Update and European consensus on a patient-centered core outcome set for multiple myeloma in clinical practice and research

To discuss outcomes with patients in daily clinical practice, and to facilitate outcome comparisons between institutions and scientific research, a standardized Core Outcome Set (COS) for patients with multiple myeloma (MM) is needed.[1] In the past five years, multiple COS have been developed for patients with MM across Europe.[2-4] Although these COS share the same objectives and include similar outcomes, the sets also exhibit differences in the definitions and measures being used. Since incidence rates in MM are relatively low,[5] standardizing these COS is warranted to accelerate data collection and data comparison. The goal of this study was, therefore, to establish a European consensus-based, standardized COS for patients with MM. This was achieved by aligning existing COS through consensus group discussions in a European and diverse group of stakeholders/experts, which resulted in an updated European consensus-based standardized COS and accompanying definitions or measures for patients with MM for use in routine clinical practice and research. The outcomes represent important indicators that are most relevant to patients with MM. With the use of this updated European consensus-based standardized COS, we expect to be able to facilitate therapeutic decision-making, allow outcome comparison across centers and countries to guide improvements in clinical practice, and accelerate scientific research.

The continuous development of new treatments for multiple myeloma (MM) provides more options to achieve increased survival, but also adds more complexity to the treatment of the disease.[6] This increase in options leads to longer treatment duration and better outcome,[7,8] often associated with a higher risk of adverse events such as acute renal failure, anemia, pneumonia/infections, cardiac toxicity, and polyneuropathy.[9] Moreover, patients might develop long-term consequences such as fatigue, pain, cognitive problems, and depression,[10] impacting patients' health-related quality of life (HRQoL).[11] Therefore, modern therapeutic strategies focus not only on improving overall survival, but also on prevention and management of acute and long-term side effects of therapy, optimizing therapy duration, and improving HRQoL.[9]

To monitor outcome progress, COS are needed. In the past five years, multiple COS have been developed for patients with MM across Europe,[2-4] highlighting the urgent need for such a tool. Since incidence rates in MM are relatively low,[5] standardizing COS is warranted to accelerate data collection and (inter)national data comparison. Also, since HRQoL becomes more pronounced as a primary or secondary outcome in MM research, comparison of HRQoL outcomes requires standardization of patient-reported outcomes (PRO) and PRO measures (PROM).[12,13]

The goal of this study was, therefore, to establish a European consensus-based, standardized COS for patients with MM, which would serve as a valuable tool for clinical practice and research as a reference framework of what and how to measure in MM. This study is part of the Health Outcomes Observatory (H2O) initiative. H2O has been designed to drive value-based health care (VBHC) in Europe by improving the sustainability of health care systems and supporting health care providers to optimize care delivery by use of COS that matter to patients.[14]

Three existing COS were identified through a literature search of MedLine, EMBASE, and the COMET database, and through the European Myeloma Network (EMN):

1. The IMPORTA project in Spain,[2] published in 2018, in which global standards for collecting outcomes (and measuring instruments) that matter most to patients were defined. The set was based on a literature review and a 2-round Delphi questionnaire among hematologists, patients, and pharmacists in Spain.
2. A VBHC MM project in the Netherlands,[4] published in 2020, in which outcomes that were most relevant to patients, and instruments to measure them for use in clinical practice, were defined. This set was based on literature review and consensus by MM experts and patients from 4 Dutch hospitals, and finalized by the Dutch MM HOVON working group.
3. The HARMONY Alliance,[3] an innovative medicines initiative (IMI) across Europe, in which a COS for patients with MM was defined for use in clinical trials in 2021. This set was based on 2 Delphi rounds with hematologists, patient representatives, representatives of pharmaceutical companies, and policymakers across Europe.

The alignment and update of the 3 existing COS was undertaken by a group of experts (N=17) consisting of delegates of the existing COS development teams, hematologists across Europe active in the EMN, patients and patient advocates from national and European patient organizations, and representatives from pharmaceutical companies. Relevant experts were approached through 'snowball sampling', and ranged with respect to age and expertise; all were based across Europe. Three online consensus meetings were held in which the 3 existing COS were used as starting point. During the meetings, the COS were discussed and compared with respect to: (1) definition of patient population,

(2) patients' condition, (3) clinical outcomes, (4) PRO, and (5) timing and measurement process.

Inclusion of the patient conditions and outcomes was based on a predefined criterion: if the patient conditions or outcomes were included in at least 2 of the existing COS, they were deemed eligible for the updated European consensus-based standardized COS. Outcomes or patient conditions included in one of the existing COS underwent thorough discussions and were subject to voting, by counting all meeting participants in favor for including an outcome or patient condition (>half of participants). Feasibility of measurement and data availability (e.g., in clinical records) were considered when discussing whether an outcome should be included in the updated COS or not. The updated

Table 1. Reasons for exclusion or addition of items to the European consensus-based standardized Core Outcome Set.

