Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative (SISAQOL-IMI): stakeholder views, objectives, and procedures

DOI:
10.1016/S1470-2045(23)00157-2

Document Version
Accepted author manuscript

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Total number of words: 4397

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms *("patient reported outcome analysis") OR ("quality of life analysis") AND "cancer" AND "clinical trials"*. No date restrictions were included. Articles were also identified through searches of the authors' own files and recommendations by the SISAQOL-IMI Consortium. Only papers published in English were reviewed. The search was conducted on July 9, 2021. The final reference list was generated based on originality and relevance to the broad scope of this Review.

Abstract (150 words unstructured summary)
Patient-reported outcomes (PROs), such as symptoms, functioning and other health-related quality of life concepts are gaining a more prominent role in the benefit/risk assessment of cancer therapies. However, varying ways of analysing, presenting and interpreting PRO data may lead to erroneous and inconsistent decisions on the part of stakeholders, adversely impacting patient care and outcomes. The *Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials - Innovative Medicines Initiative* (SISAQOL-IMI) Consortium builds on the existing SISAQOL work to establish recommendations on design, analysis, presentation, and interpretation for PRO data in cancer clinical trials. This paper presents an expanded set of topics and international stakeholder views on the need for SISAQOL-IMI, the agreed upon prioritized set of PRO objectives to focus on, and the roadmap to ensure that international consensus recommendations will be achieved.

Funding
The SISAQOL-IMI project has received funding from the Innovative Medicines Initiative (IMI) 2 Joint Undertaking under grant agreement No 945052. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Introduction

Patient-reported outcomes (PROs) are any outcome evaluated directly by the patient and based on the patient's perception of a disease and its treatment(s).[1] PROs is an umbrella term covering both single- and multi-dimensional measures of symptoms, functioning, and other health-related quality of life concepts. These PRO concepts are gaining a more prominent role in the benefit/risk assessment and relative effectiveness assessments of cancer therapies. Although various stakeholders are increasingly adopting the use of PROs in their decision-making,[2] evidence from systematic reviews has consistently shown the lack of standards and guidance on how PRO data are collected, analysed, presented and interpreted in cancer randomized clinical trials (RCTs).[3-8] Inconsistent and, at times, inappropriate PRO design, data collection, analysis and interpretation puts into question the reliability and robustness of PRO data, which in turn reduces the ability of PRO data to inform the overall risk or benefit assessment of cancer treatments.

Recommendations for handling PROs now exist for protocols (Standard Protocol Items: Recommendations for Interventional Trials-PRO extension; SPIRIT-PRO),[9,10] publications to improve reporting of PROs (Consolidated Standards of Reporting Trials Statement-PRO extension; CONSORT-PRO)[11] and for graphically displaying PRO data.[12] These and other methodologic guidance documents, as well as resources to aid in their use, are available at the PROTEUS Consortium (www.TheProteusConsortium.org). These reporting guidelines are essential since they provide key information to allow evaluation of the design and analysis used to inform PRO.[13] In addition to reporting guidelines, it is equally important that evidence-based and harmonized methodological standards are set so that PRO data from cancer clinical trials are analysed, presented and interpreted appropriately, PRO results are reproducible, and to ensure that PRO data can inform patient safety, treatment choices and policy decisions in a meaningful and reliable way.[13]

The need to improve the methodological quality of PRO design, collection, analysis and interpretation in cancer clinical trials was initially recognized by the prior "Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data" (SISAQOL) initiative, which ran from 2016 to 2020. The first "edition" of SISAQOL addressed the challenges in the analysis and interpretation of PROs in cancer randomised controlled trials (RCTs).[14] Key to this initiative was

ensuring that the recommendations remained relevant across different types of PRO measures and incorporated the perspectives from various international stakeholders, including regulators, health technology assessment (HTA) bodies, industry and academic representatives, clinicians, methodological and applied statisticians, PRO experts, and patient representatives. The first SISAQOL Consortium completed their initial work and published international consensus recommendations for PRO data analysis in RCTs in 2020.[15] These recommendations are also in line with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 (R1) estimand framework of defining clear clinical study objectives to align with the study design, endpoint, and analysis.[16]

