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DEFINING A SET OF STANDARDIZED OUTCOME MEASURES IN MULTIPLE MYELOMA. THE IMPORTA PROJECT.

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Abstract:

Objective: To define a Standard Set of outcomes and the most appropriate instruments to measure them for managing newly diagnosed multiple myeloma (MM) patients. Design: A literature review and five discussion groups facilitated the design of 2-round Delphi questionnaire. Delphi panellist (haematologists, hospital pharmacists and patients) were identified by the Scientific Committee, the Spanish Program of Haematology Treatments Foundation, the Spanish Society of Hospital Pharmacies and the Spanish Community of MM Patients. Panellist's perception about outcomes' suitability and feasibility of use were assessed on a 7-point Likert scale. Consensus was reached when at least 75% of the respondents reached agreement or disagreement. A Scientific Committee led the project.

Setting: The Spanish national health system.

Participants: More than 50 experts (haematologists, hospital pharmacists and patients) from across the country participated in the study.

Outcome measured: The degree of consensus between experts on most appropriate instruments for managing MM patients was measured.

Results: 51 and 45 panellists participated in the first and second Delphi-round, respectively. Consensus was reached to use overall survival, progression-free survival, minimal residual disease and treatment response to assess survival and disease control. Panellists agreed to measure health-related quality of life, pain, performance status, fatigue, psychosocial status, symptoms, self-perception on body image, sexuality, and preferences/satisfaction. However, panellist did not reached consensus about the feasibility of assessing in routine practice psychosocial status, symptoms, self-perception on body image and sexuality. Consensus was reached to collect PROs through the EORTC-QLQ-C30 questionnaire, three items from EORTC-QLQ-MY20 and EORTC-QLQ-BR23, pain visual analogue scale, Morisky-Green and ad-hoc questions about patients' preferences/satisfaction.

Conclusions: A consensual Standard Set of outcomes for managing newly diagnosed MM patients has been defined. The feasibility of its implementation in routine practice will be assessed in a future pilot study.

INTRODUCTION

Multiple myeloma (MM) accounts for 1% of all cancers and represents 13% of all haematological malignancies.[1] It is estimated that about 86,000 new cases of MM and 63,000 deaths occur annually worldwide.[2] The incidence of MM increases with age, therefore, an ageing population has led to an increase of new diagnoses of MM in the last decades[3] and potentially will continue to rise in the coming years. Despite the substantial advances in treatment options, MM remains incurable with a short median survival (6-7 and 2 years for standard and high risk patients, respectively).[2,4] Moreover, Health Related Quality of Life (HRQoL) in patients with MM is commonly affected by symptoms associated with the disease itself and the toxicity of the treatment.[5,6]

Quality healthcare encompasses not only achieving disease remission, but also easing patients' discomfort, and helping them manage their disease. Emerging strategies encourage maximizing the value for patients (achieving the best outcomes at the lowest cost), moving towards a patient-centred system organized around patients' needs.[6] To do this effectively and efficiently requires an integrative approach. Thus, collecting holistic outcomes data from patients is crucial. Assessing regularly patient-reported outcomes (PROs) in clinical practice, complementary to the use of traditional biomedical markers, could contribute to this convergence improving MM management.[7–9] From the point of view of a healthcare provider, this approach could lead to institutional improvements, foster the dissemination of best practices, and prompt competition around value.

During the last years, efforts have been made to quantify MM outcomes accurately using validated instruments.[10] This has led to a wide variability across instruments and variables. Paradoxically, the broad range of instruments and variables hinder outcome comparisons between physicians, institutions and regions. As a result, the current goal is not so much a question of developing new outcome measures, but to agree on which ones are well validated and should be used. Pioneer initiatives such as the one performed by the International Consortium for Health Outcomes Measurement (ICHOM) have focused on this concern, developing standard sets for various diseases, among which MM is not included.[11]

In collaboration with the Spanish Society of Hospital Pharmacies (SEFH) and the Spanish Program for Haematology Treatments foundation (PETHEMA), we aim to cover the existing needs defining a set of global standards for collecting outcomes that matter most to patients with MM, and select a proper instrument for the measurement of these outcomes.

METHODS

Scientific Committee

A Scientific Committee led and coordinated the project. It consisted of five highly qualified experts in MM: two haematologists and two hospital pharmacists with extensive experience in MM, and one patient with MM. They were chosen on the basis of their longstanding expertise in MM management.

Literature review

A literature search was performed to identify clinical outcomes and PROs, and instruments to measure them used in clinical practice for the management and follow-up of MM patients. The search included original articles, systematic reviews and clinical practice guidelines published in English or Spanish between January 2010 and October 2015. The information obtained in the literature review was used to steer five discussion groups.

Discussion groups

The objective of the discussion groups was to share experiences and opinions about outcome variables, definitions, measures of relevance, and to establish the target population, in order to designate the consensual outcomes. Haematologists and pharmacists covered all topics (clinical and PROs), whilst patients covered only PROs. From March to April 2016, different discussion groups were held: three with haematologists (n=4) and hospital pharmacists (n=4), and two with patients with MM (n=7). Patients were divided in two groups of 3 and 4 people to facilitate discussion about their perspective of general MM management and PROs.

The information obtained in the discussion groups was used to design the Delphi questionnaire.

Delphi consultation

A national 2-round Delphi consultation was conducted to establish consensus regarding the most important outcome variables and their proper measurements for managing MM. The Delphi technique is a structured process that consists of the application of subsequent questionnaires in a series of rounds in which the group's responses to one round are used to produce the questionnaire for the next round, providing feedback to respondents in each consecutive round [12].