	Exclusion of or addition to European consensus-based standardized COS	Reason for exclusion or addition
Patient conditions		
Family history	Exclude	Not specific enough to be standardized
Anemia at baseline	Exclude	Condition of limited value and too difficult to control data registry prior to diagnosis
Bone lesions	Exclude	Condition that is too difficult to categorize in an uniform manner with uniform techniques in different centers and countries
Neuropathy at baseline	Exclude	Condition of limited value and too difficult to control data registry prior to diagnosis
Transplant eligible	Addition	Added for a more comprehensive treatment registration
Induction or maintenance therapy	Addition	Added for a more comprehensive treatment registration
Reason of treatment discontinuation	Addition	Added for a more comprehensive treatment registration
Healthcare access	Addition, optional	Based upon concerns with respect to unequal access to care raised by patient advocates.
Ethnicity	Optional (not for cross country comparison)	Legal restriction in some countries
Socio-economic status	Optional (not for cross country comparison)	Not informative and less reliable for cross country comparison
Clinical outcomes		
Completion of treatment	Exclude	Measured by other treatment-related outcomes
Place of death: hospital?	Exclude	Outcome of limited value
Relapse	Addition	Needed to calculate PFS
Relapse date	Addition	Needed to calculate PFS
Treatment adjustment: date of treatment adjustment	Addition	Needed for a more comprehensive treatment registration
Second primary malignancy	Addition	Added as it may influence treatment strategy
Patient-reported outcomes		
Pathological fractures	Exclude	Outcome of limited value
Fear of physical exercise	Exclude	Outcome of limited value
Preferences and satisfaction	Exclude	Too diverse; should be included in separate PREM
Treatment adherence	Exclude	Outcome relevant to a limited group of patients with MM (only for oral medication).
Motor neuropathy	Addition	Raised by patients as one of the most important outcomes

COS: Core Outcome Set; MM: multiple myeloma; PFS: progression-free survival; PREM: patient-reported experience measures.

European consensus-based standardized COS was distributed via email to the expert group for final confirmation and was approved by all.

The population definitions were slightly different across the 3 COS: the IMPORTA set was developed for patients with newly diagnosed MM, the VBHC-MM set for patients with symptomatic MM aged ≥18 years who fulfil the International Myeloma Working Group (IMWG) criteria, and the HARMONY-Alliance set for all patients with MM without any further specification. After substantial discussion, the panellists reached consensus about the following patient population definition: patients with MM aged ≥18 years of age who are newly diagnosed or had a relapse/became refractory and patients with smoldering (asymptomatic) MM (according to the IMWG criteria). Exclusion criteria were defined as: patients aged <18 years and patients with monoclonal gammopathy of undetermined significance (MGUS).

The following patient conditions: age, gender, date of diagnosis, Revised-Multiple Myeloma International Staging System (R-ISS) disease stage, comorbidities, treatment, and functioning disability and health were included in the updated European consensus-based standardized COS (*Online Supplementary Table S1*) because these were all part of both the IMPORTA and the VBHC-MM set (*Online Supplementary Table S2*); the HARMONY-Alliance set did not define patient conditions. For some of the patient conditions, definitions slightly differed across the sets and were aligned after consensus discussion. Furthermore, related to treatment, 3 items were added for a more comprehensive treatment registration, i.e., transplant eligibility, induction or maintenance therapy, and reason of treatment discontinuation. Other patient conditions that were part of one of the sets, and that were included in the updated COS after consensus discussion, were ethnicity (optional), living situation, cytogenetic risk, frailty, height, weight, and educational level (optional). Moreover, an additional item about healthcare access (access to care and barriers to accessing care) was added as an optional item based upon concerns with respect to unequal access to care raised by patient advocates. The reasons for exclusion and addition of items are listed in Table 1.

The clinical outcomes overall survival, progression-free survival, infections, neuropathy, renal failure, anemia, cardiovascular toxicities, and venous thromboembolism were included in 2 or all 3 sets, and were, therefore, included in the updated European consensus-based standardized COS. Other clinical outcomes that were part of one of the sets, and that were included in the updated European consensus-based standardized COS, were minimal residual disease, response, therapy-free interval, date of death, and active treatment <30 days before death. Furthermore, relapse, treatment adjustment, and second primary malignancy were added with the reasons for addition listed in *Online Supplementary Table S2*.

The PRO HRQoL, mobility, overall daily functioning, anxiety, depressive symptoms, cognitive problems, social participation and work, fatigue, dyspnea, nausea, pain, sleep problems, appetite loss, gastrointestinal problems, financial problems, body image, peripheral neuropathy, relational and sexual problems were included in 2 or all 3 sets and were, therefore, included in the updated, European consensus-based standardized COS. The EORTC QLQ-C30 and QLQ-MY20 were in all sets defined as the measures to use for the included PRO. In the HARMONY-Alliance set, mainly PROM (e.g., EORTC QLQ-C30 and QLQ-MY20) were defined, overlapping the PRO determined in the other 2 sets.

The timing of measurement in all sets was determined based on clinical relevance and feasibility. This differs between countries, and probably also between hospitals/clinics. To set a preferred standard, it is advised that all clinical- and patient-reported outcomes are to be collected at time of diagnosis and at least every three months during the 1st year, every six months during the 2nd and 3rd years, and then annually. To be able to discuss outcomes during visits, it is necessary to collect PRO-data aligned with individual clinical care.

This study resulted in an updated European consensus-based standardized COS and accompanying definitions or measures for patients with MM for use in routine clinical practice and research. This COS will be implemented in Europe as part of the H2O initiative.

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Data-sharing statement

The data dictionary that supports the European consensus-based standardized core outcome set as displayed in Online Supplementary Table S1 is available from the corresponding author upon reasonable request.

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