Unmet need in healthcare: ambiguity in the definition does not help setting priorities

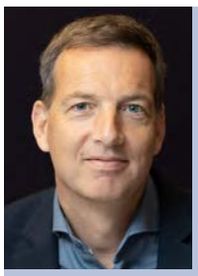
Maarten J. IJzerman, Erasmus School of Health Policy & Management, Rotterdam, the Netherlands, University of Melbourne, Melbourne School of Population and Global Health, Australia | Jorien Veldwijk, Erasmus School of Health Policy & Management, Rotterdam, Erasmus Choice Modelling Centre, Erasmus University Rotterdam | Tom Belleman, Erasmus School of Health Policy & Management, Rotterdam | Jennifer A. Soon, University of Melbourne, Melbourne School of Population and Global Health, Peter MacCallum Cancer Centre, Melbourne

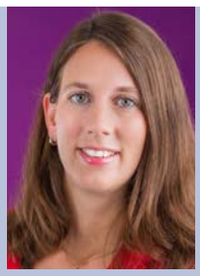
The term „Unmet Need" is used multiple times in European Union (EU) Health Technology Assessment (HTA) regulations, the EU pharmaceutical legislation and in HTA guidelines in member states (MS). There is no consensus about the definition of unmet need, yet in most guidance documents it refers to the unavailability of treatment options for patients with severe conditions or for patients suffering from significant residual disease. Examples are orphan or neurodegenerative diseases like Alzheimer. Proxies or determinants of unmet need, referred to as decision modifiers, may be also considered to inform payment decisions in MS. Amongst others, they include rarity, disease severity, intended treatment aim, innovative treatments or cross-sector benefits. Others have argued to include other value components in the appraisal, such as the value of knowing or value of hope. However, these terms are ambiguous and not actionable. For many treatments, a cascade of factors ultimately determines if medical products will be available to patients in MS and, hence, interpreting unmet need as a binary outcome is not appropriate. Concerns have been raised that prioritising R&D efforts to areas of unmet need should be aligned with the right incentives to mitigate commercial risks, e.g. by (financial) protection measures.

Background

The European Regulatory Framework for Health Technology Assessment (HTA) came into effect in January 2025.[1] This regulation presents guidance for Joint Clinical Assessments across Member States (MS) which is considered a step forward in harmonising HTA across the the European Union (EU). In the regulations reference is made to medical products that address unmet needs, particularly to define exemptions for MS to make independent national assessments. The rationale for this exception is that, while evidence generation may be transferrable across health settings, the assessment of relative effectiveness and/or the availability of treatment options is context dependent. Also, early access to medicines in circumstance of high unmet need may be subject to decisions of individual MS. While these exemptions are guided by „unmet needs", no clear definition of unmet needs is provided nor implemented across regulations or MS.

In addition, a large literature exists that aims to define priorities for reimbursement (and accelerated approval) based on unmet needs identified by eliciting (patient) preferences. Most of this work is done within the jurisdiction of individual MS. One of the very first examples in Germany was the IQWiG pilot, testing multiple methodologies to prioritise patient-relevant endpoints for anti-depressive medication (Danner et al, 2011). The study, employing Multi-Criteria Decision Analysis, aimed to prioritise treatment-related outcomes and adverse events. The notion that patient preferences and other non-clinical value components played an important role in national coverage decisions has grown since then, with pivotal studies reviewing and validating prioritisation or preference elicitation methodologies (Thokala et al, 2016; Soekhai et al, 2019; Whichello et al, 2020), the qualification of the PREFER framework on





Professor Maarten IJzerman *is the Dean of the Erasmus School of Health Policy & Management in Rotterdam, The Netherlands. He is a Professor at the University of Melbourne School of Population and Global Health as well as the Collaborative Centre for Genomic Medicine in Melbourne, Australia. He drives a program leveraging the secondary use of real-world data to improve access and cancer outcomes. He has been a member of HTA Committees in Australia and The Netherlands and involved in various international Task Forces developing methodological guidance in health economics and outcomes research.*

Dr Jorien Veldwijk *has been appointed as an Associate Professor at the Erasmus School of Health Policy & Management in Rotterdam. She also serves as the Director of the Erasmus Choice Modelling Centre. Her research focuses on the accurate measurement of patient and public preferences and developing methods for measuring benefit-risk preferences, thereby amplifying the patient's voice, and aligning policy decisions more closely with patient needs. Her research has led to numerous collaborations in (inter)national projects involving various stakeholders, as well as various peer-reviewed publications.*

