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Health Policy Analysis

Unmet Medical Need: An Introduction to Definitions and Stakeholder Perceptions

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ABSTRACT

Background: Despite increasing informal and formal use of unmet medical need (UMN) in drug development, regulation, and assessment, there is no insight into its definitions in use. This study aims to provide insight into the current definitions in use and to provide a starting point for a multi-stakeholder discussion on alignment.

Methods: A scoping and a gray literature review were performed to locate definitions of UMN in literature and on stakeholder websites. These definitions were categorized and then discussed among the multi-stakeholder author group via semistructured group discussions and open session workshops with a broader stakeholder audience. Issues with the formation of a common definition and mechanisms for use were discussed.

Results: The reviews yielded 16 definitions. Differences were evident, but all included 1 or more of the following elements: (adequacy of) available treatments (16 of 16: 100%), disease severity or burden (6 of 16: 38%), and patient population size (1 of 16: 6%). The stakeholder discussions led to a suggestion for a definition including the first 2 items and, depending on context, population size. The discussions also showed that quantification of UMN is highly dependent on the scope and the value framework in which it is used based on different stakeholder preferences and responsibilities.

Conclusion: We encourage stakeholders that want to promote alignment on the concept of UMN to prospectively discuss the scope in which they want to apply the concept, what elements they find important for consideration in each case, and how they would measure UMN within the broader regulatory or value framework applicable.

Keywords: collaboration, early access, evidence generation, health technology assessment, patient access, regulation, reimbursement, technology development, therapeutic need, unmet medical need, unmet need.

VALUE HEALTH. 2019; 22(11):1275–1282

Introduction

The varying interpretations of the concept of unmet medical need (UMN) have been identified as a topic of importance by European stakeholders, for example by the European Medicines Agency (EMA), the European Network for Health Technology Assessment (EUnetHTA), and payers through the EMA-payer community meeting and the EMA-EUnetHTA work plan.[1,2] Decision makers in the healthcare sector need to find a balance between the encouragement of early patient access to novel technologies on the one hand and promoting increased certainty considering the benefits and harms (including sustainability issues) of technologies on the other.[3,4] This challenge spans from regulatory and development considerations to decision making on reimbursement and pricing of new health technologies, where stakeholders in different countries struggle to find an appropriate relation between UMN and reimbursement levels, leading to intercountry differences.[5-7] A study comparing health technology assessment (HTA) recommendations across 4 European countries also recommended the policymakers align better on the concept of UMN.[8]

The concept of UMN in regulatory considerations has been mostly studied in relation to orphan medicinal products. One study found that products for which an UMN was present (defined

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https://doi.org/10.1016/j.jval.2019.07.007

as the lack of alternative therapy for the disease) were more likely to receive a positive opinion from the Committee for Human Medicinal Products with a limited dataset than products for which UMN was not that evident.[9] This might be due to the recognized challenges in generating evidence for orphan products, which relates to the small size of the patient population.[10] Nevertheless, another study, comparing orphan with non-orphan products, indicated that UMN was equally present in both groups and that evidentiary standards were equal.[11] Unmet medical need has become a criterion for eligibility to enter procedures such as conditional marketing authorization and accelerated assessment, and it is used for prioritization of eligible products within the EMA's Priority Medicines scheme.

In the scientific literature, the concept is also being used for a wide range of situations. A study that investigated the use of UMN in oncology found that the presence of high unmet need was frequently claimed for indications that occur commonly, have many treatment alternatives, and have relatively encouraging expectations for survival.[12] Standardization was advised by the researchers.

A recent survey on the alignment between regulatory and HTA found that 75% of company respondents, 86% of regulatory respondents, and 63% of HTA respondents thought that the definition of UMN was a top area for potential alignment between stakeholders.[13] Thus, there is an aspiration to find alignment between stakeholder groups on UMN definitions and their interpretation.