Contents of the Delphi consultation: first and second questionnaires

Four groups of categories were addressed in the first questionnaire: basal variables of sociodemographic and clinical characteristics (9 issues), follow-up clinical variables (6 issues), follow-up treatment variables (1 issue) and follow-up PROMs and patient reported experience measure (PREMs) variables (10 issues). Affirmative statements assessed the participants' perception related to outcome suitability and feasibility for use in routine clinical practice (within a 5-year period), on a 7-point Likert scale (from 1 = in total disagreement; to 7 = in total agreement). The scientific committee reviewed the questionnaire to ensure that the statements were clear, unambiguous and non-leading.

The second questionnaire included all statements for which consensus was not reached in the first round. Each Delphi panellist obtained their own score and the average score given by the whole group for the same statement in the previous round.

Delphi panellists

Delphi panellists (haematologists, hospital pharmacists and MM patients involved in MM management) were identified by the Scientific Committee, PETHEMA foundation, SEFH and the Spanish Community of Patients with MM (CEMMp). Participants were invited by e-mail receiving the link of the study, username and password (unique for each participant).

Consensus definition

The definition of consensus was established before data analyses, according to the common criteria.[13] Consensus was reached for each statement when at least 75% of the respondents concurred (*entirely agree, mostly agree or somewhat agree*) or disagreed (entirely disagree, mostly disagree or somewhat disagree).

Data analysis

The percentage of participants who selected each option and percentile distributions (25, 50 and 75) were calculated using STATA statistical software, v14. The percentages described in the text refer to the final scores [score of the round in which consensus was achieved for each question (1st or 2nd), or second round in the event that consensus was not reached].

RESULTS

The number of panellists who participated in the first and second Delphi rounds were, respectively: 51 (20 haematologists, 24 hospital pharmacists and 7 patients) and 45 (18 haematologists, 22 hospital pharmacists and 5 patients).

Condition Scope

The participants in the discussion groups agreed that the patients with newly diagnosed MM would be the target population for the MM Standard Set. This comprised those patients eligible for autologous stem cell transplantation and those who were not, and covering induction, consolidation and maintenance treatments. Thus, a broad range of stages of the disease and its treatments could be followed by means of active surveillance.

Outcome domains and measures

Survival and disease control

Due to the high mortality rate and short life expectancy of patients with MM, the health professionals who participated in the discussions group pre-selected the following variables: overall survival (OS), progression-free survival (PFS), minimal residual disease (MRD), and response criteria (RC). Treatment efficacy would be measured by the RC according to the International Myeloma Working Group (IMWG). Subsequently, the expert panellists also agreed to include these variables in the MM Standard Set (Table 1).

Table 1. Basal and follow-up variables, instruments and timing for registering them.

Measure	Details/instrument	Timing	Data source
Basal characteristics			
Age	Data of birth	Basal	CD
Gender	Gender (male/female)	Basal	CD
Ethnicity	Race	Basal	CD

Family history	Family history of cancer or myeloma	Basal	CD or PR
ISSr	International staging system (revised)	Basal	CD
Renal failure	Renal failure prior to treatment/ Creatinine clearance	Basal	CD
Anaemia	Anaemia prior to treatment/ haemoglobin	Basal	CD
Bone lesions	Number and location/ X-Ray, PET, etc.	Basal	CD
Neuropathies	Neuropathies prior to treatment	Basal	CD
Comorbidities	Comorbidities and/or other non-related myeloma diseases	Basal	CD
Type of treatment	Type of treatment initiated (standard or not)	After deciding to treat	CD
Survival and disease control			
OS	Overall survival / Data of diagnosis and death	Basal, death	CD or AD
PFS	Progression-free survival/ from treatment initiation to progression or death.	Treatment initiation, progression or death	CD
MRD	Minimal residual disease/ Flow cytometry: 4-8 colours panel	When complete remission was reached	CD
Treatment response	Time for best response, according to the IMWG	Monthly during treatment, and then every 2-3 months	CD
Complications			
Treatment and adverse events	Completed treatment (with or without dosage reduction) and side effects that hamper the patient's daily activities or those that imply changes in the pattern of treatment / Registry	Monthly during treatment, and then every 2-3 months	CD
PROMs and PREMs			
Treatment adherence	Morisky-Green + Dispensing control	At each dispensation	CD or PR
HRQoL	Health related quality of life/ EORTC-QLQ-C30	Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months	PR
Pain	Pain intensity/ EORTC-QLQ-C30 (pain scale) + VAS	VAS: Basal, before treatment, monthly during treatment, and following every 3 months. QLQ-C30: Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months	PR
Performance status	Patients' level of functioning in terms of their ability to care for themselves, daily activity, and physical ability / EORTC-QLQ-C30 (Physical functioning and Role functioning scales) + ECOG	ECOG: Basal, before treatment, monthly during treatment, and following every 3 months. QLQ-C30: Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months	CD and PR

Asthenia/fatigue	Weakness or general asthenia that makes it difficult to perform tasks that are normally done easily / EORTC-QLQ-C30 (Fatigue scale)	Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months.	PR
Psychosocial status	Impact of disease on cognitive, emotional and social skills / EORTC-QLQ-C30 (Emotional functioning, cognitive functioning and social functioning)	Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months.	PR
Symptoms	Intensity of symptoms due to illness or treatment / EORTC-QLQ-C30 (Symptoms scales)	Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months.	PR
Preferences & satisfaction	*Ad-hoc items*	**Preferences**: Prior to first visit **Satisfaction**: After treatment	PR
Body image	Self-perception of body image /EORTC-QLQ-MY20 (Body image scale)	Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months.	PR
Sexuality	Self-perception on sexual life/ Adapted from EORTC-QLQ-BR23 (Sexual functioning scale)	Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months.	PR

ISSr, International staging system revised. PET, Positron Emission Tomography. OS, Overall Survival. PFS, progression-free survival. MRD, minimal residual disease. HRQoL, Health-Related Quality of life. VAS, visual analogic scale. CD, clinical data. PR, patient-reported. AD, administrative data.

