The regulatory-HTA decision-making interface: What the medical writer should know

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Abstract

For a new medicine to reach patients, it must achieve both regulatory marketing authorisation and reimbursement from the payer. Because regulators assess the benefits and risks of a medicine while the health technology assessment (HTA) bodies assess its value to the system, their informational needs differ. Two different but potentially aligned dossiers are therefore required: the regulatory dossier and the HTA submission dossier. The medical writer must be prepared to contribute to both. Herein we review the basic elements of the regulatory dossier, the Global Value Dossier and the HTA submission dossier. For the medical writer, an important challenge is how to determine whether there can be alignment and synergies between regulatory data and HTA data to support the respective decision-making processes. Practical approaches to the construction of the submission documents are provided here. These approaches bring consistency to the documents, serve as a checklist for relevant information, and facilitate the review by the assessor.

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Aligning regulatory and HTA expectations

Bringing a new medicine to the market is dependent on two successful processes: achieving market authorisation from the regulatory agency and for single-payer countries, reimbursement from a payer. Because the healthcare environment is faced with growing pressures to control healthcare costs, payers need to make decisions on the reimbursement of medicines to maximise public health outcomes within limited health budgets. Consequently, an important stakeholder has emerged – the health technology assessment (HTA) body whose goal is to make recommendations on reimbursement on the basis of the value of a new therapy to both the patient population and the healthcare system. Consequently, drug developers seeking to deliver new medicines need to coordinate a development programme to generate evidence that meets the needs of both regulatory and HTA agencies.[1] Using a "piggyback" approach in which health-economic data are collected within an otherwise typical clinical trial, has been explored as one way to coordinate the efficient collection of information that will be useful for both the regulatory and HTA submission.[2]

Medicine regulators evaluate the quality, safety, and efficacy of products to ensure that the products they authorise meet local and, where applicable, regional, or international standards. Assessments of novel products are based on dossiers prepared and submitted by the pharmaceutical sponsors. To facilitate the presentation of regulatory information in a consistent manner, under the auspices of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), the standardised presentation format designated the Common Technical Document (CTD), has been implemented. This approach has standardised the submission format and content, made the regulatory review process more efficient, and has led to harmonised electronic submissions that, in turn, have enabled the implementation of good submission and review practices. For pharmaceutical sponsors, it strives to reduce the need to reformat the information for submission to different regulatory authorities.

The CTD is organised into five modules. Module 1 is region specific, and Modules 2, 3, 4, and 5 are intended to be common for all regions. Details of the format of the CTD are available here: https://www.ich.org/page/ctd. While it is not within the scope of this article to review the component elements of the CTD, the medical writer who is responsible for preparing regulatory submissions must be thoroughly familiar with the structure and format of the CTD. Consequently, the medical writer must be well informed about the components of the CTD and to be able to construct the various types of documents within the submission. These range from detailed clinical study reports to section summaries and more succinct overviews. ICH guidelines provide the details that ensure consistency and completeness of the submission. Consistency of structure underpins efficiency and addresses the clear presentation and availability of data to support quality, safety, and efficacy and the expectations of regulatory reviewers.

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When the structural components of the CTD are addressed, the CTD is designed to provide the regulator with sufficient information to make an informed decision of the balance between the clinical benefits of the product and its risks. If harms are to be expected, then the CTD defines ways to mitigate and control for these harms. While clinical data comparing the new product to another active comparator may form part of the submission, comparative efficacy is generally not a requirement for the evaluation of efficacy. Therefore, where ethically possible, placebo comparisons and the use of other novel comparator approaches may form the basis for the regulatory benefit-risk decision. Consistent with making decisions on specialised data sets that may not be able to address all the uncertainties regarding the benefits and harms of a product, is the importance of post-authorisation commitments and their reporting through periodic benefit-risk evaluation reports (PBRERs). Many medical writers focus their attention on these specialised reports.

The approaches that regulators take to making their benefit-risk decisions have a defined scope. The decisions do not typically address the comparative efficacy of the new product to an existing therapy nor do regulatory decisions consider the cost of the therapy or its pharmacoeconomic impact to a healthcare system. It is therefore the role of the HTA body to address the "value" of the new medicine to the healthcare system.[3] Is the efficacy of the product an improvement above existing standards of care? Does an improvement in the safety profile or dosing regimen contribute to adherence and better outcomes? Is the proposed cost of the product to the healthcare system worth these benefits? These are questions that HTA bodies must address, and it is the role of the medical writer to provide the substantive evidence required to support the HTA decision making process.