In current practice, UMN is being applied in multiple stakeholder processes. For example, in the discussion on the benefit-risk balance in the European Public Assessment Reports of Glybera and Zalmoxis, UMN was mentioned as an important consideration when reaching a positive conclusion on (conditional) approval. Another application of UMN within decision making is evident for the Priority Medicines product Yescarta. The EMA and the National Institute for Health and Care Excellence both independently concluded on the existence of UMN in the indicated patient population.[13,14]

This study has 3 goals. First, it provides a (gray) literature review to outline the definitions of UMN in use by different stakeholders. Second, it provides insight into the meaning and the consideration of UMN for each stakeholder. Finally, through multi-stakeholder discussions, the elements for unmet medical need considered in regulatory and reimbursement processes are discussed.

Methods

Methods for the Scoping and Gray Literature Review

Previous research shows that for policy reviews, systematic review through electronic databases may fail to identify important evidence.[14] Given the scope of this research, which relates to policy approaches and UMN definitions rather than to clinical practice or claims of UMN in specific therapeutic areas, a scoping literature review was combined with a gray literature review. An initial scoping review was done by 2 targeted and 2 broad searches in PubMed. The first targeted search was for "unmet medical need" in the title. For the second targeted search, we combined *unmet medical need* and related terms (not limited to title) with burden of disease terms: ("unmet medical need" OR "therapeutic need" OR "medical need") AND ("burden of disease" OR "disease burden" OR "disease severity") AND ("medical" OR "disease"). Additionally, 2 broad searches were performed including the more general search terms "burden of disease" and "priority setting" AND ("medical" OR "disease"). The references of included articles and citing articles were also screened[12] For policy research, targeted screening of stakeholder publications and reference searching methods are particularly suited to identify high-quality sources.[14,15] Thus, a gray literature review was performed by starting with online resources of a broad range of stakeholders who are using the concept of UMN or are affected by it. Publications from regulatory agencies, HTA bodies, industry associations, payer networks, healthcare professional organizations, and patient organizations were included, as well as many other relevant institutions such as the World Health Organization. See Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.07.007 for the full list of included organizations. All published documents that stated a definition of UMN or some form of use of it from which an implied definition could be established were included. Documents that stated unmet need for specific diseases without an explanation of what constituted this UMN were excluded. Search functions on online sources were used when available, using terms such as "unmet medical need," "unmet need," or "therapeutic need" alone and in combination with "definition." Additionally, these terms were put into Google together with the name of the stakeholder or institute to find definitions that could not be found through search queries on the websites of the specific stakeholders. Data elements included in the data abstraction form were author or institution name(s), publication year, title of the document, definition(s) of UMN provided, and a free field for additional information (eg, for documents based on European regulation in the referred article). This database was used to develop a categorization of existing definitions.

Methods for Gathering Insight Into Current Use of UMN by Stakeholders

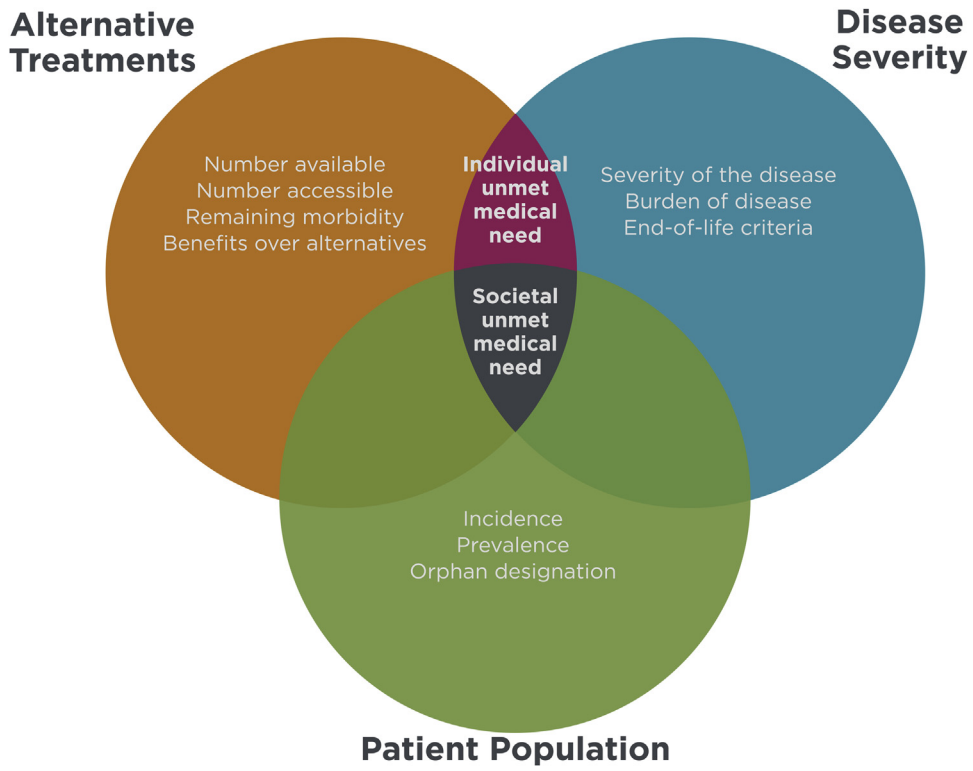
Each of the authors of this paper representing a specific stakeholder group was asked to describe what UMN meant for them and how they currently used it in practice. The stakeholder representatives were selected based on their positions as stated in their affiliations and based on their involvement in policy discussions. Stakeholders included were patient representatives, manufacturers, regulators, HTA bodies, and payers.

