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

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Complete List of Authors:	Blade, Joan; Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Hematology Department Calleja, Miguel Angel; Hospital Virgen Macarena, Pharmacy Department Lahuerta, Juan Jose; Hospital 12 de Octubre, Hematology Department Poveda, Jose Luis; Hospital Universitario y Politécnico La Fe, Pharmacy Department de Paz, Hector David; Outcomes'10 Lizan Tudela, Luis; Outcomes 10,
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3 **DEFINING A SET OF STANDARDIZED OUTCOME MEASURES IN**
4 **MULTIPLE MYELOMA. THE IMPORTA PROJECT.**
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7 **Blade Joan ^a, Calleja Miguel Ángel ^b, Lahuerta Juan José ^c, Poveda José Luis ^d, de**
8 **Paz Héctor David ^e, Lizán Luis ^{e*}**
9

10
11 5 ^a Hematology Department, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi I
12 Sunyer (IDIBAPS), Barcelona, Spain.

13
14 ^b Pharmacy Department, Hospital Virgen Macarena, Sevilla, Spain.

15
16 ^c Hematology Department, Hospital 12 de Octubre, Madrid, Spain.

17
18 ^d Pharmacy Department, Hospital Universitario y Politécnico La Fe, Valencia, Spain.

19
20
21 10 ^e Outcomes'10, Castellón, Spain.

22
23 * Corresponding author: Outcomes'10. Jaume I university. Parc Científic Tecnològic i
24 Empresarial Edificio Espaitec 2, Avda. Sos Baynat s/n, 12071, Castellón, Spain. E-mail address:
25 lizan@outcomes10.com. Telephone number: 0034 964 831 997
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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.

45 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]

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3 In collaboration with the Spanish Society of Hospital Pharmacies (SEFH) and the
4 Spanish Program for Haematology Treatments foundation (PETHEMA), we aim to
5 cover the existing needs defining a set of global standards for collecting outcomes that
6 matter most to patients with MM, and select a proper instrument for the measurement of
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10 80 these outcomes.

11 **METHODS**

12 **Scientific Committee**

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15 A Scientific Committee led and coordinated the project. It consisted of five highly
16 qualified experts in MM: two haematologists and two hospital pharmacists with
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19 85 extensive experience in MM, and one patient with MM. They were chosen on the basis
20 of their longstanding expertise in MM management.
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23 **Literature review**

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25 A literature search was performed to identify clinical outcomes and PROs, and
26 instruments to measure them used in clinical practice for the management and follow-up
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29 90 of MM patients. The search included original articles, systematic reviews and clinical
30 practice guidelines published in English or Spanish between January 2010 and October
31 2015. The information obtained in the literature review was used to steer five discussion
32 groups.
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36 **Discussion groups**

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39 95 The objective of the discussion groups was to share experiences and opinions about
40 outcome variables, definitions, measures of relevance, and to establish the target
41 population, in order to designate the consensual outcomes. Haematologists and
42 pharmacists covered all topics (clinical and PROs), whilst patients covered only PROs.
43 From March to April 2016, different discussion groups were held: three with
44 haematologists (n=4) and hospital pharmacists (n=4), and two with patients with MM
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47 100 (n=7). Patients were divided in two groups of 3 and 4 people to facilitate discussion
48 about their perspective of general MM management and PROs.
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52 The information obtained in the discussion groups was used to design the Delphi
53 questionnaire.
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55 **Delphi consultation**

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3 A national 2-round Delphi consultation was conducted to establish consensus regarding
4 the most important outcome variables and their proper measurements for managing
5 MM. The Delphi technique is a structured process that consists of the application of
6 subsequent questionnaires in a series of rounds in which the group's responses to one
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10 110 round are used to produce the questionnaire for the next round, providing feedback to
11 respondents in each consecutive round [12].
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13 *Contents of the Delphi consultation: first and second questionnaires*