The medical writer has several tools at their disposal to address the concept of a product's value. These include the Global Value Dossier and the HTA submission dossier. To establish, support, and convey a product's value during the lifecycle of a product, companies will prepare a Global Value Dossier, which serves as a dynamic value roadmap for internal use and then as the core information resource for HTA submissions.[4]

As with the regulatory dossier for the regulator, the HTA submission dossier provides information that will help the HTA body decide about the relative value of a new therapy. HTA bodies seek information through a dossier of pharmacoeconomic information to make a value recommendation to a payer. Unlike a regulatory dossier, the HTA submission dossier may address relative efficacy (the extent to which an intervention does more good than harm, under ideal circumstances such as a clinical trial, compared with one or more alternative interventions) and relative effectiveness (the extent to which an intervention does more good than harm compared with one or more alternative interventions for achieving the desired results when provided under the usual real-world circumstances of healthcare practice).[5] Because the local affiliate often has the best knowledge of the specific country's health economic issues, the local affiliate will use the Global Value Dossier as the basis for their HTA submission, with adaptations to meet the local medical, pharmacoeconomic, and value contexts.

In the past, however, the content of the HTA submission dossier has been inconsistent and has not always provided the substantive data in a clear and well-organised manner. Therefore, through its recent evolution, the HTA submission dossier has benefited from the development of a generic approach to the communication of the observations, similar to the way that the CTD

has evolved. The pharmaceutical sponsor can now more easily present their observations in a cogent, well-organised manner in order to support a local HTA submission. And as the database of experience with a product continues growing, this approach also encourages the dynamic refinement of the comprehensive Global Value Dossier. While the medical writer may be the primary author of an HTA submission dossier, they may collaborate with a pharmacoeconomist in this activity.

Having the information presented in a consistent manner has several advantages: it serves as a checklist for the sponsor to identify the kinds of information that the HTA body will need to support its scientific assessment of the value of a therapy; it allows for the HTA body to conduct section-to-section comparisons across dossiers; and it facilitates conversations between the HTA body and sponsor by being able to point to easily accessed details.

A clear value message presented by the sponsor in the local HTA submission may also accelerate the HTA assessment process. Timely recommendations by the HTA bodies for drug reimbursement by the relevant payers are critical to ensure that patient access to medicines of therapeutic value is not delayed. As part of an ongoing study to monitor regulatory and HTA performance, Cai et al.[6] assesed data on new active substances appraised between 2015 and 2019 by eight HTA bodies. Of the studied HTA bodies, Germany had the highest proportion of products recommended within one year of regulatory approval (92% in 2019). Australia had the shortest median time between regulatory approval and HTA recommendation (24 days) in 2015–2019, followed by Germany (132 days). The authors analysed new active substance products rolled out to seven jurisdictions and identified 37 products that received a recommendation by all HTA agencies during the period of 2015–2019. Germany provided the highest number of recommendations as the first country of appraisal (30%), followed by Australia (24%). This variability reflects the divergences of the organization, processes, and methodology among HTA agencies, and calls for development of standards for best practice in HTA as well as the refinement of practical HTA tools.

Several approaches have evolved for structuring an HTA submission dossier. One approach is to use the PICO (Patient-Intervention-Comparator-Outcome) strategy, which helps organise thoughts and data.[7] PICO is not widely used but can be considered a tool to organise thoughts.

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For each HTA body, their defined value dossier submission template will be different; this is because each has been designed to meet the need of their own review process. PICO and related elements remain key to the dossier. Therefore, using a template to present data in an HTA submission dossier is as helpful as using the CTD structure to present regulatory information. The challenges faced by the medical writer are the divergences across the templates and lack of standard framework. One example of a template for the presentation of HTA data has been developed by the National Institute for Health and Care Excellence (NICE) and can be found via this link: https://www.nice. org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/company-evidence-submission-template-apr-17.docx).

Another important approach that has evolved to address this issue is referred to as the Core Model (Figure 1). The European Network for Health Technology Assessment (EUnetHTA) provided details of how this model can be used by an HTA body to summarize the evaluation of a value dossier. The medical writer should familiarise themselves with the various ways that the Core Model can be used so that they can construct a value dossier that is consistent with the needs of the model.

At the base of the approach is the HTA Core Model for the production of core HTA assessments. An outcome of the EUnetHTA Joint Action on HTA (2012–2015), the HTA Core Model v 3.0 was developed as a component of Work Package 8 – Maintenance of HTA Core Model® infrastructure to support shared production and sharing of HTA information (see: https://eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf). EUnetHTA notes that the main aim of the HTA Core Model is to enable international collaboration in producing HTA information and efficient sharing of the results so that redundant overlapping work in different countries and regions can be avoided. Normally, an HTA assessment contains a vast amount of information. The content, focus, quality, and reporting of these observations vary significantly; this makes finding and transferring the information into local contexts difficult. The HTA Core Model addresses these problems. The model defines the content elements to be considered in an assessment and enables standardised reporting, consequently providing a common framework for the production of the assessment.