The resulting data were then converted to a graphical representation of the current meaning and use of UMN by stakeholders. Stakeholders gave 1 final round of comments before finalizing this graphic.

Methods for the Stakeholder Discussions

The overview of UMN definitions was discussed among the author group, representing relevant stakeholders. This discussion included 6 1-hour teleconferences between October 2017 and March 2018, and 2 workshops in April 2018. We used open-ended input owing to the broad nature of the discussion. The process started with discussing the summarized definitions and identifying where discrepancies in interpretation existed. In the next step, possible quantification mechanisms for UMN were discussed. The final step included a discussion of the place of UMN within broader value frameworks for the prioritization of health technologies. These discussions were summarized by authors R.V. and I.H. The resulting reflections were presented in the first workshop, which was an open session with 69 people from regulatory agencies, industry, payers, HTA bodies, patient organizations, healthcare, and academia. The second workshop was a closed session with the authors and 1 to 2 representatives of each stakeholder group (patients, payers, industry, HTA, regulators). The results of these discussions were again summarized by authors R.V. and I.H. and reflected back to the author group.

Figure 1. Elements of unmet medical need found in definitions and possible ways to measure them based on the review.



Additional comments were added through 2 1-hour teleconferences and on paper.

Results

Results of the Scoping Literature Review and the Gray Literature Review

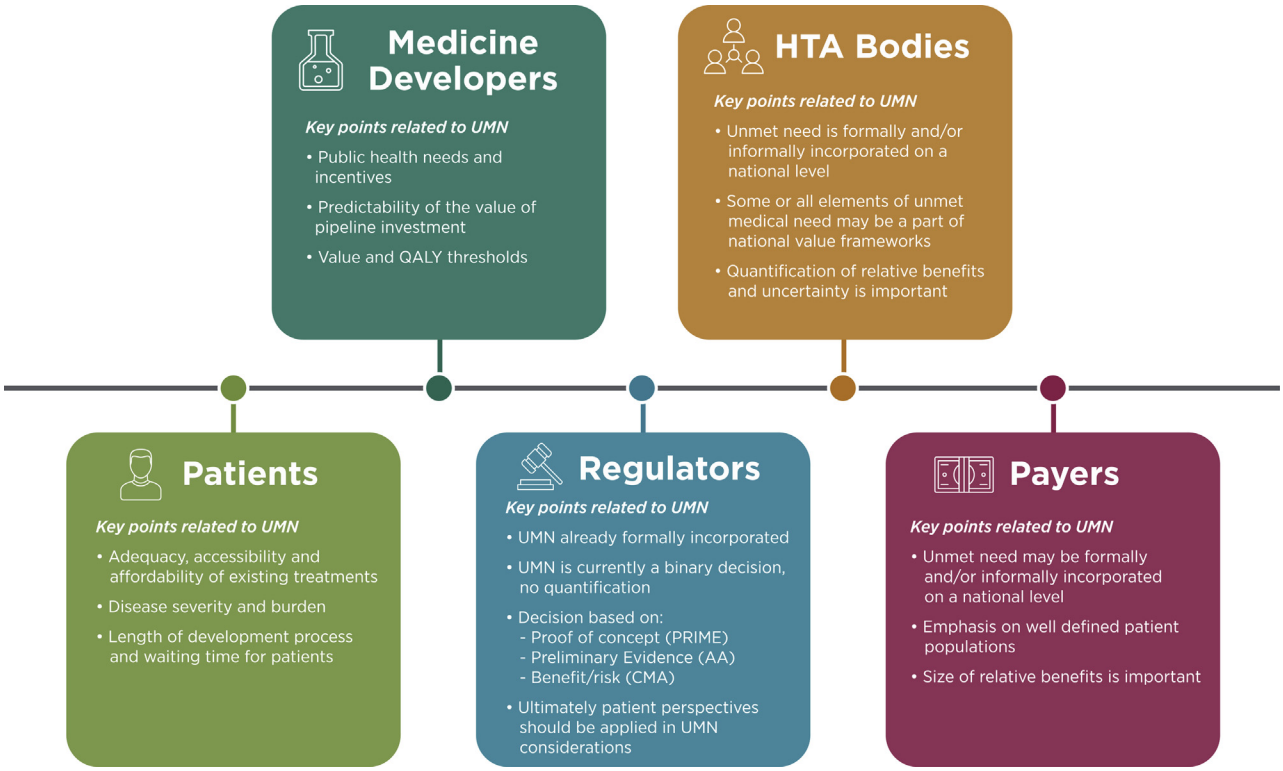
Results for the 2 targeted searches of "Unmet Medical Need"[Title] and the combination of unmet medical need and burden of disease on PubMed resulted in 52 and 29 hits, respectively, of which 51 and 29 related to claims of UMN in specific populations, ranging from potential impacts of social policies to specific disease areas such as oncology. Only 1 article related to the concept of UMN.[12] The broad searches of "burden of disease" or "priority setting" AND ("medical" OR "disease") resulted respectively in 8464 and 1019 hits, of which 19 and 48 were selected for abstract review and 6 and 16 for full paper review. None were considered relevant for discussing the concept of UMN because the articles only described specific cases where UMN was claimed, described the processes of resource allocation, or provided a burden-of-disease study with the disability-adjusted life years model. The lack of relevant results in this relatively broad search illustrates the widespread use and interpretation of the concept in the literature.