SISAQOL-IMI

The demand for better standards on the design and analysis of cancer clinical trials with PRO data has been further highlighted by a recent call of the Innovative Medicines Initiative (IMI).[17] The IMI Joint Undertaking (JU) is a public-private partnership (PPP) between the European Union (EU), represented by the European Commission (EC), and the European Federation of Pharmaceutical Industries and Associations (EFPIA).[18,19] IMI's aim is to address unmet needs in drug development that can be efficiently resolved within a pre-competitive space through multidisciplinary, multi-stakeholder collaborations. This specific IMI call emphasized the need to establish international standards and extend coverage in the analysis of PRO data, such as symptom and functional outcomes, in cancer clinical trials. IMI envisions that such standards will not only support the use of PRO data for optimal drug development and device approval by regulators and HTA bodies, but also help better communicate PRO results between clinicians and patients for the purposes of shared decision-making.[17] It is worth noting that SISAQOL-IMI is not about the development and validation of patient-reported outcomes, which are available in other sources.[20-24]

Recommendations from the first SISAQOL Consortium provided the initial step towards generating international consensus-based standards for the design and analysis of PRO data in RCTs. Based on the first SISAQOL Consortium, the original participants joined new collaborators to respond to the IMI call in 2019. Knowledge and experience gained from prior work was leveraged with the goal to continue to

advance international consensus recommendations on PRO data analyses. The new Consortium is referred to as SISAQOL-IMI (see Appendix 3 Figure 1 on page 25 for the development from SISAQOL to SISAQOL-IMI).

The aim of SISAQOL-IMI is to develop recommendations on the design, analysis, presentation and interpretation of PRO data considering the estimand framework[25] that address the needs of the entire spectrum of stakeholders. This is achieved by bringing together an extensive collection of international experts to collaborate and agree on a set of PRO data analysis recommendations (see Table 1 for a full list of organizations involved in SISAQOL-IMI). These stakeholder groups include academics, industry, non-profit/cancer organisations, small to mid-size enterprises or contract research organisations (CRO), regulators, HTA bodies, and patients' representatives.

Moreover, SISAQOL-IMI builds on the first SISAQOL Consortium effort by harmonising and updating available recommendations based on stakeholder needs and recent developments in the methodological literature. SISAQOL-IMI will also broaden its scope by not only developing recommendations for the design and analysis of PRO data within RCTs, but also exploring the feasibility of recommendations for non-RCTs (with a specific focus on single-arm studies), improving presentation of PRO results and producing guidance on how to define clinically meaningful differences. Using case studies, validation or testing work will also be done for these newly developed recommendations, specifically in assessing whether these recommendations are understandable and feasible to implement in protocols and statistical analysis plans in cancer clinical trials.

To ensure that these goals are achieved, the project is organised into five scientific work packages (WPs), and three cross-cutting WPs (see Appendix 3 Figure 2 on page 25 for the project structure and interaction between the WPs). The scientific WPs will focus on developing recommendations that are of high methodological quality; whereas the cross-cutting WPs will ensure that the output of the various SISAQOL-IMI scientific WPs remain cohesive and harmonised, that the consensus process is transparent, and the final SISAQOL-IMI consensus-based recommendations address the needs of the various stakeholder groups.

Although individual stakeholders have broad guidelines on the use of PROs in cancer clinical trials,[26-31] a harmonised set of standards that are methodologically

rigorous, practical and feasible to implement is needed. This can improve confidence that conclusions based on PRO data from cancer clinical trials are reliable, replicable, robust, interpretable, and clinically meaningful. Similar to the first SISAQOL Consortium, SISAQOL-IMI recommendations are intended to be generalisable to all validated PRO measures. Figure 1 in Appendix 3 on page 25 presents the workflow towards developing the final SISAQOL-IMI recommendations.

