particularly motivational or cognitive biases, examples of which are discussed elsewhere[13]. Strategies include providing relevant background evidence, framing questions in a way to avoid anchoring and ambiguity and collecting rationales from experts[13]. HTA should be free of commercial influence. To this end Applicants are required to provide a declaration of potential conflicts of interests from all clinical experts recruited[6]. Similarly, all experts contributing to an NCPE assessment are asked to declare relevant interests. Such interests do not necessarily preclude involvement, but are declared to provide reassurance on impartiality. There are also a number of practical challenges with gathering

clinical expert opinion. In particular, clinical experts face time constraints which may impact engagement.

Future directions

A recent systematic literature review of studies that evaluated global pivotal trials (for novel drugs) has indicated a trend towards less rigorous trial design (e.g. less frequent randomization, double-blinding, and active controls). Also, an increased use of surrogate outcomes (not well correlated with clinical outcomes) was noted[14]. Thus, clinical expert opinion, to inform knowledge gaps, will be increasingly valuable. Also, it is suggested that, there will be increasing use of more formal structured expert elicitation exercises in HTA. Structured expert elicitation aims to make the process of obtaining quantitative clinical expert opinion as rigorous and scientific as possible. These methods allow experts to specify a quantity of interest as well as the associated uncertainty around it which can be encoded as a probability distribution[12, 13]. Structured expert elicitation has been used by Applicants to inform HTA submissions globally[15]. The use of these methodologies to inform HTA is likely to become more common place over time.

In conclusion, clinical expert opinion informed all 18 Applicant HTAs submitted over our study period. The NCPE also seeks clinical expert opinion to inform assessments. Clinical expert opinion can be used to inform economic model assumptions over a wide variety of domains. It is likely that structured expert elicitation will be increasingly used to inform HTA globally. Clinical experts providing opinion for HTA at both a local or global level continue to make a valuable contribution to the decision-making process on drug reimbursement, enabling access to the most effective, safe and value for money drugs for patients in Ireland.

Table 1: Domains of the Health Technology Assessment informed by clinical expert opinion – from submissions made to the NCPE (July 2019-June 2020, n=18)*

Model domain	No. of HTA submissions (%)
Patients/Population	
Target populations in Ireland	5 (28%)
Estimates of patient numbers	14 (78%)
Use of drugs in clinical practice	
Standard of care in Ireland	13 (72%)
Subsequent treatments and/or concomitant treatments	12 (67%)
Estimates of market share	8 (44%)
Duration of drug treatments	5 (28%)

Dose regimens	5 (28%)
Treatment effectiveness	
Plausibility of long-term survival predictions of cancer drugs	6 (33%)
Expected duration of treatment effects	4 (22%)
Timepoint at which patient can be considered 'cured'	2 (11%)
Resource use	
Estimates of healthcare resource use	14 (78%)
Companion diagnostics	4 (22%)
Health-related quality of life	
Health-related quality of life measures	5 (28%)

* This advice was sought by Applicant Pharmaceutical Companies over the study period. This is not an exhaustive list of the type of advice that will be sought for future submissions

Declarations of Conflicts of Interest:
None declared.

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