The gray literature review delivered 16 definitions of UMN of 34 online sources consulted. Most of the searched publications did mention UMN as relevant to patients or institutional processes or decisions yet failed to define how it is established. The full database of definitions found through the review is available in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.07.007. Definitions of UMN provided by the review could be divided into 3 categories: (1) definitions that only include availability of alternative treatments; (2) definitions that include availability of alternative treatments and some form of disease severity or disease burden; or (3) definitions that include availability of alternative treatments, some form of disease severity or disease burden, and size of the population. Availability of alternative treatments was present in all definitions (16 of 16; 100%), but there were 3 types of inclusion: the criterion of sheer presence of alternative treatments (eg, none/some/many), which was the case for 3 definitions (19%); the criterion for a lack of satisfactory available treatments (7 of 16: 44%); and the criterion that the new therapy has a benefit over available treatments (6 of 16: 38%). The difference between the second and third types is that the second type is reasoned from the perspective of the available treatments (they are not satisfactory/significant morbidity or mortality remains), whereas the third type is reasoned from the perspective of a novel therapy (it provides additional benefit). Disease burden or severity was part of 6 definitions (38%) and population size was part of only 1 (6%). The inclusion of population size in only 1 definition indicates that available treatments and disease burden represent first-order elements, whereas population size is a second-order element. Figure 1 shows these 3 elements that may be considered for an UMN definition and some suggestions for methods of quantification of these elements, based on the definitions found through the literature search.

Results of the Exploration of Current Use of the Concept of UMN by Stakeholders

Figure 2 shows an overview of the current considerations on UMN by different stakeholders as provided by the author group. Where some stakeholders have formal processes that use the concept of UMN (eg, conditional marketing authorization for the

Figure 2. Stakeholder considerations on unmet medical need.



AA indicates accelerated approval; CMA, conditional marketing authorization; HTA, health technology assessment; PRIME, Priority Medicines; QALY, quality-adjusted life year; UMN, unmet medical need.