The panellists also reached consensus regarding the inclusion of the M-protein and plasma cell immunophenotype. However, considering that these variables are instruments integrated in other outcome variables such as ISS or RC, the Scientific Committee agreed to discard them to avoid duplicities and to optimize the set.

Consensus was reached in collecting OS (from diagnosis to death), PFS (from the beginning of the treatment to disease progression or death), MRD (when/if patient achieved complete remission), and treatment response (monthly during treatment and subsequently every 2 or 3 months) (Table 1 and Figure 1).

Complications

Completed treatment and side effects

The participants in the discussion group considered that the side effects of MM treatments were important outcomes since they commonly cause considerable morbidity

and low HRQoL in MM patients. [5,14,15] To facilitate data collection, the health professionals proposed a simplified version of the Common Terminology Criteria for Adverse Events (CTCAE) v.4,[16] clustering them into general categories (bone marrow suppression, constitutional, cardiovascular, hepatic, renal, neurological, gastrointestinal, skin, infection, and others). The Delphi panellists agreed to collet each completed treatment (with or without dosage reduction) and those side effects that hamper the patient's daily activities or those that imply changes in the treatment pattern (Table 1). Consensus was achieved to collect this information monthly during treatment and every 2 or 3 months during periods without treatment (Table 1 and Figure 1).

Patient Reported Outcomes and Patient Reported Experiences

Adherence

The Delphi panellists agreed on an adherence multi-measure approach, including the self-reported Morisky-Green questionnaire (4 items) and dispensing control performed by hospital pharmacists in each medication provision.

PROs

HRQoL and other existing PROs identified in the literature (such as pain, functional status, fatigue, symptoms, and psychosocial status) were considered of importance during the discussion groups. Moreover, patients expressed the relevance of their perception of body image and sexuality. The health professionals participating in the discussion groups recommended the European Organization for the Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) as the PROM covering most of these variables. This questionnaire covers the most important domains (general HRQoL, pain, functional status, fatigue, symptoms, psychosocial status) and it is a validated tool that is internationally recognized and available in many languages.[17] The expert participants in the discussion groups were aware that the QLQ-MY20 module[18] includes questions that specifically target MM aspects. However, trying to balance applicability vs. essential information, and considering that the QLQ-MY20 module adds little information in terms of predicting utility values,[19] the use of the EORTC-QLQ-C30 questionnaire alone was considered the best balanced choice.

The panellists agreed to collect HRQoL, pain, functional status, fatigue, symptoms, and psychosocial status with the EORTC-QLQ-C30 questionnaire. They also agreed to collect self-perception of body image with the Body Image scale (1 item) of the QLQ-MY20 questionnaire, and sexuality by two sexuality items adapted from the EORTC-QLQ-BR23 questionnaire.[20] Furthermore, due to the high relevance of pain intensity and functional status in patients with MM, the panellists agreed to collect them in combination with other straightforward and rapid tools: the pain Visual Analogic Scale (VAS) and the ECOG test,[21] respectively. Despite the panellists agreeing to collect all these PROMs, there was no consensus as to the feasibility of measuring some of them in routine clinical practice during the next 5 years. Specifically, consensus was not reached for psychosocial status (71.1%), symptoms (73.3%), body image (64.4%) and sexuality (66.7%).

The panellists reached consensus in assessing PROMs at baseline (diagnostic), before and after the treatment, and subsequently every 6 months during follow-up/maintenance. In continuous and long-term treatments (>6 months), the assessment would be performed every 3 months. The Pain Visual Analogic Scale (VAS) and the ECOG test would be collected in the same time frame, and monthly during treatment.

Preference and satisfaction

The Delphi panellists agreed to collect patient preferences and satisfaction. Preferences (about the information they would like to receive and about their preferred role in the decision-making) and satisfaction (about the same questions) will be processed with a short *ad hoc* questionnaire. Whereas preferences will be assessed prior to the first consultation satisfaction will be assessed after treatment.

Nevertheless, consensus about the feasibility of collecting them in routine clinical practice was not reached (73.3%).

Basal characteristics

Considering that baseline clinical and sociodemographic factors are related to both disease control and PROs outcomes,[22,23] participants in the discussion groups perceived their inclusion in Delphi consultation necessary.

The expert panellists agreed to collect age, gender, ethnicity, family history and stage of the disease. Regarding the latter, consensus was reached to use the revised International

Staging System (rISS) for MM, recently proposed by the IMWG as a simple and powerful prognostic staging system for newly-diagnosed MM.[23] However, due to the current barriers that exist in some centres to accurately detect chromosomal abnormalities, the panellists agreed to use the traditional ISS in these cases. In addition, it was agreed to collect renal failure, anaemia, bone lesions, neuropathies and comorbidities not associated to MM before treatment initiation, since disease progression and treatment toxicity could alter these issues during the follow-up. All basal characteristics that reached consensus are listed in Table 1.

DISCUSSION

Healthcare systems are currently experiencing a critical shift in their model towards a patient-centred system.[6] However, value-based healthcare has to deal with barriers such as the absence of standardized outcomes that are meaningful for patients,[24] which hampers the comparison of results between providers, physicians and regions. Standardization favours simplicity and minimizes variations allowing comparing results, at the same time as aligning all different collectives involved in the management of MM towards a common goal: to improve healthcare quality. At present, there are no commonly accepted standards for defining the optimal outcome parameters for use in patients with MM. A minimum Standard Set of important outcomes for MM patients could help to improve healthcare quality, supporting informed decision-making, and reducing healthcare costs.