Need for SISAQOL-IMI: Views from stakeholder groups

During the SISAQOL-IMI kick-off meeting in March 2021, representatives from various SISAQOL-IMI stakeholder groups (clinicians, patients, academic, industry, regulatory and HTA bodies) presented their views on the current use of PROs and their expectations from the SISAQOL-IMI recommendations. Although stakeholders presented different views on the use of PROs for treatment decision-making, participants agreed that PRO data can be as important as other common clinical endpoints (e.g., overall survival, progression free survival) and they also provide complementary information to clinician-reported outcomes. However, standards and guidance for PRO data analysis in cancer clinical trials are needed to facilitate its use in stakeholder decision-making.

From *the clinicians' and patients' perspective*, it is essential that PRO data are collected in cancer clinical trials and analyzed optimally so that they can have information, directly from patients themselves, on the impact of cancer treatments on how patients feel and function. The analysis, presentation and interpretation of results should clearly highlight not only statistical significance, but also patient benefit and risk since these data may be used for the assessment of the overall clinical benefit of cancer treatments (e.g., see European Society for Medical Oncology-Magnitude of Clinical Benefit Scale[32]) and will have real-world impact on clinician-patient communication regarding treatment decisions.[26]

Academic and industry representatives discussed the many challenges when including PROs in the design of cancer clinical trials. The complexity of clinical trial development increases when PRO endpoints are added. This includes aligning PROs with other (primary) clinical endpoints, designing the timing of PRO data collection, selecting appropriate analyses, handling intercurrent events (e.g., death and treatment discontinuation[16,25]) and missing data, and ensuring accurate communication and interpretation of PRO findings. These challenges have hindered

the optimal use of PROs in clinical trials. SISAQOL-IMI is expected to help address these hurdles by providing recommendations for standardizing each of the aforementioned aspects of rigorously incorporating PROs in a clinical trial setting. Having such recommendations can help to focus on stakeholder needs, reduce patient burden and “research waste” by ensuring efficiency of PRO data collection and producing results based on meaningful analyses that will be useful for patient and other stakeholder decision-making.

Finally, r*egulators and HTA* bodies touched upon the issues they face when evaluating PRO data submitted by sponsors (trialists). For example, submissions often lack a clear PRO research objective, PROs are often positioned as exploratory endpoints, and there can be large amounts of missing PRO data, putting into question the robustness and reliability of the PRO data to inform the benefit and risks of cancer therapies. For this stakeholder group, the need for SISAQOL-IMI is to improve the standards of assessing PROs in cancer clinical trials by informing design, data collection and analysis practices so that PRO data can be fully considered in regulatory and HTA decision-making.

Work scope of SISAQOL-IMI: Setting PRO research objective priorities

Defining clear PRO objectives for cancer clinical trials has been a challenging task. PRO objectives in cancer clinical trials tend to be vague (e.g., to demonstrate that health-related quality of life is better with Treatment A than with Treatment B), leading to the use of varied analysis methods and producing seemingly conflicting PRO findings.[14] Therefore, as a starting point, the SISAQOL-IMI Consortium agreed on the importance of creating a priority set of PRO research objectives for which to evaluate and develop design and analysis recommendations. The taxonomy of PRO research objectives developed by the first SISAQOL Consortium was used to achieve this goal.

Prior to the SISAQOL-IMI kick-off meeting, each of the 41 organizations within the SISAQOL-IMI Consortium was presented with a series of PRO objectives previously identified by the first SISAQOL Consortium in a survey (see Appendix 1 for the survey questions). Each organization was encouraged to consult with various internal experts to produce a single response. To ensure that the patient voice is well-represented in the Consortium, the Workgroup of European Cancer Patient

Advocacy Networks (WECAN) is one of the organizations in SISAQOL-IMI. WECAN is an umbrella organization representing 23 Pan-European cancer patient organisations. The views and responses of these patient networks are coordinated by Myeloma Patients Europe (MPE) and are sent in as a single response to the survey.

A PRO research objective was identified as high priority if at least two-thirds of the organization representatives responded “yes”. An objective was identified as low priority if less than half of the representatives responded “yes” on the PRO objective. A statement was “for discussion” if it did not meet the high or low priority criteria. Organization representatives who responded “don’t know” for a specific objective were not included in the denominator when calculating percent agreement.