EMA and differential incremental cost-effectiveness ratio thresholds for HTA agencies), most stakeholders do not formally incorporate it in their processes. Most indicated that the concept was of importance for decision making.

Results of the Stakeholder Discussions

The first topic raised was elements that may constitute a definition of UMN. Stakeholders could find consensus that they should definitely include available treatments and some form of disease severity or burden. The discussions made clear that the second-order element of population size may only be relevant for specific scopes. Payer representatives emphasized that for the element of disease severity, they preferred the inclusion of the presence of severely debilitating or life-threatening diseases.

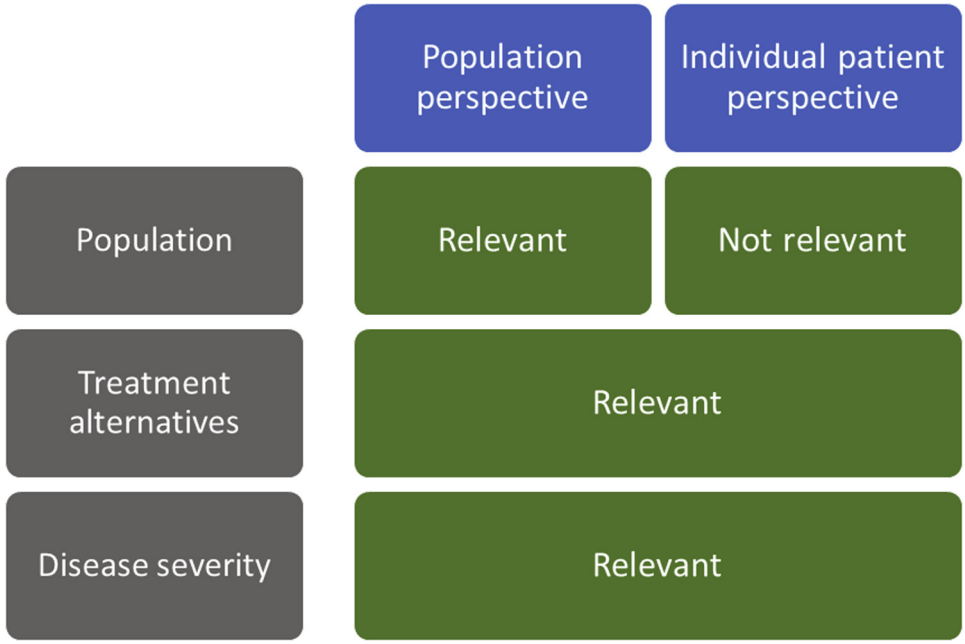
Stakeholders did not arrive at an aligned conclusion on how to measure each of these 3 elements. Some stakeholders were of the opinion that orphan designation should be included as an element of its own next to disease prevalence, whereas others considered it is implied in prevalence and would constitute double-counting. Stakeholders agreed that when measuring the size of the patient population, UMN would increase with growing population size if a societal or population perspective was considered. If an individual perspective was considered, population size would be irrelevant. The stakeholders noted that there is a perception that very small patient groups (eg, those defined by orphan designation) have a relatively higher UMN. This appears contrary to the intuition that societal unmet medical need grows with larger populations, and it was acknowledged that this effect is probably also due to the historically low number of available treatments for such small populations. Nevertheless, the precise relation among available treatments, population size, and UMN could not be elucidated through our stakeholder discussions.

Considering quantification, all stakeholders agreed that a complete lack of alternative treatments would mean a high score on the element of adequacy of alternative treatments. Nevertheless, it was unclear how UMN would be quantified if some alternative treatments exist but these are not satisfactory to patients or if patients cannot access them. Counting the sheer number of alternative treatments was considered inadequate. For medicine prioritization, alternative treatments should be taken into account relative to the benefits of the technology under assessment. If a new technology could provide significant benefits for patients over existing treatments, this would contribute to fulfilling the UMN more. Benefits in relation to available therapies are not necessarily part of benefit-risk assessment within the regulatory processes. Additionally, from an HTA and payer perspective, it would be important to discuss how the process would work if prioritization for HTA assessment would be based on relative benefit over a comparator, while this relative benefit is only established during HTA assessment. Establishing UMN within a population may differ from establishing the UMN that a novel technology might address. It can differ per stakeholder which type of UMN is relevant within their scope.