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16 Four groups of categories were addressed in the first questionnaire: basal variables of
17 sociodemographic and clinical characteristics (9 issues), follow-up clinical variables (6
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19 115 issues), follow-up treatment variables (1 issue) and follow-up PROMs and patient
20 reported experience measure (PREMs) variables (10 issues). Affirmative statements
21 assessed the participants' perception related to outcome suitability and feasibility for
22 use in routine clinical practice (within a 5-year period), on a 7-point Likert scale (from 1
23 = in total disagreement; to 7 = in total agreement). The scientific committee reviewed
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27 120 the questionnaire to ensure that the statements were clear, unambiguous and non-
28 leading.
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31 The second questionnaire included all statements for which consensus was not reached
32 in the first round. Each Delphi panellist obtained their own score and the average score
33 given by the whole group for the same statement in the previous round.
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36 125 *Delphi panellists*

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39 Delphi panellists (haematologists, hospital pharmacists and MM patients involved in
40 MM management) were identified by the Scientific Committee, PETHEMA foundation,
41 SEFH and the Spanish Community of Patients with MM (CEMMp). Participants were
42 invited by e-mail receiving the link of the study, username and password (unique for
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46 130 each participant).
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48 *Consensus definition*

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50 The definition of consensus was established before data analyses, according to the
51 common criteria.[13] Consensus was reached for each statement when at least 75% of
52 the respondents concurred (*entirely agree, mostly agree or somewhat agree*) or
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56 135 disagreed (*entirely disagree, mostly disagree or somewhat disagree*).
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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

1				
2				
3	Family history	Family history of cancer or myeloma	Basal	CD or PR
4	ISSr	International staging system (revised)	Basal	CD
5	Renal failure	Renal failure prior to treatment/ Creatinine clearance	Basal	CD
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7				
8				
9	Anaemia	Anaemia prior to treatment/ haemoglobin	Basal	CD
10	Bone lesions	Number and location/ X-Ray, PET, etc.	Basal	CD
11	Neuropathies	Neuropathies prior to treatment	Basal	CD
12	Comorbidities	Comorbidities and/or other non-related myeloma diseases	Basal	CD
13	Type of treatment	Type of treatment initiated (standard or not)	After deciding to treat	CD
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3	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
4				
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8	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
9				
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13	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
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19	Preferences & satisfaction	<i>Ad-hoc items</i>	Preferences: Prior to first visit Satisfaction: After treatment	PR
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21	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
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27	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
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165 *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.*

170 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.

175 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

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3 180 and low HRQoL in MM patients. [5,14,15] To facilitate data collection, the health
4 professionals proposed a simplified version of the Common Terminology Criteria for
5 Adverse Events (CTCAE) v.4,[16] clustering them into general categories (bone
6 marrow suppression, constitutional, cardiovascular, hepatic, renal, neurological,
7 gastrointestinal, skin, infection, and others). The Delphi panellists agreed to collect each
8 completed treatment (with or without dosage reduction) and those side effects that
9 hamper the patient's daily activities or those that imply changes in the treatment pattern
10 (Table 1). Consensus was achieved to collect this information monthly during treatment
11 and every 2 or 3 months during periods without treatment (Table 1 and Figure 1).
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19 *Patient Reported Outcomes and Patient Reported Experiences*