An overall summary of the agreed high priority broad PRO objectives and endpoints is presented in the next sections below and a plain language version summary can be found on the project website as PowerPoint Presentation with voice-over narration, https://www.sisaqol-imi.org (see Appendix 4 for the slides). However, it should be noted that when developing a consensus position, reaching 100% agreement among the Consortium members is not always possible. Even if there is high level of agreement and a statement is accepted by two-thirds majority, there might be stakeholders with substantive concerns or different views which need to be considered. Additionally, the number of organizations representing each stakeholder group differ and stakeholder groups which are less represented may be underrepresented in the voting results.

To address these concerns, a diverging views document was drafted and agreed upon by all Consortium members (see Appendix 2). In addition to the overall results of the priority setting, more detailed results on the level of agreement by stakeholder group are also provided. Tables 2 and 3 presents the overall results of the priority setting of PRO research objectives and initial stakeholder concerns and views on these objectives for RCTs and single arm studies, respectively. Tables 4 and 5 describe in more detail the level of agreement by stakeholder group for each PRO research objective and endpoint.

[INSERT TABLE 2, 3, 4 and 5 HERE]

Descriptive/exploratory PRO objectives. For both RCTs (32/39, 82% of survey participants that responded to this question) and single-arm studies (36/41, 88%), it

was considered high priority to develop standards for descriptive PRO objectives (i.e., describing PRO data without drawing confirmatory conclusions; no hypothesis testing is conducted). Currently, many trials include PROs as descriptive / exploratory objectives, in addition to other primary or secondary endpoints. Given the lack of recommendations, the quality of the collected data tends to be substandard (e.g., high rates of missing data) and there is a risk of selective reporting. Other non-PRO trial data is often presented descriptively (e.g., CTCAE safety data, dose modifications, etc.), and the goal of SISAQOL-IMI is to improve the design, analysis, presentation, and interpretation of all PRO data, including descriptive objectives. This will ensure that the gathered data are not wasted; instead, the data can be used to reliably describe the patient perspective regarding treatment and inform the decisions of various stakeholders.

***Confirmatory PRO objectives (superiority and equivalence/non-inferiority**).* For RCTs, it was considered high priority to develop recommendations about the design and analysis of confirmatory PRO objectives, in which PRO data can be used to draw conclusions about treatment efficacy/clinical benefit. Conclusions about treatment efficacy/clinical benefit can be achieved either by demonstrating that the treatment arm is superior (40/41, 98%) or equivalent/non-inferior (38/40, 95%) to the control arm. The clear distinction between superiority and equivalent/non-inferiority as a PRO objective is critical. This will help avoid drawing conclusions about equivalence/non-inferiority from a statistical test addressing a PRO superiority objective. Instead, PRO non-inferiority/equivalence objectives require pre-specification of meaningful non-inferiority/equivalence margins.[166] The goal of SISAQOL-IMI is to ensure that, when PROs are included as confirmatory objectives (i.e., the aim is to either conclude superiority or equivalence/non-inferiority of the treatment arm relative to the control arm), the standards for the design, analysis, presentation and interpretation of PRO data are on the same level as other clinical endpoints.

PRO endpoint: Magnitude of change at specific time point(s) and response patterns/profiles over a specified time frame. The aim of these two endpoints is to assess the level of change at a specific time point (time as discrete) or time frame (time as continuous) for a specific PRO domain. These endpoints require pre-specifying clinically relevant thresholds at the group level. Magnitude of change and

response patterns/profiles (whether measured as change scores or as severity levels) were considered as high priority PRO endpoints for RCTs (magnitude of change: 37/40, 93%; response patterns/profiles: 31/34, 91%) and for single-arm studies (magnitude of change: 33/38, 87%; response patterns/profiles: 28/36, 78%). Divergence in recommendations is expected for the time element; that is, whether time is considered discrete or continuous will have an impact on the design and analysis of these endpoints. For magnitude of change at specific time point(s), initial stakeholder views highlighted the importance of the choice of the relevant time points and defining a clinically relevant change/difference for both superiority and non-inferiority objectives. For response patterns/profiles over a specified time frame, concerns were raised regarding the feasibility of developing a pre-defined hypothesis to implement this endpoint for a confirmatory objective, and that this endpoint may be more useful in a descriptive setting.