Disease burden or severity was considered relevant to the measurement of UMN by all stakeholders. Whether this should be measured by a simple scoring of disease severity or some form of burden of disease was not discussed.

The discussion did not aim to quantify UMN precisely. Nevertheless, it became clear that such an exercise would encounter considerable difficulties owing to the different opinions on measuring population size, alternative treatments, and disease burden, explained by different scopes of the stakeholders.

Figure 3. A proposal for the relevance of the different elements in Figure 1 from a population and a patient perspective.



Measurement of UMN may be different when viewed from an individual patient who is not adequately treated with the current set of available treatments versus viewing it from a population perspective when most patients are adequately treated. Figure 3 represents a proposal for the relevance of the different elements of UMN in relation to the scope within which they are assessed by any stakeholder. In the review of definitions, it became apparent that almost no definition included population size. This suggests that currently, an individual patient view is the more common approach to assessing UMN.

As an important finding, stakeholders agreed that UMN cannot be separated from the broader value framework. This was most apparent in the discussions on alternative treatments, where it became clear that benefits over existing treatments should be taken into account as opposed to the number of alternative treatments. Additionally, stakeholders agreed that measuring UMN could indicate double-counting within existing value and regulatory frameworks. This would, for example, apply when burden of disease would be used to quantify the size of UMN in value frameworks where the accepted incremental cost-effectiveness ratio willingness-to-pay threshold is already dependent on burden of disease.[16] For example, in the Netherlands, for indications with a high burden of disease, society is willing to pay more per quality-adjusted life year. If the UMN formula would lead to higher willingness-to-pay thresholds with higher UMN and would also use burden of disease, this affects the threshold twice. In Sweden, the acceptable cost per QALY is also dependent on disease severity.[17]

