The medical writer's role in health technology assessment submissions

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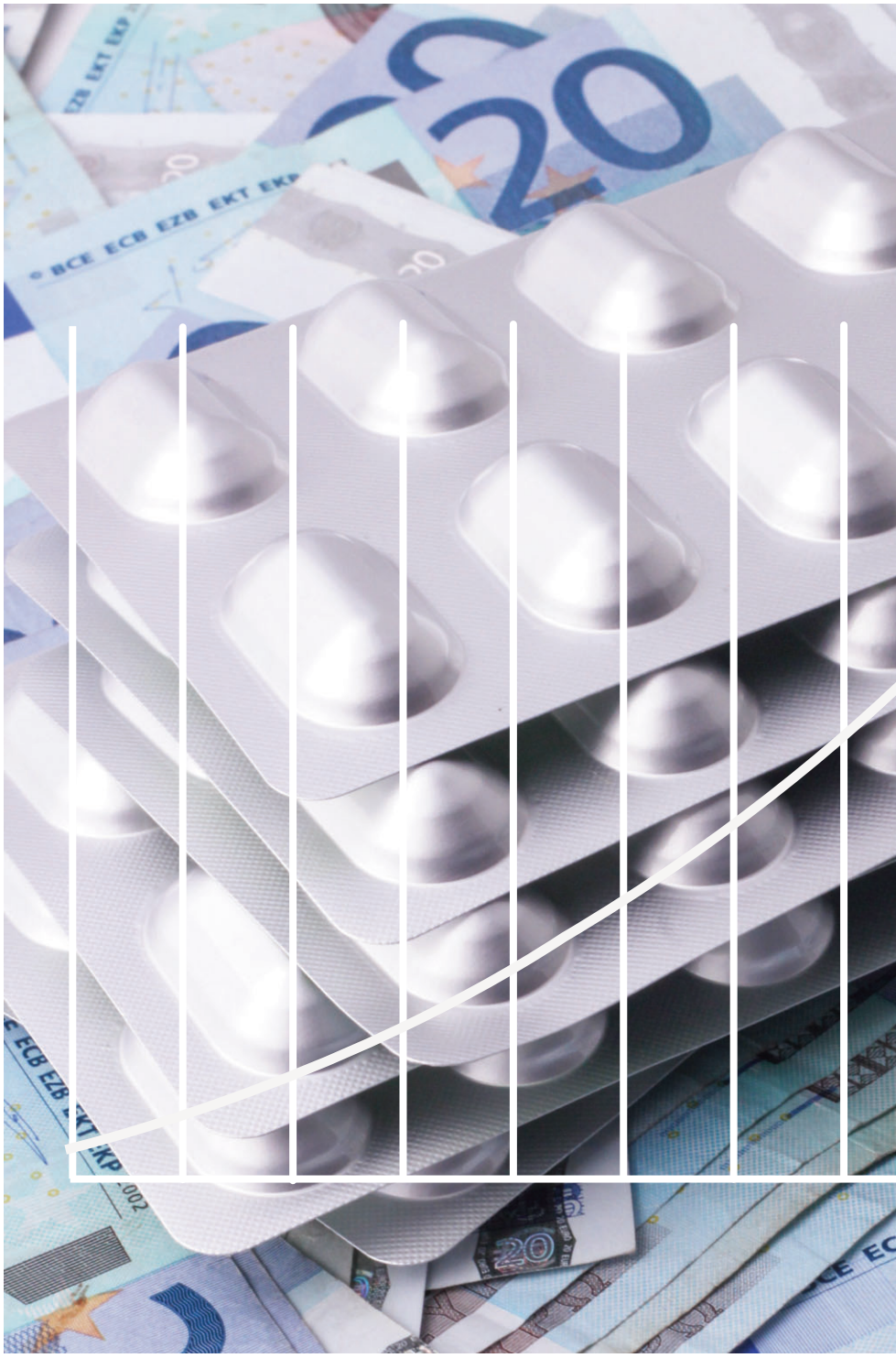
Abstract
Writing health technology assessment (HTA) submissions is a challenging and rewarding area of medical writing, being part of the process of giving patients access to new medicines. Submission requirements differ between countries but all require clear communication of the new product's value. This article looks at the medical writer's role in UK and German submissions, but many of the points covered will be generalisable to other jurisdictions.