In recent years, several initiatives led by the ICHOM have developed Standard Sets of health outcomes for a wide variety of diseases including prostate cancer, breast cancer, lung cancer, coronary artery diseases, stroke, Parkinson, hip and knee osteoarthritis dementia and depression.[11] Recently, some institutions and registries that measure health outcomes such as Ramsay Healthcare, Fortis Healthcare and Mayo Clinic, have started a second phase implementing some of these Standard Sets.[25] Some promising early results concerning these implementations have been recently published. The use of the Cleft lip and palate Standard Set at the Erasmus University Medical Centre in the Netherlands has shown a high compliance with the proposed measures (90-100%) and good positive feedback from both patients and clinicians.[26] The implementation of a Standard Set for Parkinson's disease at Aneurin Bevan University Health Board in south Wales showed similar results after optimizing the electronic forms.[27] Another

example is the use of the ICHOM Standard Set for coronary artery disease implemented in the Coronary Angiogram Database of South Australia (CADOSA). This initiative has allowed the standardization of procedures for percutaneous coronary intervention among hospitals, increasing radial access and reducing bleeding-related complications.[28]

To our knowledge, our project is the first initiative to carry out a standardization process for MM. We performed an in-depth literature search identifying almost 40 outcomes and more than 70 instruments. In fact, the biggest challenge was to choose from the huge variety of variables, especially for PROMs. HRQoL is particularly relevant for MM patients taking into account that many of them, especially the older ones, consider HRQoL even more important than overall survival.[29] During the discussion groups, patients also recommended the inclusion of self-perception of body image and sexuality, which are usually evaluated in routine clinical practice for other malignant diseases such as breast cancer but not for MM. Regarding to the recording of treatment adherence, consensus was achieved. It could be thought that treatment for serious diseases present high rates of adherence. However, it is important to note that nonadherence to oral drugs could be really low,[30] leading to suboptimal drug efficacy, poor clinical outcomes and increased healthcare costs.[31]

The minimum set of standardized outcome measures was compiled from the perspectives of more than 50 participants, including expert health professionals (haematologists and hospital pharmacists) and patients with MM. The broad consensus reached is the main strength of this study. However, a number of limitations remain present. Although most of the selected instruments are validated, the set as a whole has not been, which is one of the main limitations of the present study. In addition, the Standard Set is derived from expert consensus rather than high levels of evidence.

These recommendations represent an initial approach for collecting a minimum Standard Set of outcomes for MM management. Nonetheless, future steps should be taken to validate the Standard Set and refine it towards a global standard. We are aware that the burden of answering all proposed items at each interval could be significant for some patients. Likewise, data input could represent an additional workload for health professionals. In fact, when holding discussion groups, health professionals were of the opinion that its acceptance could be associated with the time-consuming process. In this

sense, an electronic questionnaire directly filled in by patients and the easy inclusion of the results in their medical history could guarantee broad acceptance. In addition, future computer-adaptive PROMs would decrease respondent burden[31] and smartphone or telehealth surveys would pave the way towards piloting inexpensive forms of digital data collection.[2] In this sense, the feasibility of the MM Standard Set should be evaluated via a pilot study using the Set in routine clinical practice.

SUMMARY

It has been defined a minimum recommended set of consensus outcomes, including clinical and PROs, to be collected for patients with MM in routine clinical practice. The use of this standard set would allow learning from each other through meaningful comparison, helping to improve MM management and developing a quality and cost-effective patient-centred healthcare system.

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Contributor ship statement

BJ, CMA, LJJ and PJL coordinated the project, assisted in the identification of participants, and was involved in design of study, construction of the Delphi questionnaire, interpretation of results, and critically reviewed the manuscript for important intellectual content. LL designed the study, was involved in the construction of the Delphi questionnaire, interpretation of results, and drafted the manuscript. dPHD was involved in data collection, data analysis and critically reviewed the manuscript.

Conflict of interest statement

The authors declare no conflicts of interest.

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Data sharing statement

No additional unpublished data from the study are available.

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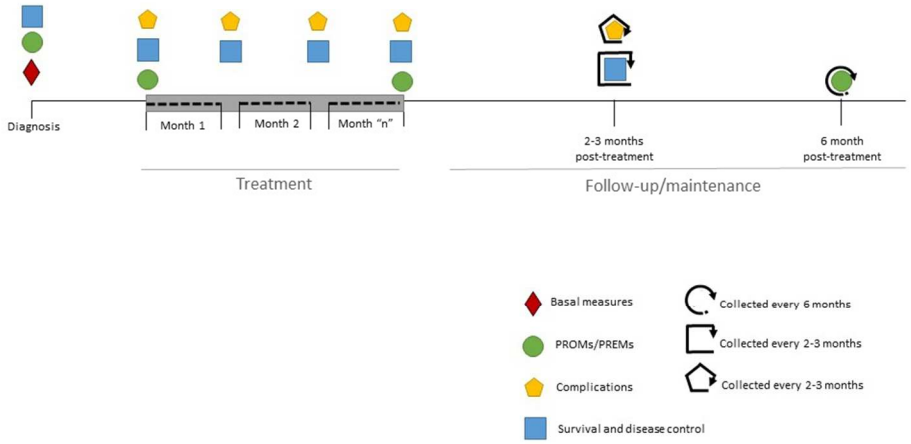

Figure 1. Timeline illustrating when the key outcomes should be collected.

275x190mm (96 x 96 DPI)

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DEFINING A SET OF STANDARDIZED OUTCOME MEASURES FOR NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS USING THE DELPHI CONSENSUS METHOD. THE IMPORTA PROJECT.