Time to improvement and Time to worsening. The aim of these two PRO endpoints is to evaluate the time it takes before a clinically relevant improvement (or worsening) is observed. For PRO domains or items that tend to be more susceptible to change, additional information on sustained improvement (or worsening) will be relevant to describe the change (e.g., duration of improvement or worsening). These two endpoints require pre-specifying a clinically meaningful improvement (or worsening) at the patient level. Time to improvement and time to worsening were considered as high priority for both RCTs (time to improvement: 32/37, 86%; time to worsening: 37/40, 93%) and single-arm studies (time to improvement: 30/39, 77%; time to worsening: 31/38, 82%). Although these two PRO endpoints have differing within-treatment assumptions (i.e., whether an improvement or worsening is expected among the patients), when formulating recommendations, they will be evaluated together because both rely on time to event design and analysis assumptions. Initial stakeholder views indicated concerns regarding the implementation of this endpoint, including defining a clinically relevant PRO event (improvement or worsening), the need for prolonged relatively high frequency of assessments, lack of standards on how intercurrent events such as death would be addressed, and the difficulty in interpreting the resulting treatment estimates. Additionally, this endpoint assumes that if all patients are followed up long enough, they will eventually experience an improvement (time to improvement) or worsening (time to worsening) on that specific PRO domain.

Responder improvement and responder worsening at specific time point(s). The aim of these two PRO endpoints is to identify the number of patients with an improvement (or worsening) at a specific time point for a specific PRO domain. These endpoints require pre-specifying a meaningful improvement (or worsening) at the patient level. Responder improvement and responder worsening were considered as high priority for both RCTs (responder improvement: 34/38, 89%; responder worsening: 31/37, 84%) and single-arm studies (responder improvement: 30/38, 79%; responder worsening: 26/36, 72%). Similar to the time to event outcomes, when formulating recommendations for responder analyses, these two PRO endpoints will be evaluated together since both rely on similar design and analysis assumptions. Initial stakeholder views highlighted the importance of the choice of relevant time points and defining a clinically meaningful responder (improvement/worsening). Whether the responder will be defined based on an absolute value or change scores needs to be considered.

Overall average/median over a specified time frame and area under the curve over a specified time frame. The aim of these two PRO endpoints is to summarize all available scores for a specific PRO measure over a pre-specified time frame into a single data point per patient (either the average/median or area under the curve). Pre-defined clinically relevant thresholds at the group level are needed to aid interpretation of these endpoints. Overall average/median over a specified time frame and area under the curve over a specified time frame were considered as high priority for RCTs (overall average/median: 27/34, 79%; area under the curve: 32/35, 91%), but not for single-arm studies (overall average/median: 22/33, 67%; area under the curve: 21/35, 60%). When formulating recommendations, these two endpoints will be evaluated together since they are both summary measures that rely on similar design and analysis assumptions. Initial stakeholder views indicated concerns regarding the interpretation of these two endpoints. That is, different patterns of observed PRO assessments may lead to similar AUC or average scores, which may make the interpretation of these endpoints challenging. An added concern if it is used in single-arm trials, it becomes even more difficult to interpret in the absence of a control group.

Procedure of SISAQOL-IMI: Developing consensus recommendations

A critical part of SISAQOL-IMI will be to ensure recommendations for the prioritized objectives and endpoints are based on consensus and address the needs of relevant, key stakeholder groups. Since the goal of SISAQOL-IMI is to improve standards, it is critical that the consensus recommendations balance high methodological quality and feasibility.