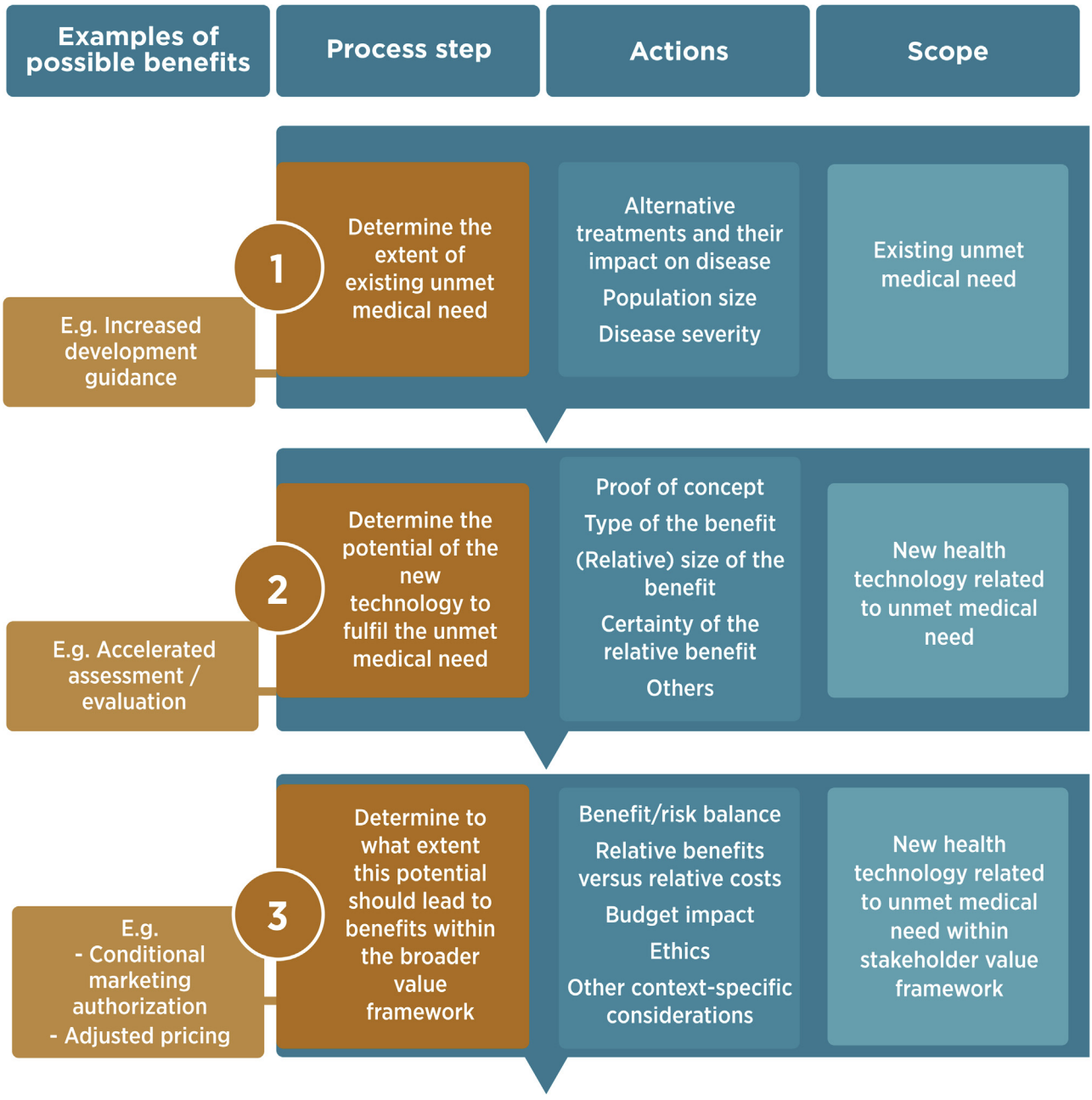
As a conclusion of the stakeholder discussions, a framework was discussed based on the established elements for UMN and other considerations. This framework includes a primary assessment and 2 subsequent evaluation steps. The primary assessment includes an evaluation of available alternative treatments and the extent to which morbidity or mortality remains, an evaluation of the population size, and an assessment of disease severity or burden, as presented in Figure 1. From these elements, different indications and subpopulations can be ranked by their existing need. If the existing UMN is established, technologies that aim to address the highest unmet needs may for example receive additional development support. In step 2, the extent to which a novel technology actually may fulfill the UMN is assessed. This preliminary assessment before full regulatory or HTA assessment may lead to benefits, for example, faster full evaluation. During the full evaluation, the exact eligibility for benefits related to the potential of the treatment to address the UMN and to the value framework in which the treatment is applied will be determined. Examples of benefits are conditional marketing authorization or adjusted pricing. The process is shown in Figure 4 and could be applied to any decision maker who applies the concept (eg, regulatory/HTA). The representatives of each stakeholder group acknowledged the relevance of a systematic framework to incorporate UMN in decision making but emphasized that the precise framework would be stakeholder-specific because elements in the framework (such as relative costs) are relevant to some stakeholders but not all.

Discussion

Summary of Results

The results of our review of definitions show that multiple criteria are being considered by different stakeholders, but that they can be categorized into 1 of 3 categories, including adequacy of alternative treatments, disease burden, or population size. The input of stakeholders highlighted that UMN is an important concept for each stakeholder, but for most of the stakeholders this is informal. Our multi-stakeholder author group could find consensus on the inclusion of these 3 criteria for an UMN definition, but simultaneously emphasized that the application of the definition within a broader framework depends on the scope of the stakeholder. We did not attempt to establish a common method for the measurement of UMN owing to diverse opinions on what methods for measuring would suit different situations and the shared opinion that separation from context-specific

Figure 4. Proposal for a staggered approach to evaluation of health technologies based on unmet medical need by decision makers. Elements considered are non-exhaustive and depend on the decision maker.



broader value frameworks for health technologies is not appropriate. Additional research into quantification mechanisms is encouraged. The criteria and the framework discussed in this paper are recommended as a starting point for the discussion to progress with alignment and understanding between the stakeholders.

Context and Implications

The inclusion of UMN need in stakeholder processes has led to discussions on its precise definition, specifically in the EMA-payer community meeting.[2] Additionally, insight into its interpretation is part of the EMA-EUnetHTA joint work plan 2017 to 2020.[1] Satisfaction of the criterion of unmet medical need for one stakeholder does not necessarily means satisfaction of the criterion for another. We found multiple definitions in use by different stakeholders, which emphasizes this issue. The scope and criteria included may differ per stakeholder, which should be made explicit in discussions on the application of UMN.