20 *Adherence*

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

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31 195 HRQoL and other existing PROs identified in the literature (such as pain, functional
32 status, fatigue, symptoms, and psychosocial status) were considered of importance
33 during the discussion groups. Moreover, patients expressed the relevance of their
34 perception of body image and sexuality. The health professionals participating in the
35 discussion groups recommended the European Organization for the Research and
36 Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) as the PROM
37 covering most of these variables. This questionnaire covers the most important domains
38 (general HRQoL, pain, functional status, fatigue, symptoms, psychosocial status) and it
39 is a validated tool that is internationally recognized and available in many
40 languages.[17] The expert participants in the discussion groups were aware that the
41 QLQ-MY20 module[18] includes questions that specifically target MM aspects.
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48 However, trying to balance applicability vs. essential information, and considering that
49 the QLQ-MY20 module adds little information in terms of predicting utility values,[19]
50 the use of the EORTC-QLQ-C30 questionnaire alone was considered the best balanced
51 choice.
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3 210 The panellists agreed to collect HRQoL, pain, functional status, fatigue, symptoms, and
4 psychosocial status with the EORTC-QLQ-C30 questionnaire. They also agreed to
5 collect self-perception of body image with the Body Image scale (1 item) of the QLQ-
6 MY20 questionnaire, and sexuality by two sexuality items adapted from the EORTC-
7 QLQ-BR23 questionnaire.[20] Furthermore, due to the high relevance of pain intensity
8 and functional status in patients with MM, the panellists agreed to collect them in
9 combination with other straightforward and rapid tools: the pain Visual Analogic Scale
10 (VAS) and the ECOG test,[21] respectively. Despite the panellists agreeing to collect all
11 these PROMs, there was no consensus as to the feasibility of measuring some of them
12 in routine clinical practice during the next 5 years. Specifically, consensus was not
13 reached for psychosocial status (71.1%), symptoms (73.3%), body image (64.4%) and
14 sexuality (66.7%).
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24 The panellists reached consensus in assessing PROMs at baseline (diagnostic), before
25 and after the treatment, and subsequently every 6 months during follow-
26 up/maintenance. In continuous and long-term treatments (>6 months), the assessment
27 would be performed every 3 months. The Pain Visual Analogic Scale (VAS) and the
28 ECOG test would be collected in the same time frame, and monthly during treatment.
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33 *Preference and satisfaction*

34 The Delphi panellists agreed to collect patient preferences and satisfaction. Preferences
35 (about the information they would like to receive and about their preferred role in the
36 decision-making) and satisfaction (about the same questions) will be processed with a
37 short *ad hoc* questionnaire. Whereas preferences will be assessed prior to the first
38 consultation satisfaction will be assessed after treatment.
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44 Nevertheless, consensus about the feasibility of collecting them in routine clinical
45 practice was not reached (73.3%).
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48 **Basal characteristics**

49 Considering that baseline clinical and sociodemographic factors are related to both
50 disease control and PROs outcomes,[22,23] participants in the discussion groups
51 perceived their inclusion in Delphi consultation necessary.
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55 The expert panellists agreed to collect age, gender, ethnicity, family history and stage of
56 the disease. Regarding the latter, consensus was reached to use the revised International
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3 Staging System (rISS) for MM, recently proposed by the IMWG as a simple and
4 powerful prognostic staging system for newly-diagnosed MM.[23] However, due to the
5 current barriers that exist in some centres to accurately detect chromosomal
6 abnormalities, the panellists agreed to use the traditional ISS in these cases. In addition,
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10 245 it was agreed to collect renal failure, anaemia, bone lesions, neuropathies and
11 comorbidities not associated to MM before treatment initiation, since disease
12 progression and treatment toxicity could alter these issues during the follow-up. All
13 basal characteristics that reached consensus are listed in Table 1.
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16 17 **DISCUSSION**