The model describes 9 key domains:

- Health problem and current use of technology (CUR)
- Description and technical characteristics of technology (TEC)
- Safety (SAF)
- Clinical effectiveness (EFF)
- Costs and economic evaluation (ECO)
- Ethical analysis (ETH)
- Organisational aspects (ORG)
- Patients and Social aspects (SOC)
- Legal aspects (LEG).

Each domain is described in detail in the model. The domains of the Core Model address the range of elements that inform value assessments of HTA. Domains 1 to 4 are of a more general nature, while domains 5 to 9 are more jurisdiction-specific. The HTA Core Model, apart from standardising reporting and helping to avoid overlap, addresses the needs of individual countries' different requirements and different local conditions; therefore, the medical writer will have a meaningful framework to construct the Global Value Dossier from which one can produce the submission dossier, which can support the local HTA review.

Through the activities of the Joint Action on HTA 2012–2015 Work Package WP5, EUNetHTA developed in 2015 the HTA Core Model for the production of Rapid Relative Effectiveness Assessments (also called the Model for Rapid REA, version 4.2). The aims of the Model for Rapid REA are similar to those of the Core Model: to improve the applicability of HTA information in other (e.g. national or regional) HTA projects; to enable actual collaboration between HTA agencies by providing a common

framework for the production of rapid REA; and to avoid duplication of work. Being derived from the HTA Core Model, the Model for Rapid REA provides an overview for producers of rapid REAs on the basic steps involved and on important generic research questions that should be considered in an HTA assessment. Rapid REAs contain an analysis of the product in comparison with one or more relevant alternative interventions, but the Rapid REA is limited to a subset of domains and performed within a limited timeframe (Figure 2). Item 5 is specific to a particular jurisdictional submission.

The Model for Rapid REA covers generic research questions for pharmaceuticals, diagnostics, medical, and surgical interventions, and screening technologies. For a detailed description of the domains, the guidance concerning assessments of specific types of technologies and other research questions to be considered within a rapid REA, is available at https://eunethta.eu/wp-content/uploads/2018/06/HTACoreModel_ForRapidREAs4.2-3.pdf.

It is important to note that the Core Model is helpful as a conceptual framework to help construct the evidence that will support an HTA submission but is not currently used by most medical writers unless they are preparing a submission for the EUnetHTA rapid assessment. However, a joint review by multiple HTAs may eventually become a norm in the EU, so it will gain importance at some point in future. (See https://eunethta.eu/wp-content/uploads/2018/01/roche_pharma_report_on_ the_hta_core_model_december2014_0.pdf).

An information source of increasing significance in informing HTA decisions is the European Public Assessment Report (EPAR) created by the European Medicines Agency (EMA) for each newly approved medicine. While it has long been recognised that HTA bodies often are limited in the way that they can integrate data that support a regulatory decision into their value models (e.g. phase 2 data that support the safety and efficacy of a product may not be sufficiently robust to predict a long-term benefit and therefore may have limited applicability in determining the pharmacoeconomic value), it has also been recognised that the EPAR can serve as an important source of validated information to help inform the HTA assessment.[8] Collaborations between the EMA and HTA bodies are resulting in the development of EPARs that can be used more effectively by