Health technology assessments (HTA) help inform payer decisions about what medicines and other technologies to fund, and at what price. These may be carried out by official national bodies, such as England's National Institute for Health and Care Excellence (NICE), France's National Authority for Health (HAS), and Germany's Federal Joint Committee (G-BA), or at local and regional levels. Medical writers play an important role in the writing and managing of dossiers submitted by manufacturers to the decision-making bodies. This article outlines the medical writer's role in HTA submissions (also known as reimbursement submissions) and examines how we can add value in the quest for a successful appraisal, one which culminates in patient access to novel medicines and reimbursement at a satisfactory price for both the manufacturer and the health system.

Writing HTA submissions is a challenging and rewarding role that sits somewhere between

regulatory medical writing and medical communications. The medical writer is a key part of a submission team that also includes health economists, data analysts, market access professionals, and systematic reviewers. HTA submissions are sometimes handled in-house by the pharmaceutical or device company, but more typically the sponsor company (often called the "manufacturer") will engage a consultancy to carry out the economic modelling, advise on strategy, and create the submission dossier. This article is written from the perspective of the authors' experience in writing UK and Irish HTA submissions (to NICE, the Scottish Medicines Consortium, All Wales Medicines Strategy Group, and the National Committee for Pharmacoeconomics), but many of the principles covered are transferrable to other jurisdictions. Tina Krieger looks more closely at the writer's role in German HTA submissions.

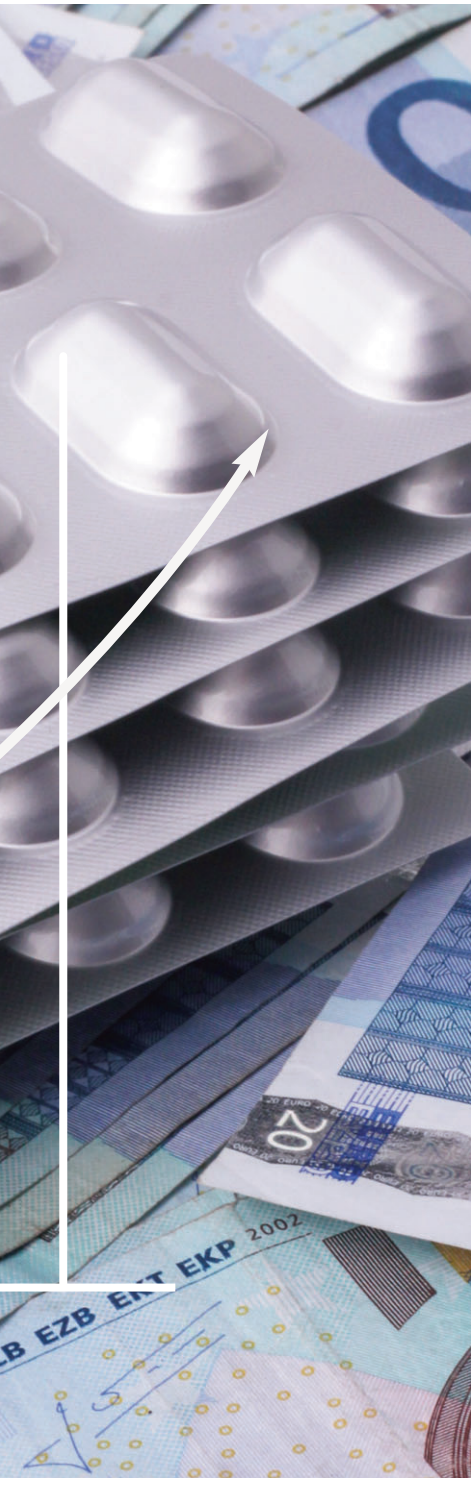


Photo: Marek Studzinski

What makes a good HTA submission?

In the UK system – and in a few other countries including the Netherlands, Sweden, Canada, and Australia – economic modelling is central to the HTA process. In the UK, this takes the form of cost-effectiveness analysis. Health economists attempt to represent the disease and its treatment within established modelling approaches such as Markov models or partitioned survival analyses. The primary inputs to these economic models are the relative efficacy of the treatment under assessment versus the designated comparators (the current treatments that the new technology would be expected to displace), the costs of the treatments (including acquisition costs but also the costs of administration, monitoring, treatment of adverse events, and any other costs or cost savings associated with the treatments), and the effects of the different choices on patients' health-related quality of life (HRQoL). These are (usually) modelled over a lifetime horizon, requiring the use of statistical techniques to extrapolate beyond the term of the trial.

> A good submission has a consistent narrative that brings out the product's value.