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ABSTRACT

Objective: To define a Standard Set of outcomes and the most appropriate instruments to measure them for managing newly diagnosed multiple myeloma (MM) patients. **Methods**: A literature review and five discussion groups facilitated the design of 2-round Delphi questionnaire. Delphi panellist (haematologists, hospital pharmacists and patients) were identified by the Scientific Committee, the Spanish Program of Haematology Treatments Foundation, the Spanish Society of Hospital Pharmacies and the Spanish Community of MM Patients. Panellist's perception about outcomes' suitability and feasibility of use were assessed on a 7-point Likert scale. Consensus was reached when at least 75% of the respondents reached agreement or disagreement. A Scientific Committee led the project. **Results**: Fifty-one and forty-five panellists participated in the first and second Delphi-round, respectively. Consensus was reached to use overall survival, progression-free survival, minimal residual disease and treatment response to assess survival and disease control. Panellists agreed to measure health-related quality of life, pain, performance status, fatigue, psychosocial status, symptoms, self-perception on body image, sexuality, and preferences/satisfaction. However, panellist did not reached consensus about the feasibility of assessing in routine practice psychosocial status, symptoms, self-perception on body image and sexuality. Consensus was reached to collect PROs through the EORTC-QLQ-C30 questionnaire, three items from EORTC-QLQ-MY20 and EORTC-QLQ-BR23, pain visual analogue scale, Morisky-Green and ad-hoc questions about patients' preferences/satisfaction. **Conclusions**: A consensual Standard Set of outcomes for managing newly diagnosed MM patients has been defined. The feasibility of its implementation in routine practice will be assessed in a future pilot study.

Keywords: multiple myeloma, outcome, patient-centered, standardization.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- It is the first initiative to carry out a standardization process for MM.
- A broad consensus has been achieved with the participation of more than 50 patients and health professionals.
- Highly qualified experts in MM were identified by the Scientific Committee, the Spanish Society of Hospital Pharmacies (SEFH), the Spanish Program for

Haematology Treatments foundation (PETHEMA) and the Spanish Community of Patients with MM (CEMMp).

- Although most of the selected instruments are validated, the set as a whole has not been.

INTRODUCTION

Multiple myeloma (MM) accounts for 1% of all cancers and represents 13% of all haematological malignancies.[1] It is estimated that about 86,000 new cases of MM and 63,000 deaths occur annually worldwide.[2] The incidence of MM increases with age, therefore, an ageing population has led to an increase of new diagnoses of MM in the last decades[3] and potentially will continue to rise in the coming years. Despite the substantial advances in treatment options, MM remains incurable with a short median survival (6-7 and 2 years for standard and high risk patients, respectively).[2,4] Moreover, Health Related Quality of Life (HRQoL) in patients with MM is commonly affected by symptoms associated with the disease itself and the toxicity of the treatment.[5,6]

Quality healthcare encompasses not only achieving disease remission, but also easing patients' discomfort, and helping them manage their disease. Emerging strategies encourage maximizing the value for patients (achieving the best outcomes at the lowest cost), moving towards a patient-centred system organized around patients' needs.[6] To do this effectively and efficiently requires an integrative approach. Thus, collecting holistic outcomes data from patients is crucial. Assessing regularly patient-reported outcomes (PROs) in clinical practice, complementary to the use of traditional biomedical markers, could contribute to this convergence improving MM management.[7–9] From the point of view of a healthcare provider, this approach could lead to institutional improvements, foster the dissemination of best practices, and prompt competition around value.

During the last years, efforts have been made to quantify MM outcomes accurately using validated instruments.[10] This has led to a wide variability across instruments and variables. Paradoxically, the broad range of instruments and variables hinder outcome comparisons between physicians, institutions and regions. As a result, the current goal is not so much a question of developing new outcome measures, but to agree on which ones are well validated and should be used. Pioneer initiatives such as the one performed by the International Consortium for Health Outcomes Measurement (ICHOM) have focused on this concern, developing standard sets for various diseases, among which MM is not included.[11]

In collaboration with the Spanish Society of Hospital Pharmacies (SEFH) and the Spanish Program for Haematology Treatments foundation (PETHEMA), we aim to cover the existing needs defining a set of global standards for collecting outcomes that matter most to patients with MM, and select a proper instrument for the measurement of these outcomes.

METHODS

The study comprised three phases: (1) Literature review; (2) Discussion groups; (3) Delphi consultation.

Scientific Committee

A Scientific Committee led and coordinated the project. It consisted of five highly qualified experts in MM: two haematologists and two hospital pharmacists with extensive experience in MM, and one patient with MM. They were chosen on the basis of their longstanding expertise in MM management.

Literature review

A literature search was performed to identify clinical outcomes and PROs, and instruments to measure them used in clinical practice for the management and follow-up of MM patients. The search included original articles, systematic reviews and clinical practice guidelines published in English or Spanish between January 2010 and October 2015. The information obtained in the literature review was used to steer five discussion groups. Presetting of instruments was done by the scientific committee considering the availability of a validated version in the Spanish population, the level of evidence (Oxford CEBM Levels of Evidence) of the reviewed studies and their agreement of its utilization (according to bibliography references). Consensus of ¾ was necessary for inclusion.

Discussion groups

The objective of the discussion groups was to share experiences and opinions about outcome variables, definitions, measures of relevance, and to establish the target population, in order to designate the consensual outcomes. Haematologists and pharmacists covered all topics (clinical and PROs), whilst patients covered only PROs. Outcomes and instruments were appraised according to their use in the Spanish routine clinical practice (expert opinion), the simplicity of completion, and the grade of

disease's impact on the variables from patient's view. From March to April 2016, different discussion groups were held: three with haematologists (n=4) and hospital pharmacists (n=4), and two with patients with MM (n=7). Patients were divided in two groups of 3 and 4 people to facilitate discussion about their perspective of general MM management and PROs.

The information obtained in the discussion groups was used to design the Delphi questionnaire.

Variables and instruments that achieved consensus for their inclusion (¾) and those controversial (½), were included in Delphi consultation.

Delphi consultation

A national 2-round Delphi consultation was conducted to establish consensus regarding the most important outcome variables and their proper measurements for managing MM. The Delphi technique is a structured process that consists of the application of subsequent questionnaires in a series of rounds in which the group's responses to one round are used to produce the questionnaire for the next round, providing feedback to respondents in each consecutive round [12].