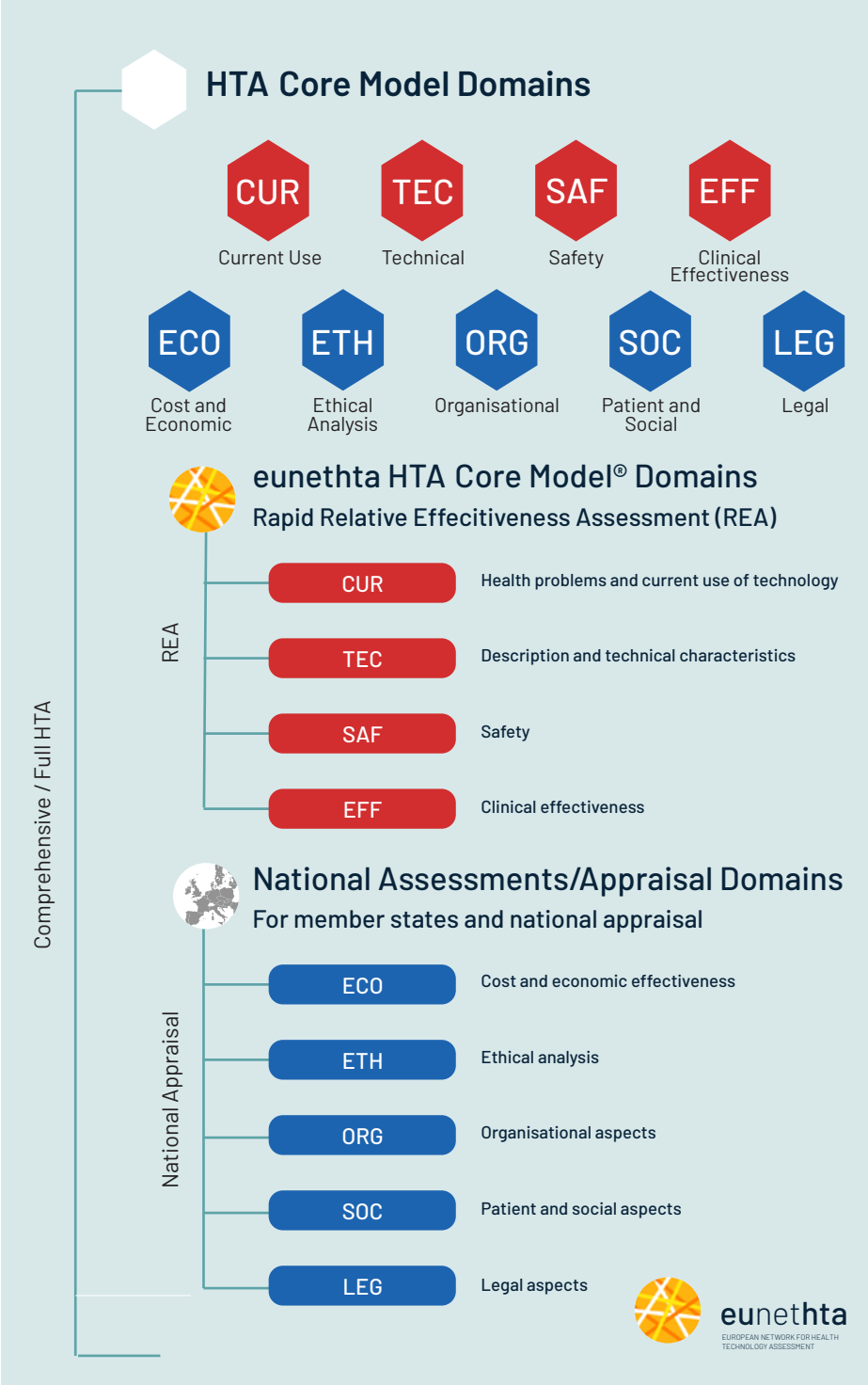
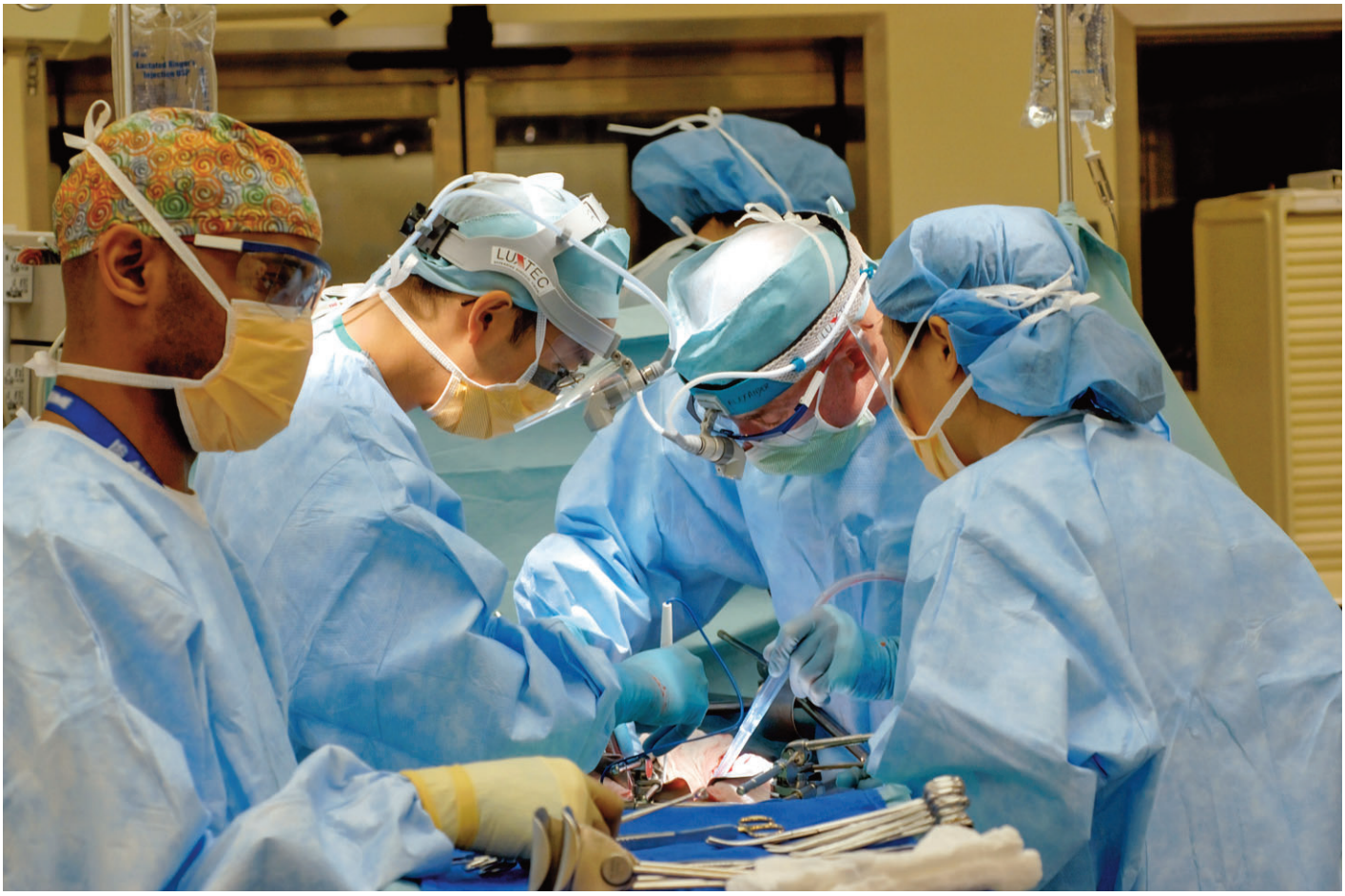