However, the HTA submission is more than just the economic modelling. A good submission dossier has a consistent narrative that argues the case for the new treatment – from the burden of the disease and the unmet medical need, through to the benefits of the new treatment to patients, its innovative nature (if applicable), and why it represents a good use of healthcare resources. In addition, the clinical evidence and the economic modelling must both be clearly communicated, and someone must manage the dossier. The medical writer is typically responsible for all of these aspects.

The medical writer's role

The medical writer's role in HTA submissions has three main aspects: populating the clinical sections of the dossier template, supporting the health economists/analysts, and managing the dossier. We will now look at each of these more closely.

Writing the clinical section

Each HTA body has its own submission template and an accompanying user guide. Be sure to download these freshly for each submission in case there have been changes, and follow the user guide carefully.

To write a successful clinical section, the writer must gain a good understanding of the disease area, the current treatment pathway, and the new treatment and its trial data. From this, it is essential to construct a clear "value story". What is the unmet medical need? How does this product address it? What advantages (i.e., what "added value") does it offer over current treatment – to patients, caregivers, health services, and (perhaps) from a societal perspective? Sometimes the manufacturer will already have a clear story and may have developed materials such as a global value dossier to help communicate it. But in a drive to give patients access to new medicines as quickly as possible, HTA dossiers are often prepared before regulatory approval has been granted, and sometimes no clear value story has been set out. It is important to be clear on these issues within the submission team, or the submission will lack a coherent argument. The clinical section of the submission should give a balanced picture of the health condition but should focus particularly on the needs that the new product meets, from both the patient and the healthcare system perspectives. It is also crucial for the medical writer to understand how the condition is going to be represented in the economic model. For example, the health states in an economic model of HIV might be based on CD4+ cell count. The clinical section of the submission must therefore explain the importance of the CD4+ count and its relationship to clinical outcomes and health-related quality of life.

Furthermore, it is important to define the population for which the new technology should be funded, and to provide an estimate of population size. Linked to this, there must be a clear description of the current treatment pathway based on national clinical guidelines and protocols, and of where in the pathway the technology will sit and what (if any) current treatments it is expected to displace. These treatments are known as the comparators. Unlike clinical trials, where there is typically a single comparator, payers compare new technologies against all current treatments.

The clinical section of the dossier also presents the pivotal clinical trial. This section should give the HTA body a clear understanding of the trial methodology and population so that they can critically appraise the results. The medical writer must use their judgement about what to include, within the template requirements. Decision-making committees have limited time to spend on each submission, so the case must be made clearly and succinctly. However, in most jurisdictions the submission will also be scrutinised by a technical review body that will advise the committee, so they must be given sufficient detail to form a good understanding. The key question is "Will this information aid the payer in their decision-making?", either as key data or as context. If not, better to leave it out so that the core narrative does not get lost in a welter of additional detail. The Clinical Study Report will usually be supplied as a reference.

The final element of the clinical section focuses on interpretation and contextualisation of the clinical data. It is important to show payers that the trial data are representative of the likely effects in the local real-world population. How generalisable are the trial data to the health system in question? Is the trial population comparable to patients who will receive the technology in local clinical practice? This can be addressed by comparing the population with that of country-specific registries or publications of large national or regional case series. Any differences should be explored and contextualised, for example by comparing outcomes in the comparator arm with those from more representative trials or series. Any evidence gaps, such as the absence of head-to-head data versus one or more comparators or a lack of data on health-related quality of life, should be stated, and the way that these issues will be addressed in the submission should be explained. This means working closely with the health economics team to understand the approach being taken so that the clinical section provides the information and argumentation needed to support it. Close cooperation with the team at the sponsor company is also important.

Medical writers also have an important role in the post-submission phase, which involves providing clarifications and responses to questions from the HTA body.

Supporting the health economics team

As a result of researching and writing the clinical section, the medical writer is usually the team member with the most knowledge of the disease and its treatment. Writers can thus be an important sounding board for health economists when the latter are developing modelling assumptions and inputs (validation of the modelling approach by clinical experts is also key). Frequent cross-talk between the writing and modelling teams improves the ability of both specialisms to optimise the overall submission and can avert problems such as the modelling team using an assumption that is open to clinical challenge. Writers need to be able to spot when arguments made in the economic section are not compatible with those in the clinical section – or vice versa – so that conflicts can be resolved early.

> Frequent cross-talk between writing and modelling teams is needed to optimise the submission.

The economic section of the submission template is usually drafted by the health economists, but the medical writer should review it from both a communication and an editorial standpoint to ensure that the economic concepts are clearly communicated and are anchored in the relevant literature and guidelines.