Many researchers agree that no design and statistical method exists that can address all concerns. The choice of design and statistical methods is always a balance between feasibility, usefulness, and robustness, and is highly dependent on the study aims. Therefore, SISAQOL-IMI will ensure that the strengths and limitations of each recommendation will be specified based on evidence from the methodological literature, and that deviations from recommendations are acceptable with justification.

Based on literature reviews and expert discussions, the WPs will generate lists of recommendation statements that consortium members will review and provide feedback on via surveys. Five consensus meetings will be held where results will be presented and discussed with all SISAQOL-IMI members. During the planned consensus meetings, SISAQOL-IMI members will agree on recommendation statements through a defined consensus process. According to the rules agreed on by the SISAQOL-IMI Consortium, a proposed statement is accepted if at least two-thirds of the voters agreed on the statement. A statement is rejected if less than half of the voters agreed on the statement. A statement is postponed or noted for discussion if it does not meet the agreement or rejection criteria, or if it is agreed by the consortium that more discussion is needed. Even if there is high level of agreement and a statement is accepted by two-thirds majority, there might be stakeholders with substantive concerns or different views. To address these various views whilst maintaining the notion of consensus, the SISAQOL-IMI Consortium will note where readers should take into consideration that individual organizations might have different views on specific recommendations given their institutional or stakeholder standpoint. To this purpose, for each *accepted* recommendation, together with the percentage agreement, the other diverging views will be included under “considerations”. In addition, a table showing percentage agreement by stakeholder group will be presented to inform readers about which stakeholder group might have a different position on a given recommendation statement. Finally,

SISAQOL-IMI will provide concrete reasons when recommendation statements do not reach consensus for standards of methodological quality. For more details on this, see the diverging views document in Appendix 2.

To ensure that the consensus recommendation statements have external validity, three independent processes will be implemented by the SISAQOL-IMI Consortium. A *scientific work package* aims to independently validate the recommendation statements by assigning “blinded members” (i.e., SISAQOL-IMI organizations will assign this task to colleagues who are not involved in the development of the recommendations) to test the feasibility of implementing the recommendations and to provide feedback on the formulation of the recommendation statements. Blinded members will be given tasks with respect to writing a study protocol, the statistical analysis plan (SAP), and the visualization and presentation of results. They will be asked to complete these tasks making use of the recommendations. An *independent scientific advisory board* has been set-up to provide independent and critical review of the scientific quality of the recommendations. Finally, based on discussions with the European Medicines Agency (EMA), submission of SISAQOL-IMI outputs or recommendations for *qualification advice or opinion for novel methodologies* at EMA are being pursued. All these independent processes occur during the lifetime of the SISAQOL-IMI project to ensure that feedback from external experts and stakeholders are considered in the final SISAQOL-IMI recommendation statements.

Critical to the work of SISAQOL-IMI is the involvement of patients, caregivers and patient representatives in the development of these recommendations. This stakeholder group has a deep understanding and experience with the disease and treatment. They provide valuable insight into the research questions to be asked (research objectives), study design (timing and frequency of assessments) and interpretation of PRO findings (meaning to patients and their families). Their contribution will help make the SISAQOL-IMI recommendations relevant and meaningful to the patient experience.

Since all recommendations from SISAQOL-IMI are based on a multi-stakeholder consensus process, the proposed recommendation statements for the consensus meetings and the final recommendations should be interpretable by stakeholders with statistical and non-statistical backgrounds. To achieve this objective, different

experts (statisticians, methodologists, PRO experts, clinicians, patients, and caregivers and patient representatives) are included in the process of developing these recommendations. To facilitate discussion among the stakeholders and to ensure harmonised terminology across WPs, an extensive glossary with both scientific and plain-language terminology and definitions will be developed alongside the consensus statements.

Two final consensus recommendation documents will be developed: (1) a technical document with an integrated technical/statistical section for statisticians and similar stakeholders who will need to execute or review the design, collection, analysis, and written/visual data interpretations, and (2) a plain-language version that can be used by the patient, caregiver, and clinical communities to facilitate interpretation and communication of the technical document and support the communication between users with different levels of statistical/technical expertise. This will allow parallel discussions at different statistical/technical levels and safeguard the importance of having recommendations that are understandable and meaningful to stakeholders irrespective of their statistical knowledge and methodological background.