Contents of the Delphi consultation: first and second questionnaires

Four groups of categories were addressed in the first questionnaire: basal variables of sociodemographic and clinical characteristics (9 issues), follow-up clinical variables (6 issues), follow-up treatment variables (1 issue) and follow-up PROMs and patient reported experience measure (PREMs) variables (10 issues). Affirmative statements assessed the participants' perception related to outcome suitability and feasibility for use in routine clinical practice (within a 5-year period), on a 7-point Likert scale (from 1 = in total disagreement; to 7 = in total agreement). The scientific committee reviewed the questionnaire to ensure that the statements were clear, unambiguous and non-leading.

The second questionnaire included all statements for which consensus was not reached in the first round. Each Delphi panellist obtained their own score and the average score given by the whole group for the same statement in the previous round.

Delphi panellists

Delphi panellists (haematologists, hospital pharmacists and MM patients involved in MM management) were identified by the Scientific Committee, PETHEMA foundation, SEFH and the Spanish Community of Patients with MM (CEMMp). Participants were invited by e-mail receiving the link of the study, username and password (unique for each participant).

Consensus definition

The definition of consensus was established before data analyses, according to the common criteria.[13] Consensus was reached for each statement when at least 75% of the respondents concurred (*entirely agree, mostly agree or somewhat agree*) or disagreed (entirely disagree, mostly disagree or somewhat disagree).

Data analysis

The percentage of participants who selected each option and percentile distributions (25, 50 and 75) were calculated using STATA statistical software, v14. The percentages described in the text refer to the final scores [score of the round in which consensus was achieved for each question (1st or 2nd), or second round in the event that consensus was not reached].

RESULTS

We performed an in-depth literature search identifying almost 40 outcomes and more than 70 instruments. In fact, the biggest challenge was to choose from the huge variety of variables, especially for PROMs. The whole outcomes, clinical instruments, and 30 PROMs were preselected by the scientific committee. From those, 18 follow-up variables and 21 instruments were included in Delphi consultation after deliberation in discussion groups. The standard set includes 15 follow-up variables and 18 measure instruments.

The number of panellists who participated in the first and second Delphi rounds were, respectively: 51 (20 haematologists, 24 hospital pharmacists and 7 patients) and 45 (18 haematologists, 22 hospital pharmacists and 5 patients).

Condition Scope

The participants in the discussion groups agreed that the patients with newly diagnosed MM would be the target population for the MM Standard Set. This comprised those

patients eligible for autologous stem cell transplantation and those who were not, and covering induction, consolidation and maintenance treatments. Thus, a broad range of stages of the disease and its treatments could be followed by means of active surveillance.

Outcome domains and measures

Survival and disease control

Due to the high mortality rate and short life expectancy of patients with MM, the health professionals who participated in the discussions group pre-selected the following variables: overall survival (OS), progression-free survival (PFS), minimal residual disease (MRD), and response criteria (RC). Treatment efficacy would be measured by the RC according to the International Myeloma Working Group (IMWG). Subsequently, the expert panellists also agreed to include these variables in the MM Standard Set (Table 1).

Table 1. Basal and follow-up variables, instruments and timing for registering them.

Measure	Details/instrument	Timing	Data source
Basal characteristics			
Age	Data of birth	Basal	CD
Gender	Gender (male/female)	Basal	CD
Ethnicity	Race	Basal	CD
Family history	Family history of myeloma or other type of cancer	Basal	CD or PR
ISSr	International staging system (revised)	Basal	CD
Renal failure	Renal failure prior to treatment/ Creatinine clearance	Basal	CD
Anaemia	Anaemia prior to treatment/ haemoglobin	Basal	CD
Bone lesions	Number and location/ X-Ray, PET, etc.	Basal	CD
Neuropathies	Neuropathies prior to treatment	Basal	CD
Comorbidities	Comorbidities and/or other non-related myeloma diseases	Basal	CD
Type of treatment	Type of treatment initiated (standard or not)	After deciding to treat	CD
Survival and disease control			
OS	Overall survival / Data of diagnosis and death	Basal, death	CD or AD
PFS	Progression-free survival/ from treatment initiation to progression or death.	Treatment initiation, progression or death	CD
MRD	Minimal residual disease/ Flow cytometry: 4-8 colours panel	When complete remission was reached	CD
Treatment response	Time for best response, according to the IMWG	Monthly during treatment, and then every 2-3 months	CD
Complications			

Treatment and adverse events	Completed treatment (with or without dosage reduction) and side effects that hamper the patient's daily activities or those that imply changes in the pattern of treatment / Registry	Monthly during treatment, and then every 2-3 months	CD
PROMs and PREMs			
Treatment adherence	Morisky-Green + Dispensing control	At each dispensation	CD or PR
HRQoL	Health related quality of life/ EORTC-QLQ-C30	Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months	PR
Pain	Pain intensity/ EORTC-QLQ-C30 (pain scale) + VAS	VAS: Basal, before treatment, monthly during treatment, and following every 3 months. QLQ-C30: Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months	PR
Performance status	Patients' level of functioning in terms of their ability to care for themselves, daily activity, and physical ability / EORTC-QLQ-C30 (Physical functioning and Role functioning scales) + ECOG	ECOG: Basal, before treatment, monthly during treatment, and following every 3 months. QLQ-C30: Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months	CD and PR
Asthenia/fatigue	Weakness or general asthenia that makes it difficult to perform tasks that are normally done easily / EORTC-QLQ-C30 (Fatigue scale)	Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months.	PR
Psychosocial status	Impact of disease on cognitive, emotional and social skills / EORTC-QLQ-C30 (Emotional functioning, cognitive functioning and social functioning)	Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months.	PR
Symptoms	Intensity of symptoms due to illness or treatment / EORTC-QLQ-C30 (Symptoms scales)	Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months.	PR
Preferences & satisfaction	*Ad-hoc items*	**Preferences**: Prior to first visit **Satisfaction**: After treatment	PR
Body image	Self-perception of body image /EORTC-QLQ-MY20 (Body image scale)	Basal **Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months.	PR
Sexuality	Self-perception on sexual life/	Basal	PR

Adapted from EORTC-QLQ-BR23 (Sexual functioning scale)	**Treatment**: before and after treatment. In continuous and long-term treatments (>6 months), every 2-3 months. **Follow-up/maintenance**: every 6 months.