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19 250 Healthcare systems are currently experiencing a critical shift in their model towards a
20 patient-centred system.[6] However, value-based healthcare has to deal with barriers
21 such as the absence of standardized outcomes that are meaningful for patients,[24]
22 which hampers the comparison of results between providers, physicians and regions.
23 Standardization favours simplicity and minimizes variations allowing comparing
24 results, at the same time as aligning all different collectives involved in the management
25 of MM towards a common goal: to improve healthcare quality. At present, there are no
26 commonly accepted standards for defining the optimal outcome parameters for use in
27 patients with MM. A minimum Standard Set of important outcomes for MM patients
28 could help to improve healthcare quality, supporting informed decision-making, and
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35 260 reducing healthcare costs.
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45 265 In recent years, several initiatives led by the ICHOM have developed Standard Sets of
46 health outcomes for a wide variety of diseases including prostate cancer, breast cancer,
47 lung cancer, coronary artery diseases, stroke, Parkinson, hip and knee osteoarthritis
48 dementia and depression.[11] Recently, some institutions and registries that measure
49 health outcomes such as Ramsay Healthcare, Fortis Healthcare and Mayo Clinic, have
50 started a second phase implementing some of these Standard Sets.[25] Some promising
51 early results concerning these implementations have been recently published. The use of
52 the Cleft lip and palate Standard Set at the Erasmus University Medical Centre in the
53 Netherlands has shown a high compliance with the proposed measures (90-100%) and
54
55 270 good positive feedback from both patients and clinicians.[26] The implementation of a
56 Standard Set for Parkinson's disease at Aneurin Bevan University Health Board in
57 south Wales showed similar results after optimizing the electronic forms.[27] Another
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3 example is the use of the ICHOM Standard Set for coronary artery disease implemented
4 in the Coronary Angiogram Database of South Australia (CADOSA). This initiative has
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6 275 allowed the standardization of procedures for percutaneous coronary intervention
7 among hospitals, increasing radial access and reducing bleeding-related
8 complications.[28]
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11 To our knowledge, our project is the first initiative to carry out a standardization process
12 for MM. We performed an in-depth literature search identifying almost 40 outcomes
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14 280 and more than 70 instruments. In fact, the biggest challenge was to choose from the
15 huge variety of variables, especially for PROMs. HRQoL is particularly relevant for
16 MM patients taking into account that many of them, especially the older ones, consider
17 HRQoL even more important than overall survival.[29] During the discussion groups,
18 patients also recommended the inclusion of self-perception of body image and
19
20 285 sexuality, which are usually evaluated in routine clinical practice for other malignant
21 diseases such as breast cancer but not for MM. Regarding to the recording of treatment
22 adherence, consensus was achieved. It could be thought that treatment for serious
23 diseases present high rates of adherence. However, it is important to note that
24 nonadherence to oral drugs could be really low,[30] leading to suboptimal drug efficacy,
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26 290 poor clinical outcomes and increased healthcare costs.[31]
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29 The minimum set of standardized outcome measures was compiled from the
30 perspectives of more than 50 participants, including expert health professionals
31 (haematologists and hospital pharmacists) and patients with MM. The broad consensus
32 reached is the main strength of this study. However, a number of limitations remain
33
34 295 present. Although most of the selected instruments are validated, the set as a whole has
35 not been, which is one of the main limitations of the present study. In addition, the
36 Standard Set is derived from expert consensus rather than high levels of evidence.
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39 These recommendations represent an initial approach for collecting a minimum
40 Standard Set of outcomes for MM management. Nonetheless, future steps should be
41
42 300 taken to validate the Standard Set and refine it towards a global standard. We are aware
43 that the burden of answering all proposed items at each interval could be significant for
44 some patients. Likewise, data input could represent an additional workload for health
45 professionals. In fact, when holding discussion groups, health professionals were of the
46 opinion that its acceptance could be associated with the time-consuming process. In this
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3 305 sense, an electronic questionnaire directly filled in by patients and the easy inclusion of
4 the results in their medical history could guarantee broad acceptance. In addition, future
5 computer-adaptive PROMs would decrease respondent burden[31] and smartphone or
6 telehealth surveys would pave the way towards piloting inexpensive forms of digital
7 data collection.[2] In this sense, the feasibility of the MM Standard Set should be
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11 310 evaluated via a pilot study using the Set in routine clinical practice.
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13 **SUMMARY**

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15 It has been defined a minimum recommended set of consensus outcomes, including
16 clinical and PROs, to be collected for patients with MM in routine clinical practice. The
17 use of this standard set would allow learning from each other through meaningful
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21 315 comparison, helping to improve MM management and developing a quality and cost-
22 effective patient-centred healthcare system.
23

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25
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28
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32 their contribution in the discussion groups.
33

34 **Contributor ship statement**

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38
39 325 BJ, CMA, LJJ and PJL coordinated the project, assisted in the identification of
40 participants, and was involved in design of study, construction of the Delphi
41 questionnaire, interpretation of results, and critically reviewed the manuscript for
42 important intellectual content. LL designed the study, was involved in the construction
43 of the Delphi questionnaire, interpretation of results, and drafted the manuscript. dPHD
44 was involved in data collection, data analysis and critically reviewed the manuscript.
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46
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48 330 **Conflict of interest statement**

49
50 The authors declare no conflicts of interest.
51

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55 foundation (PETHEMA) and the Spanish Society of Hospital Pharmacies (SEFH).
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58 335 **Data sharing statement**

No additional unpublished data from the study are available.