A recent example where discussions on UMN were relevant is the deliberation on adaptive pathways, where it was already mentioned that one should not separate UMN from other value

elements.[4] The authors of that study advocated that needs alone should not drive prioritization decisions and that the benefit/risk balance should be the leading argument for approval regardless of the existing need.[4] For downstream stakeholders (namely HTA bodies/payers), a benefit/risk balance can be seen in a wider perspective where the risks also include the opportunity costs of funding a technology. Thus, HTA bodies and payers might prefer unmet needs-driven reimbursement as opposed to approving any product with a positive benefit/risk balance (or positive cost-effectiveness for HTA). Clearly, context is important when applying the concept and definition of unmet need. This includes the choice between using UMN as a binary element or using it for matters of quantification. In legal terms (as laid down in Article 4, paragraph 2 of Commission Regulation [EC] No. 507/2006), UMN has a very simple definition that constitutes solely the availability of adequate alternative treatments. Nevertheless, when stakeholders decide on marketing authorization or prioritization of resources for reimbursement, they use a framework that considers other elements beyond the availability of adequate alternative treatments. Literature on regulatory and value frameworks is extensive, including quantification case studies with multi-criteria decision analysis.[18-21]

An important unaddressed issue is the precise quantification of UMN and the interplay of different possible UMN elements (available treatments, disease burden, population). Precise quantification might be less relevant when UMN is used as a binary concept (eg, in regulation) but very important for downstream decision makers. Burden of disease can be measured in multiple ways.[22-24] Alternatively, one could consider specific rules such as end-of-life criteria (eg, the HTA process in the United Kingdom). Recently, the concept of condition severity was posed as a way to unify treatment availability and disease severity.[25] The proposal of those authors is to quantify the remaining unmet need through correcting for disease severity and available treatments in relation to a state of optimal health.[25] The authors of that study argue that condition severity should replace UMN altogether.[25] Our work has illustrated that different methods could define the relation between individual UMN elements. It would be worthwhile to investigate further how condition severity may play a role. Nevertheless, the measurement solely of condition severity might also have its shortcomings because stakeholders also might want to compare specific disease severity irrespective of available treatments.

Strengths and Limitations

The nature of UMN warranted us to do a scoping review in combination with a gray literature review and a snowball approach instead of a full systematic literature review through academic literature databases. Theoretically, it is possible that we have not included some relevant academic papers in our selection process. Nevertheless, the nature of the UMN definitions that we have found through our search and the commonalities in the definitions indicate that it is unlikely that we would find greatly different definitions if we would include more documents. Additionally, our stakeholder group is not necessarily a full representation of the stakeholders involved. Some stakeholders, such as healthcare professionals, were not included in the discussion, and none of the authors are formal representatives of any stakeholder group. Thus, we emphasize that the opinions stated in this article are the opinions of individual experts and not the opinions of stakeholder groups as a whole. This is a common feature of multi-stakeholder collaborations because stakeholders generally have differentiated opinions within their own group. The nature and structure of our group discussions (semi-structured, open) may introduce group thinking as opposed to more formal discussion mechanisms, such as a Delphi process.

Conclusion

This study shows that the definitions of UMN that are being used by stakeholders fall within 3 categories, including 1 or more elements that represent (impact of) available treatments, patient population size, or disease severity. The main challenges lie within quantification and applying the concept within the broader value framework of each stakeholder. We encourage stakeholders that want to promote alignment of UMN to prospectively discuss the scope in which they want to apply UMN, what elements they find important for UMN within this scope, and how they would measure UMN within the broader value framework.

The ultimate goal of these efforts should be an increasingly aligned and predictable pathway for the development, regulation, reimbursement, and use of health technologies, to meet the needs of patients.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organizations with which the authors are affiliated.

Acknowledgments

The authors would like to acknowledge Talana Bertschi for her help in designing the graphics.

Source of financial support: This research did not receive any specific grant or financial support from funding agencies in the public, commercial, or not-for-profit sectors.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https: https://doi.org/10.1016/j.jval.2019.07.007.

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