ISSr, International staging system revised. PET, Positron Emission Tomography. OS, Overall Survival. PFS, progression-free survival. MRD, minimal residual disease. HRQoL, Health-Related Quality of life. VAS, visual analogic scale. CD, clinical data. PR, patient-reported. AD, administrative data.

The panellists also reached consensus regarding the inclusion of the M-protein and plasma cell immunophenotype. However, considering that these variables are instruments integrated in other outcome variables such as ISS or RC, the Scientific Committee agreed to discard them to avoid duplicities and to optimize the set.

Consensus was reached in collecting OS (from diagnosis to death), PFS (from the beginning of the treatment to disease progression or death), MRD (when/if patient achieved complete remission), and treatment response (monthly during treatment and subsequently every 2 or 3 months) (Table 1 and Figure 1).

Complications

Completed treatment and side effects

The participants in the discussion group considered that the side effects of MM treatments were important outcomes since they commonly cause considerable morbidity and low HRQoL in MM patients. [5,14,15] To facilitate data collection, the health professionals proposed a simplified version of the Common Terminology Criteria for Adverse Events (CTCAE) v.4,[16] clustering them into general categories (bone marrow suppression, constitutional, cardiovascular, hepatic, renal, neurological, gastrointestinal, skin, infection, and others). The Delphi panellists agreed to collet each completed treatment (with or without dosage reduction) and those side effects that hamper the patient's daily activities or those that imply changes in the treatment pattern (Table 1). Consensus was achieved to collect this information monthly during treatment and every 2 or 3 months during periods without treatment (Table 1 and Figure 1).

Patient Reported Outcomes and Patient Reported Experiences

Adherence

The Delphi panellists agreed on an adherence multi-measure approach, including the self-reported Morisky-Green questionnaire (4 items) and dispensing control performed by hospital pharmacists in each medication provision.

PROs

HRQoL and other existing PROs identified in the literature (such as pain, functional status, fatigue, symptoms, and psychosocial status) were considered of importance during the discussion groups. Moreover, patients expressed the relevance of their perception of body image and sexuality. The health professionals participating in the discussion groups recommended the European Organization for the Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) as the PROM covering most of these variables. This questionnaire covers the most important domains (general HRQoL, pain, functional status, fatigue, symptoms, psychosocial status) and it is a validated tool that is internationally recognized and available in many languages.[17] The expert participants in the discussion groups were aware that the QLQ-MY20 module[18] or FACT-MM[19] includes questions that specifically target MM aspects. However, trying to balance feasibility of use and essential information, the use of the EORTC-QLQ-C30 questionnaire alone was considered the best balanced choice, since it is widely used for other type of cancer.

The panellists agreed to collect HRQoL, pain, functional status, fatigue, symptoms, and psychosocial status with the EORTC-QLQ-C30 questionnaire. They also agreed to collect self-perception of body image with the Body Image scale (1 item) of the QLQ-MY20 questionnaire, and sexuality by two sexuality items adapted from the EORTC-QLQ-BR23 questionnaire.[20] Furthermore, due to the high relevance of pain intensity and functional status in patients with MM, the panellists agreed to collect them with the EORTC-QLQ-C30 plus other straightforward and rapid tools: the pain Visual Analogic Scale (VAS) and the ECOG test,[21] respectively. Despite the panellists agreeing to collect all these PROMs, there was no consensus as to the feasibility of measuring some of them in routine clinical practice during the next 5 years. Specifically, consensus was not reached for psychosocial status (71.1%), symptoms (73.3%), body image (64.4%) and sexuality (66.7%).

The panellists reached consensus in assessing PROMs at baseline (diagnostic), before and after the treatment, and subsequently every 6 months during follow-

up/maintenance. In continuous and long-term treatments (>6 months), the assessment would be performed every 3 months. The Pain Visual Analogic Scale (VAS) and the ECOG test would be collected in the same time frame than the EORTC-QLQ-C30, and additionally monthly during treatment.

Preference and satisfaction

The Delphi panellists agreed to collect patient preferences and satisfaction. Preferences (about the information they would like to receive and about their preferred role in the decision-making) and satisfaction (about the same questions) will be processed with a short *ad hoc* questionnaire. Whereas preferences will be assessed prior to the first consultation satisfaction will be assessed after treatment.

Nevertheless, consensus about the feasibility of collecting them in routine clinical practice was not reached (73.3%).

Basal characteristics

Considering that baseline clinical and sociodemographic factors are related to both disease control and PROs outcomes,[22,23] participants in the discussion groups perceived their inclusion in Delphi consultation necessary.

The expert panellists agreed to collect age, gender, ethnicity, family history and stage of the disease. Regarding the latter, consensus was reached to use the revised International Staging System (rISS) for MM, recently proposed by the IMWG as a simple and powerful prognostic staging system for newly-diagnosed MM.[23] However, due to the current barriers that exist in some centres to accurately detect chromosomal abnormalities, the panellists agreed to use the traditional ISS in these cases. In addition, it was agreed to collect renal failure, anaemia, bone lesions, neuropathies and comorbidities not associated to MM before treatment initiation, since disease progression and treatment toxicity could alter these issues during the follow-up. All basal characteristics that reached consensus are listed in Table 1.

DISCUSSION

Healthcare systems are currently experiencing a critical shift in their model towards a patient-centred system.[6] However, value-based healthcare has to deal with barriers such as the absence of standardized outcomes that are meaningful for patients,[24] which hampers the comparison of results between providers, physicians and regions.