For peer review only

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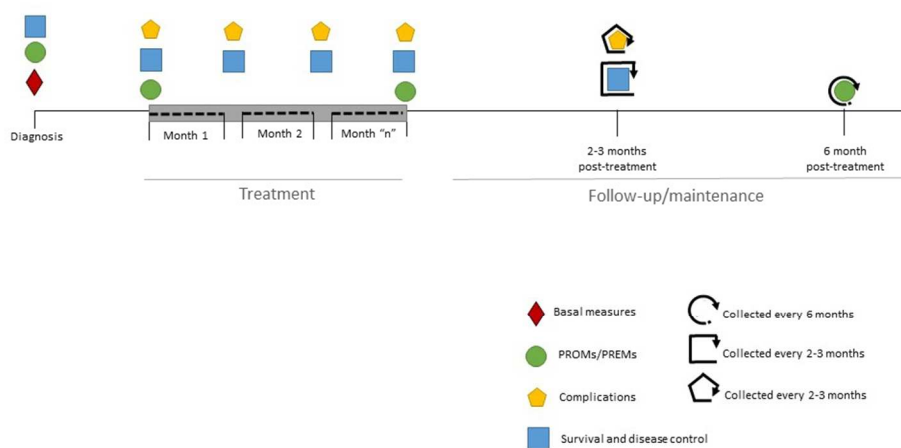


Figure 1. Timeline illustrating when the key outcomes should be collected.

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BMJ Open

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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8 **Blade Joan ^a, Calleja Miguel Ángel ^b, Lahuerta Juan José ^c, Poveda José Luis ^d, de**
9 **Paz Héctor David ^e, Lizán Luis ^{e*}**
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11

12 ^a Hematology Department, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi I
13 Sunyer (IDIBAPS), Barcelona, Spain.
14

15 ^b Pharmacy Department, Hospital Virgen Macarena, Sevilla, Spain.
16
17

18 ^c Hematology Department, Hospital 12 de Octubre, Madrid, Spain.
19

20 ^d Pharmacy Department, Hospital Universitario y Politécnico La Fe, Valencia, Spain.
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22 ^e Outcomes'10, Castellón, Spain.
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24

25 * Corresponding author: Outcomes'10. Jaume I university. Parc Científic Tecnològic i
26 Empresarial Edificio Espaitec 2, Avda. Sos Baynat s/n, 12071, Castellón, Spain. E-mail address:
27 lizan@outcomes10.com. Telephone number: 0034 964 831 997
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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

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

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6 • Although most of the selected instruments are validated, the set as a whole has not
7 been.
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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]

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3 In collaboration with the Spanish Society of Hospital Pharmacies (SEFH) and the
4 Spanish Program for Haematology Treatments foundation (PETHEMA), we aim to
5 cover the existing needs defining a set of global standards for collecting outcomes that
6 matter most to patients with MM, and select a proper instrument for the measurement of
7 these outcomes.
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10 11 **METHODS**

12 The study comprised three phases: (1) Literature review; (2) Discussion groups; (3)
13 Delphi consultation.
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16 17 **Scientific Committee**

18 A Scientific Committee led and coordinated the project. It consisted of five highly
19 qualified experts in MM: two haematologists and two hospital pharmacists with
20 extensive experience in MM, and one patient with MM. They were chosen on the basis
21 of their longstanding expertise in MM management.
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27 28 **Literature review**

29 A literature search was performed to identify clinical outcomes and PROs, and
30 instruments to measure them used in clinical practice for the management and follow-up
31 of MM patients. The search included original articles, systematic reviews and clinical
32 practice guidelines published in English or Spanish between January 2010 and October
33 2015. The information obtained in the literature review was used to steer five discussion
34 groups. Presetting of instruments was done by the scientific committee considering the
35 availability of a validated version in the Spanish population, the level of evidence
36 (Oxford CEBM Levels of Evidence) of the reviewed studies and their agreement of its
37 utilization (according to bibliography references). Consensus of $\frac{3}{4}$ was necessary for
38 inclusion.
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46 47 **Discussion groups**