Figure 1. The domains of the EUnetHTA Core Model

Source: https://eunethta.eu/hta-core-model/



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HTA Core Model Domains

1. Description and technical characteristics of technology (TEC)
2. Health problem and current use of the technology (CUR)
3. Clinical effectiveness (EFF)
4. Safety (SAF)
5. Cost and economic evaluation
6. Ethical analysis
7. Organisational aspects
8. Patient and social aspects
9. Legal aspects

1-4: Rapid REA Model 6-9: Replaced by checklist

Figure 2. How the Domains of the HTA Core Model® and of the HTA Core Model for Rapid Relative Effectiveness Assessments overlap

Source: https://eunethta.eu/wp-content/uploads/ 2018/06/HTACoreModel_ForRapidREAs4.2-3.pdf

HTA bodies in their decision-making process. Therefore, the medical writer should familiarise themselves with a product's EPAR as they prepare the value dossier.

A new challenge has emerged with the preponderance of innovative products that are receiving regulatory authorisation where there is an unmet medical need and therefore, few therapeutic options. Using facilitated regulatory pathways (FRPs) such as the breakthrough therapy designation, priority and accelerated reviews and conditional marketing authorisations, important new therapeutic options with good signals of clinical efficacy are being approved in record times. However, the paucity of long-term data – and therefore the reliance on surrogate endpoints for the regulatory decision – make formulating a value recommendation complicated. Most models used by HTA bodies are limited in the manner that these short-term data are integrated to establish value. Consequently, HTA bodies and payers are investigating novel approaches to reimbursement that reassess the value of a therapy as data are accumulated, including concepts such as coverage with evidence development, cost sharing, and price-volume agreements.[9,10]

For the medical writer, an important challenge is how to determine whether there can be alignment and synergies between regulatory data and HTA data to support the respective decision-making processes.[1] As HTA bodies and regulators more closely align

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their expectation and goals, the process of developing aligned evidentiary requirements will evolve to facilitate the decision-making process.[11] As the successful work of EUnetHTA comes to an end in 2021, we are left with questions about what will the post-EUNetHTA landscape look like and what will the medical writer need to prepare for? Over the decades, medical writers have been characterised by their flexibility and adaptability. Now more than ever, the medical writer must convince their colleagues to adopt a flexible and adaptive stance in the context of evolving predictive and adaptive models of research and development. As the need to align regulatory and HTA decisions grows, so too will the new skills of the medical writer.

Conflicts of interest

The authors cite no conflicts of interest.

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