Tom Belleman *is a PhD candidate at the Erasmus School of Health Policy and Management (ESHPM), Erasmus University Rotterdam, in the Health Technology Assessment (HTA) department. His research focuses on the cost-effectiveness, market access, and reimbursement of innovative and high-cost health technologies. He is particularly interested in the role of real-world evidence and population perspectives in shaping reimbursement decisions for expensive health technologies*

Dr Jennifer Soon *is a Medical Oncologist at Peter MacCallum Cancer Centre pursuing her doctoral studies through the University of Melbourne. She has a special interest in health policy, data science and improving healthcare value and access for people. Her research has contributed to the development of a flexible and responsive method for horizon scanning of new medicines.*
Dr Soon is an Executive Committee Member of the Medical Oncology Group of Australia (MOGA) and is on the MOGA Oncology Drugs Working Group who work closely with the Pharmaceutical Benefit Advisory Committee in Australia.

when and how to elicit preferences by European Medicines Agency (EMA) (PREFER consortium, 2022) and the development of the ISPOR Value Flower concept in 2018 (Neumann et al, 2022).

With reference to these methodological and conceptual developments, this paper aims to provide some backgrounds into the definition and assessment of unmet needs and how this could facilitate European and national priorities for medical product development, reimbursement and healthcare delivery.

How is Unmet Need defined in European and National guidelines

European guidelines: unmet need refers to availability

The term „unmet medical need" appeared explicitly in 2006,[2] where it was defined as „… a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those aFected". The previously introduced EU regulation on HTA refers to unmet need, specifically as a criterion to define exemptions for joint assessments and to expedite assessment within the MS for medical products addressing a high unmet need (e.g. Article 7:4). No definition of unmet need was provided in the regulation.

Further, in 2023, the European Commission (EC) proposed a new pharmaceutical legislative framework[3] for the EU to replace the existing framework that has been in place for over 20 years. The definition used in the framework states that „… a new medical product is addressing an unmet need if (1) there is no medical product authorised or when there is still significant morbidity and mortality and (2) the medical product is for a designated orphan indication".

While the recent HTA regulations do not explicitly define unmet need, other EU regulations do. They typically refer to the limited availability of treatment options, either because they are not on the market, not supplied, or if there is significant residual morbidity or mortality in specific patient groups. Examples of diseases with (high) unmet need are neurodegenerative disorders like Alzheimer's disease or Multiple Sclerosis, many orphan diseases and rare cancers (Scavone et al, 2019).

However, although there is appreciation for the attempts to present a universal definition of unmet need, a widely accepted definition should also address the underlying causes that have hindered innovation in these areas. As such, a definition should also include principles like fairness, flexibility, feasibility and sensitivity to risk (which is when unmet need becomes more important than confirmed clinical benefit) (Bloem et al, 2025).

National guidelines: unmet need used as (reimbursement) decision modifiers

National guidelines also explicitly address medical products addressing unmet need. But this consistently is linked to national reimbursement and coverage decisions, something that EU regulators explicitly leave to national jurisdictions. Further, the emphasis on unmet need in National guidelines appears to be primarily used to accelerate access or differentiate market access pathways and payment schemes. Without intending to be complete, we reviewed the methodological guidelines for preparing and submission of value dossiers in four countries.

The Netherlands Pharmacoeconomic Guidelines (Zorginstituut[12]) do not explicitly mention unmet needs in their methodological guidance for preparing value dossiers. The dossiers follow a „reference case" format with a preferred methodology to define comparator(s), relevant

costs and outcomes, and modelling. The Advisory Committee in their appraisal phase, however, does explicitly consider „necessity" and „feasibility" in addition to clinical effectiveness and cost-effectiveness as presented in the value dossier. These additional criteria explicitly make a connection to the „availability" of treatment options in terms of unmet need, supply, and access.

The Australian guidelines (those of the Medical Services Advisory Committee or MSAC[8]) do explicitly mention unmet need and particularly point at equity and access to new medical devices and procedures. This obviously is a critical piece of deliberation with an emphasis on rural and disadvantaged or First Nation populations, including the barriers and restrictions to access health services.

Pharmaceutical Benefits Advisory Committee (PBAC) guidelines, unmet need is mentioned as an eligibility criterion for the early resubmission pathway for High-Added Therapeutic Value (HATV) medicines. However, the recent review of the HTA policies and guidelines recommends that criteria of importance to patients and clinicians (e.g. for high added therapeutic value (HATV) that addresses high unmet clinical need (HUCN)) are appropriately included and considered. From personal experience, MSAC does also explicitly discuss „feasibility" of implementation to ensure equal access across the Medicare population in both public and private hospitals.