48 The objective of the discussion groups was to share experiences and opinions about
49 outcome variables, definitions, measures of relevance, and to establish the target
50 population, in order to designate the consensual outcomes. Haematologists and
51 pharmacists covered all topics (clinical and PROs), whilst patients covered only PROs.
52 Outcomes and instruments were appraised according to their use in the Spanish routine
53 clinical practice (expert opinion), the simplicity of completion, and the grade of
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3 disease's impact on the variables from patient's view. From March to April 2016,
4 different discussion groups were held: three with haematologists (n=4) and hospital
5 pharmacists (n=4), and two with patients with MM (n=7). Patients were divided in two
6 groups of 3 and 4 people to facilitate discussion about their perspective of general MM
7 management and PROs.
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11 The information obtained in the discussion groups was used to design the Delphi
12 questionnaire.
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15 Variables and instruments that achieved consensus for their inclusion ($\frac{3}{4}$) and those
16 controversial ($\frac{1}{2}$), were included in Delphi consultation.
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19 20 **Delphi consultation**

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22 A national 2-round Delphi consultation was conducted to establish consensus regarding
23 the most important outcome variables and their proper measurements for managing
24 MM. The Delphi technique is a structured process that consists of the application of
25 subsequent questionnaires in a series of rounds in which the group's responses to one
26 round are used to produce the questionnaire for the next round, providing feedback to
27 respondents in each consecutive round [12].
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30 31 *Contents of the Delphi consultation: first and second questionnaires*

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33 Four groups of categories were addressed in the first questionnaire: basal variables of
34 sociodemographic and clinical characteristics (9 issues), follow-up clinical variables (6
35 issues), follow-up treatment variables (1 issue) and follow-up PROMs and patient
36 reported experience measure (PREMs) variables (10 issues). Affirmative statements
37 assessed the participants' perception related to outcome suitability and feasibility for
38 use in routine clinical practice (within a 5-year period), on a 7-point Likert scale (from 1
39 = in total disagreement; to 7 = in total agreement). The scientific committee reviewed
40 the questionnaire to ensure that the statements were clear, unambiguous and non-
41 leading.
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45 The second questionnaire included all statements for which consensus was not reached
46 in the first round. Each Delphi panellist obtained their own score and the average score
47 given by the whole group for the same statement in the previous round.
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50 51 *Delphi panellists*

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

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

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

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35 We performed an in-depth literature search identifying almost 40 outcomes and more
36 than 70 instruments. In fact, the biggest challenge was to choose from the huge variety
37 of variables, especially for PROMs. The whole outcomes, clinical instruments, and 30
38 PROMs were preselected by the scientific committee. From those, 18 follow-up
39 variables and 21 instruments were included in Delphi consultation after deliberation in
40 discussion groups. The standard set includes 15 follow-up variables and 18 measure
41 instruments.
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48 The number of panellists who participated in the first and second Delphi rounds were,
49 respectively: 51 (20 haematologists, 24 hospital pharmacists and 7 patients) and 45 (18
50 haematologists, 22 hospital pharmacists and 5 patients).
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54 **Condition Scope**

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

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3	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
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7				
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9	PROMs and PREMs			
10	Treatment adherence	Morisky-Green + Dispensing control	At each dispensation	CD or PR
11	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
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17	Pain	Pain intensity/ EORTC-QLQ-C30 (pain scale) + VAS	<u>VAS:</u> Basal, before treatment, monthly during treatment, and following every 3 months. <u>QLQ-C30:</u> 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
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25	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	<u>ECOG:</u> Basal, before treatment, monthly during treatment, and following every 3 months. <u>QLQ-C30:</u> 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
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33	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
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39	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
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44	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
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50	Preferences & satisfaction	<i>Ad-hoc items</i>	Preferences: Prior to first visit Satisfaction: After treatment	PR
51	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
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57	Sexuality	Self-perception on sexual life/	Basal	PR
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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 collect 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