Managing the dossier

The medical writer will typically have editorial responsibility for the dossier, including formatting, confidentiality marking, and creation of the reference pack. This can be time-consuming, and it is important to allow sufficient time for dossier finalisation in the project plan.

Medical writing for German reimbursement submissions

The German process is not an HTA process *per se* as usually no economic evaluation is required. Therefore, I will refer to the dossier as a reimbursement dossier. As described by Kohler & Christoph in this issue of *Medical Writing* (p. 22), new drugs are reimbursed in Germany as soon as they receive marketing authorisation; (see the article for further details of the German reimbursement process). A reimbursement dossier needs to be submitted to the German G-BA on the day the product is brought onto the market, or within 3 months in the case of a new indication for an approved drug. The pharmaceutical drug is compared against an appropriate comparative therapy (ACT); this

contrasts with the NICE process, where all drugs approved in the indication are taken into consideration.

The G-BA sends all reimbursement dossiers for non-orphan drugs to the Institute for Quality and Efficiency in Health Care (IQWiG) for assessment. IQWiG provides recommendations within 3 months on the additional benefit of the drug. The extent of the additional benefit is the basis for the price negotiation with the statutory health insurance (SHI). For orphan drugs, the assessment is done directly by the G-BA.

The reimbursement process starts before dossier submission. The G-BA provides the opportunity to address specific questions in an early advice meeting. An application needs to be completed prior to the meeting where all questions relating to the submission can be put, specifically which is considered the appropriate therapy, whether trial design can be considered appropriate, the patient relevance of endpoints, or whether the subgroups have been chosen correctly based on the data available. The pharmaceutical company should provide its response with all the arguments for or against a specific statement. Preparing this application requires a lot of discussion, research, and medical writing. The submission team members discuss and agree upon what questions to ask and research the replies. The research for these questions includes the review of recent national (or where not available, European or international) guidelines, to identify the ACT, and the identification of previous assessments in this or a similar indication to identify whether the endpoints chosen are patient-relevant, or to address other questions of interest.

There is a template for the reimbursement dossier on the G-BA website. The dossier consists of five modules (see Kohler & Christoph) and must be submitted in German. Module 1 is a summary of modules 2 to 4 with word restrictions and is comparable to the NICE document A. Module 5 contains all the references cited in modules 1 to 4. Module 2 is a rather small document and contains general information such as the drug's mode of action and the approved indications. The information is usually found in the Summary of Product Characteristic and in regulatory documents.

More information needs to be provided in module 3. The ACT needs to be named and its appropriateness justified. The derivation of the patient population is an important section and of interest for the price negotiation later in the process. The attention is on the target population and specifically the population for which an additional benefit is expected. The destatis.de website (https://www.destatis.de/DE/Home/_inhalt.html) is a good source to get overall patient numbers, with more specific numbers provided by trial registries or in the published literature. This module also contains a section on the cost of the therapy and its ACT, which are listed in the Lauer-Taxe database (not free of charge).

Module 4 contains the results – the medical benefit and the medical added benefit when comparing to the ACT. The result section is the critical part of the submission together with the section about the final assessment of the additional benefit, including its probability from the pharmaceutical company's view. These sections require a lot of medical writing as all the results for all endpoints measured in the described trials, preferably randomised controlled trials, need to be presented and interpreted. The primary sources of information are the clinical study reports available for the drug of interest and any published literature on the drug of interest and the ACT.

Once the reimbursement dossier is submitted, the preparation for the written statements starts; the purpose of this statement is to provide responses or clarifications to points in the IQWiG assessment, where this is considered necessary. There are only 3 weeks between the publication of the IQWiG assessment on the G-BA website and the possibility to provide written statements to the G-BA. It is advisable to summarise all possible points that may need to be addressed and prepare for them in advance. After submitting the written statements, the pharmaceutical company receives a date for an oral hearing at the G-BA for which preparations are also required. The company must prepare for different scenarios that might emerge during the meeting, and the medical writer is often involved in researching and formulating responses. The G-BA decides on the additional benefit considering the IQWiG assessment, the written statements, and the outcome of the oral hearing. The writing work on German submissions is quite challenging as there is no economic modelling, so the case for the degree of additional benefit is made solely on the basis of clinical efficacy.

Acknowledgements

The authors would like to thank Beverley Jones, Senior Manager (HTA) HEOR Ltd, for helpful comments.

Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employers or EMWA.

Conflicts of interest

The authors declare no conflicts of interest.

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