Standardization favours simplicity and minimizes variations allowing comparing results, at the same time as aligning all different collectives involved in the management of MM towards a common goal: to improve healthcare quality. At present, there are no commonly accepted standards for defining the optimal outcome parameters for use in patients with MM. A minimum Standard Set of important outcomes for MM patients could help to improve healthcare quality, supporting informed decision-making, and reducing healthcare costs.

In recent years, several initiatives led by the ICHOM have developed Standard Sets of health outcomes for a wide variety of diseases including prostate cancer, breast cancer, lung cancer, coronary artery diseases, stroke, Parkinson, hip and knee osteoarthritis dementia and depression.[11] Recently, some institutions and registries that measure health outcomes such as Ramsay Healthcare, Fortis Healthcare and Mayo Clinic, have started a second phase implementing some of these Standard Sets.[25] Some promising early results concerning these implementations have been recently published. The use of the Cleft lip and palate Standard Set at the Erasmus University Medical Centre in the Netherlands has shown a high compliance with the proposed measures (90-100%) and good positive feedback from both patients and clinicians.[26] The implementation of a Standard Set for Parkinson's disease at Aneurin Bevan University Health Board in south Wales showed similar results after optimizing the electronic forms.[27] Another example is the use of the ICHOM Standard Set for coronary artery disease implemented in the Coronary Angiogram Database of South Australia (CADOSA). This initiative has allowed the standardization of procedures for percutaneous coronary intervention among hospitals, increasing radial access and reducing bleeding-related complications.[28]

To our knowledge, our project is the first initiative to carry out a standardization process for MM. We performed an in-depth literature search identifying almost 40 outcomes and more than 70 instruments. In fact, the biggest challenge was to choose from the huge variety of variables, especially for PROMs. HRQoL is particularly relevant for MM patients taking into account that many of them, especially the older ones, consider HRQoL even more important than overall survival.[29] During the discussion groups, patients also recommended the inclusion of self-perception of body image and sexuality, which are usually evaluated in routine clinical practice for other malignant diseases such as breast cancer but not for MM. Regarding to the recording of treatment

adherence, consensus was achieved. It could be thought that treatment for serious diseases present high rates of adherence. However, it is important to note that nonadherence to oral drugs could be really low,[30] leading to suboptimal drug efficacy, poor clinical outcomes and increased healthcare costs.[31]

The minimum set of standardized outcome measures was compiled from the perspectives of more than 50 participants, including expert health professionals (haematologists and hospital pharmacists) and patients with MM. The broad consensus reached is the main strength of this study. However, a number of limitations remain present. Although most of the selected instruments are validated, the set as a whole has not been, which is one of the main limitations of the present study. In addition, the Standard Set is derived from expert consensus rather than high levels of evidence. Moreover, new therapies have risen the mean overall survival to 6-7 years [4]. Thus, develop an outcome set covering all disease stages, and not only those targeting newly diagnosed patients, would be interesting for future work.

These recommendations represent an initial approach for collecting a minimum Standard Set of outcomes for MM management. Nonetheless, future steps should be taken to validate the Standard Set and refine it towards a global standard. We are aware that the burden of answering all proposed items at each interval could be significant for some patients. Likewise, data input could represent an additional workload for health professionals. In fact, when holding discussion groups, health professionals were of the opinion that its acceptance could be associated with the time-consuming process. In this sense, an electronic questionnaire directly filled in by patients and the easy inclusion of the results in their medical history could guarantee broad acceptance. In addition, future computer-adaptive PROMs would decrease respondent burden[31] and smartphone or telehealth surveys would pave the way towards piloting inexpensive forms of digital data collection.[2] In this sense, the feasibility of the MM Standard Set should be evaluated via a pilot study using the Set in routine clinical practice.

SUMMARY

It has been defined a minimum recommended set of consensus outcomes, including clinical and PROs, to be collected for patients with MM in routine clinical practice. The use of this standard set would allow learning from each other through meaningful

comparison, helping to improve MM management and developing a quality and cost-effective patient-centred healthcare system.

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Contributor ship statement

BJ, CMA, LJJ and PJL coordinated the project, assisted in the identification of participants, and was involved in design of study, construction of the Delphi questionnaire, interpretation of results, and critically reviewed the manuscript for important intellectual content. LL designed the study, was involved in the construction of the Delphi questionnaire, interpretation of results, and drafted the manuscript. dPHD was involved in data collection, data analysis and critically reviewed the manuscript.

Conflict of interest statement

The authors declare no conflicts of interest.

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Data sharing statement

No additional unpublished data from the study are available.

FIGURES

Figure 1. Timeline illustrating when the key outcomes should be collected.

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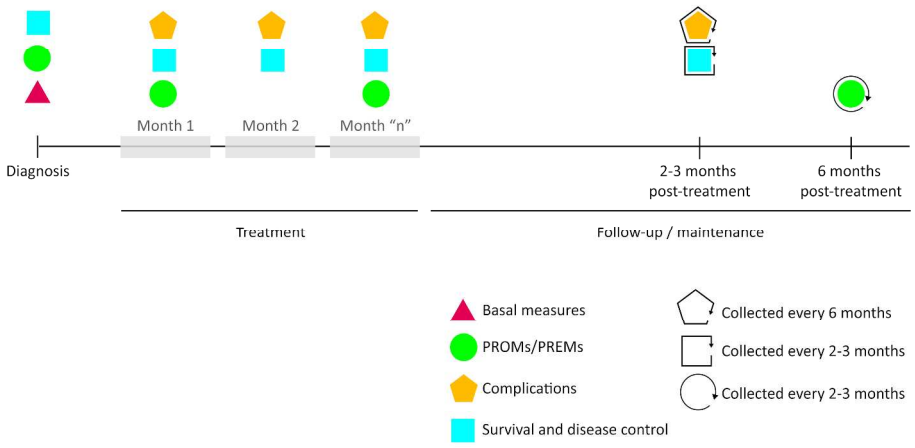

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