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

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10 HRQoL and other existing PROs identified in the literature (such as pain, functional
11 status, fatigue, symptoms, and psychosocial status) were considered of importance
12 during the discussion groups. Moreover, patients expressed the relevance of their
13 perception of body image and sexuality. The health professionals participating in the
14 discussion groups recommended the European Organization for the Research and
15 Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) as the PROM
16 covering most of these variables. This questionnaire covers the most important domains
17 (general HRQoL, pain, functional status, fatigue, symptoms, psychosocial status) and it
18 is a validated tool that is internationally recognized and available in many
19 languages.[17] The expert participants in the discussion groups were aware that the
20 QLQ-MY20 module[18] or FACT-MM[19] includes questions that specifically target
21 MM aspects. However, trying to balance feasibility of use and essential information, the
22 use of the EORTC-QLQ-C30 questionnaire alone was considered the best balanced
23 choice, since it is widely used for other type of cancer.
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35 The panellists agreed to collect HRQoL, pain, functional status, fatigue, symptoms, and
36 psychosocial status with the EORTC-QLQ-C30 questionnaire. They also agreed to
37 collect self-perception of body image with the Body Image scale (1 item) of the QLQ-
38 MY20 questionnaire, and sexuality by two sexuality items adapted from the EORTC-
39 QLQ-BR23 questionnaire.[20] Furthermore, due to the high relevance of pain intensity
40 and functional status in patients with MM, the panellists agreed to collect them with the
41 EORTC-QLQ-C30 plus other straightforward and rapid tools: the pain Visual Analogic
42 Scale (VAS) and the ECOG test,[21] respectively. Despite the panellists agreeing to
43 collect all these PROMs, there was no consensus as to the feasibility of measuring some
44 of them in routine clinical practice during the next 5 years. Specifically, consensus was
45 not reached for psychosocial status (71.1%), symptoms (73.3%), body image (64.4%)
46 and sexuality (66.7%).
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55 The panellists reached consensus in assessing PROMs at baseline (diagnostic), before
56 and after the treatment, and subsequently every 6 months during follow-
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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.

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3 Standardization favours simplicity and minimizes variations allowing comparing
4 results, at the same time as aligning all different collectives involved in the management
5 of MM towards a common goal: to improve healthcare quality. At present, there are no
6 commonly accepted standards for defining the optimal outcome parameters for use in
7 patients with MM. A minimum Standard Set of important outcomes for MM patients
8 could help to improve healthcare quality, supporting informed decision-making, and
9 reducing healthcare costs.
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15 In recent years, several initiatives led by the ICHOM have developed Standard Sets of
16 health outcomes for a wide variety of diseases including prostate cancer, breast cancer,
17 lung cancer, coronary artery diseases, stroke, Parkinson, hip and knee osteoarthritis
18 dementia and depression.[11] Recently, some institutions and registries that measure
19 health outcomes such as Ramsay Healthcare, Fortis Healthcare and Mayo Clinic, have
20 started a second phase implementing some of these Standard Sets.[25] Some promising
21 early results concerning these implementations have been recently published. The use of
22 the Cleft lip and palate Standard Set at the Erasmus University Medical Centre in the
23 Netherlands has shown a high compliance with the proposed measures (90-100%) and
24 good positive feedback from both patients and clinicians.[26] The implementation of a
25 Standard Set for Parkinson's disease at Aneurin Bevan University Health Board in
26 south Wales showed similar results after optimizing the electronic forms.[27] Another
27 example is the use of the ICHOM Standard Set for coronary artery disease implemented
28 in the Coronary Angiogram Database of South Australia (CADOSA). This initiative has
29 allowed the standardization of procedures for percutaneous coronary intervention
30 among hospitals, increasing radial access and reducing bleeding-related
31 complications.[28]
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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