The German Social Codebook[10] does not explicitly mention unmet need in their appraisal process, nor is it used by AMNOG. However, in their 2023 position paper, the Verband forschender Arzneimittelhersteller (vfa) states that unmet needs to be defined as „Ein ungedeckter medizinischen Bedarf ist ein Zustand, der durch zugelassene Medikamente und Methoden nicht angemessen verhindert, behandelt oder diagnostiziert wird". This aligns with earlier definitions of unmet need emphasising the unavailability of appropriate treatment options. Further, concerns have been raised in Germany that unmet needs should align with incentivising new developments. However, there remains uncertainty around what the right incentives are to ensure medical products are developed for those with unmet need.

The National Institute for Health and Care Excellence (NICE[9]) in the United Kingdom, in their guidance, is probably the only institute who make explicit mention of „unmet need" by stating that „the extent of unmet need is reflected within the severity definition". Unmet need or severity of the disease in this definition is considered a decision modifier (article 6.2.12), with severity of the disease determined by future health lost by people living with the disease with standard care in the NHS. This includes the availability of other treatments, diagnostics, and best supportive care.

From these four examples, it can be concluded that if a reference to „unmet need" is made, it is predominantly interpreted as either the lack of availability of treatment options and/or significant residual disease for which additional treatments should become available. If „unmet need" is not explicitly covered in the guidance documents for submission of value dossiers, agencies will likely consider and include this additional criterion in the appraisal phase.

A broader definition of unmet need to include appropriate and efficient care?

From the quick scan of European and selected National guidelines and policy documents, we find unmet need to be relatively narrowly defined as „availability of treatment" with some implicit conditional relation to disease severity. But a more detailed review of the literature should be undertaken, particularly to understand how and when unmet need is placed in the broader context of social welfare and

health. A very comprehensive and detailed description of the different perspectives of unmet needs can be found in the NEED Framework (Maertens de Noordhout et al, 2024). From their work it is concluded that there currently is no consensus on the definition of unmet needs. They state that „Needs can be defined as the essential elements that are necessary for human survival, well-being, and development. They are the basic conditions that individuals must fulfil to sustain their physical, psychological, and social welfare".

If we were to take this approach, it is inevitable to refer to the different theories of need that exist, including the theory of Human Need by Gough and Doyal (1984) and the social need taxonomy by Bradshaw (1972). Gough and Doyal argue that human needs can be categorised into eleven core categories, with healthcare (i.e. the need for access to quality healthcare services to promote and maintain good health) one of them. Bradshaw introduces the concept of social need and four definitions of need, including normative, felt, expressed and comparative need (Bradshaw, 1972).

A helpful approach presented by Stevens and Gillam (1998) provides a broader and comprehensive definition of unmet need by stating that „unmet need is the capacity to benefit from healthcare". This implies that the different phases from market approval and authorisation until the actual delivery of care are necessary to be included in determining unmet need. According to Stevens and Gillam, unmet needs may also be considered assuming some finite resources, thereby explicitly linking unmet need to scarcity and resource allocation. They suggest that the definition of unmet need requires a measure of epidemiology (how many) and a measure of effectiveness (how good) and distinguish four types of unmet need:

- Non-recipients of beneficial healthcare interventions, implying that patients have no access to care which is referred to as unmet need in its original form.
- Recipients of ineffective health care, implying resources are available to deliver care and that they should be released to do so.
- Recipients of inefficient health care, meaning that despite the treatment being effective, other, less expensive, options are available.
- Recipients of inappropriate health care, implying better treatment or care options are available.

This definition clearly takes a wider health services perspective rather than a focus on the regulatory pathway as (understandably) presented in most of the EU regulations. In other words, in many studies unmet need not only concerns medical product development and market access, but merely also the mechanism of delivering (and releasing resources for) the medical products to those who need it.

This becomes very clear when reviewing the quickly evolving evidence base employing real-world data to determine actual use, real-world outcomes and identification of underserved populations. But it is also recognised in current work on de-escalation of cancer treatments. For instance, systemic cancer treatments may be de-escalated, avoiding excessive treatment while still preserving or improving outcomes (Soon et al, 2024). This could include treatments where patients are exposed to therapies with no notable benefits or with an unfavourable benefit-risk outcome. Alternatively, this also concerns adjustments in treatment pathways, such as a shorter neoadjuvant course of check-point inhibitor immunotherapy (CPI) rather than a longer adjuvant course in resectable stage III melanoma. Obviously, all these approaches to de-escalating therapy are proposed under the assumption that clinical outcomes

are preserved and simultaneously lead to a substantial decrease in resourcing requirements, including staffing, consumables, infrastructure and carbon footprint.