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3 adherence, consensus was achieved. It could be thought that treatment for serious
4 diseases present high rates of adherence. However, it is important to note that
5 nonadherence to oral drugs could be really low,[30] leading to suboptimal drug efficacy,
6 poor clinical outcomes and increased healthcare costs.[31]
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10 The minimum set of standardized outcome measures was compiled from the
11 perspectives of more than 50 participants, including expert health professionals
12 (haematologists and hospital pharmacists) and patients with MM. The broad consensus
13 reached is the main strength of this study. However, a number of limitations remain
14 present. Although most of the selected instruments are validated, the set as a whole has
15 not been, which is one of the main limitations of the present study. In addition, the
16 Standard Set is derived from expert consensus rather than high levels of evidence.
17 Moreover, new therapies have risen the mean overall survival to 6-7 years [4]. Thus,
18 develop an outcome set covering all disease stages, and not only those targeting newly
19 diagnosed patients, would be interesting for future work.
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22 These recommendations represent an initial approach for collecting a minimum
23 Standard Set of outcomes for MM management. Nonetheless, future steps should be
24 taken to validate the Standard Set and refine it towards a global standard. We are aware
25 that the burden of answering all proposed items at each interval could be significant for
26 some patients. Likewise, data input could represent an additional workload for health
27 professionals. In fact, when holding discussion groups, health professionals were of the
28 opinion that its acceptance could be associated with the time-consuming process. In this
29 sense, an electronic questionnaire directly filled in by patients and the easy inclusion of
30 the results in their medical history could guarantee broad acceptance. In addition, future
31 computer-adaptive PROMs would decrease respondent burden[31] and smartphone or
32 telehealth surveys would pave the way towards piloting inexpensive forms of digital
33 data collection.[2] In this sense, the feasibility of the MM Standard Set should be
34 evaluated via a pilot study using the Set in routine clinical practice.
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49 SUMMARY

50 It has been defined a minimum recommended set of consensus outcomes, including
51 clinical and PROs, to be collected for patients with MM in routine clinical practice. The
52 use of this standard set would allow learning from each other through meaningful
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3 comparison, helping to improve MM management and developing a quality and cost-
4 effective patient-centred healthcare system.
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8
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16 **Contributor ship statement**

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18 BJ, CMA, LJJ and PJJ coordinated the project, assisted in the identification of
19 participants, and was involved in design of study, construction of the Delphi
20 questionnaire, interpretation of results, and critically reviewed the manuscript for
21 important intellectual content. LL designed the study, was involved in the construction
22 of the Delphi questionnaire, interpretation of results, and drafted the manuscript. dPHD
23 was involved in data collection, data analysis and critically reviewed the manuscript.
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30 **Conflict of interest statement**

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32 The authors declare no conflicts of interest.
33

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37 foundation (PETHEMA) and the Spanish Society of Hospital Pharmacies (SEFH).
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40 **Data sharing statement**

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42 No additional unpublished data from the study are available.
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FIGURES

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

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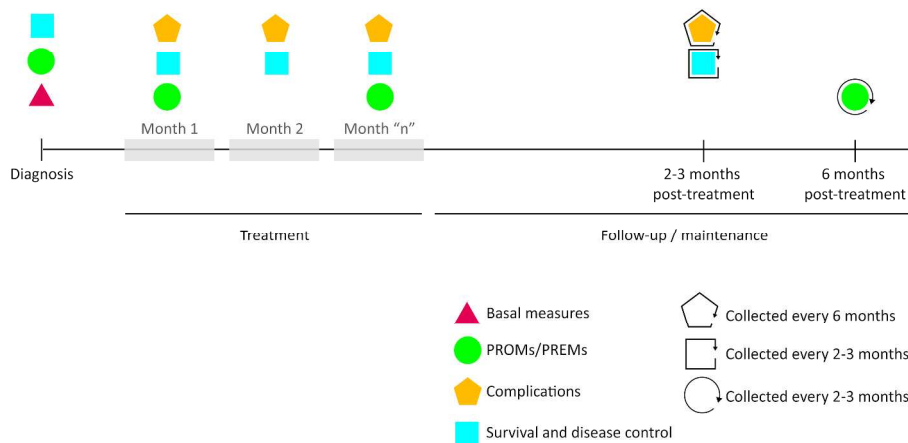
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