Elements of unmet need when allocating resources in national health systems

Stevens and Gillam explicitly include a measure of epidemiology (e.g. prevalence or severity) and a measure of effectiveness (e.g. benefit such as survival) in their approach to unmet need. While this is plausible, it immediately raises the question of what counts most: the relative benefit or the severity of the condition. And subsequently, a further question is what other factors (should) count and who will be making these judgments. Several studies have been addressing these questions, in terms of methods to define trade-offs (like Discrete-Choice Experiments, Multi-Criteria Decision Analysis or Multidimensional Thresholding) and which stakeholders to select, particularly the general public, payer or patients (Thokala et al, 2016; Soekhai et al, 2019).

In 2012, Linley and Hughes published the results of a cross-sectional survey in more than 4,000 people in the general population asking which factors are considered relevant when deciding about public funding for new medical services. Amongst other factors, like severity or disadvantaged populations, they also include „unmet need", which they defined as „no alternative treatments" or „significant unmet need". The results suggest that there is public support to include factors like severity of disease, treatments addressing an unmet need, innovative treatments or those with wider societal benefits in the resource allocation decisions by the National Health Service (NHS). However, there appeared no support for an end- of-life premium or for the prioritisation of children or disadvantaged populations like orphan diseases. In 2018, Bourke et al, confirmed this finding and concluded that the general public does not value rarity as a sufficient reason to justify special consideration for additional NHS funding of orphan drugs.

Since then, several studies have investigated which criteria should be included in reimbursement decisions, mostly at the level of individual MS. It is beyond the scope of this paper to go into further detail, but additional criteria considered are purpose of treatment (e.g. curative), equity, implications for workforce capacity, the carbon footprint and ambiguous factors like the value of hope or value of knowing. While the latter seem to address an element of value, it is controversial and questionable whether public resources should be allocated to pay for value without actually changing health outcomes. Similar, the carbon footprint and/or implications for our healthcare workforce (e.g. remote vs. hospitalised care) are critical for the efficiency and sustainability of our health service but it is not clear if and how these criteria should be incorporated in public funding decisions for new medical products.

Ambiguity and uncertainty: are we incentivising the right developments?

In this paper, we have elaborated on the definition of unmet need from the perspective of the EU regulators being focussed on the unavailability of medical products for patients with severe (residual) disease. Also, MS use a similar definition of unmet need in their national pharmacoeconomic guidelines and deliberative processes to inform reimbursement decisions.

The challenge though, arises when value judgments are to be made (e.g. benefits versus severity of the disease in one versus another population) or when taking a wider health services perspective in which unmet need is assessed in the context of either the delivery of care to patients or when making resource allocation decisions under un-

certainty. When making such trade-offs, our experiences demonstrate that neither the general population nor patients nor a group of experts find the definition of „unmet need" to be comprehendible as it aggregates several constructs into one.

This implies that „unmet need" as a criterion can be ranked low in prioritisation studies, simply because there is no clear normative framework. A further consequence is that while emphasising unmet need in EU regulations, industry is unexpectedly exposed to additional market uncertainty. Prioritising R&D investments for medical products that address (high) unmet needs does not at all ensure access nor inclusion in benefits packages in MS. Paradoxically, while „availability" of a treatment may unequivocally be determined at the EU level, this implementation is context specific in each individual MS.

The finding that several studies confirmed huge disparities between MSs regarding the availability of treatments, this is likely explained by features of the health system rather than those products not on the market. This uncertainty it creates should be recognised and anticipated on. Prioritising medical product development on the presumption of availability of (alternative) treatments alone may be a risky strategy when lack of availability is caused by inappropriate market incentives (e.g. small populations and hence market size in individual MS).

Rather, incentivising developments for populations with high unmet needs should first and foremost be based on strong evidence of improved clinical outcomes for those with diseased and confronted with healthy life years lost. Whether treatments will become available and hence, serve an unmet need, is a responsibility of MS. Fortunately, Research and Innovation, rather than healthcare per se, is funded, coordinated and regulated at the EU and thus provides opportunities to close the disparity gap.

Footnotes

[1] The European Parliament and the Council of the European Union (EU). Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU

[2] Article 4, paragraph 2 of Commission Regulation (EC) No. 507/2006 about conditional marketing authorisation. Published in 2006.

[3] Regulation of the European Parliament and of the Council for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

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