Conclusion

The aim of SISAQOL-IMI is to improve how PROs are used in cancer clinical trials by developing a consensus-based set of best practice recommendations for the design, collection, analysis, presentation and interpretation of PRO endpoints. The SISAQOL-IMI kick-off meeting was attended by all 41 SISAQOL-IMI organizations, representing various international stakeholder groups. Views from this meeting demonstrated the shared interest and commitment of the different organizations in improving standards for PRO endpoints in cancer clinical trials. A set of priority PRO objectives was agreed upon, for which SISAQOL-IMI will develop recommendations by the end of 2024. By the time that this manuscript has been completed, SISAQOL-IMI already had a second consensus meeting and agreed on their first set of recommendations. This (virtual) meeting was attended by all 41 organizations, showing a strong commitment to complete this work. A third consensus meeting is already planned for 2023. A separate manuscript will be drafted to present these recommendations by the end of 2024.

Continuing from the initial achievement of the first SISAQOL Consortium, these recommendations will contribute to the optimal use and understanding of the role of PRO measures in academic research, drug development, and approval of therapies by regulators and reimbursement decisions by HTA bodies. Having standards set for the use of PROs in cancer clinical trials will address the need to have more robust evidence on the impact of cancer treatments on patients' symptoms, functioning and general health related quality of life. This will also subsequently facilitate communication on benefits and risks of various cancer therapies by expanding existing information. Finally, it is also worth noting that some of the recommendations of SISAQOL-IMI are likely to applicable to other therapeutic areas, beyond oncology.

Contributors

All authors are members of the SISAQOL-IMI Steering Committee and were involved in the conceptualisation of this manuscript. M.Pe, A. Alanya, R. S.Falk, C.D. Amdal, K. Bjordal collected and analysed the data. M.Pe led in the drafting of the first version of the manuscript, with support from A. Alanya, R. S.Falk, C.D. Amdal, K. Bjordal A. Bottomley and I. Griebsch. All authors interpreted and reviewed the manuscript. All 41 organizations involved in SISAQOL-IMI (see member list in the on behalf of SISAQOL-IMI) reviewed and approved the final version of this manuscript.

Declaration of interests

This publication reflects the views of the individual authors and should not be construed to represent official views or policies of the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), US National Cancer Institute (NCI), Medicines and Healthcare products Regulatory Agency (MHRA), Institute for Quality and Efficiency in Health Care (IQWiG), Health Canada, the Norwegian Medicines Agency (NOMA), the American Society of Clinical Oncology (ASCO) or the European Society for Medical Oncology (ESMO) or any other institution, organization, or entity. This publication reflects the authors' view and that neither IMI nor the EU, EFPIA are responsible for any use that may be made of the information contained therein.

SR is a current employee of Pfizer Inc and ex-employee of Novartis Pharma; JC, PC, and JR are current employees of Pfizer. All other authors declare no competing interests. VP is a current employee of EMD Serono. MS is a current employee of Merk, IG is a current employee of EMD Serono. GV had received consulting fees, payment from or were related to the following organizations Pfizer, Eisai, Roche, Novartis, Astra Zeneca, Sanofi, Seattle Genetics, EORTC QoL Group, EORTC Board. KO's organization has received sponsorship funding/grants for various of our annual programmes/activities from the following companies: Bristol-Myers Squibb, Novocure, Pfizer, Bayer, Novartis, Northwest Biotherapeutics, Karyopharm, MagForce, Medac, Photonamic, Apogenix, Elekta, GW Pharmaceuticals/Jazz Pharmaceuticals, consulting fees from Bristol-Myers Squibb and Novartis, honoraria from Sanofi, Sharing Progress in Cancer Care and Seagen. KO participated in an advisory board for Novartis, Novocure, Seagen, Eisai, BMS, Sanofi and undertook leadership roles in a number of organizations.

This study received no funding from the US National Institutes of Health (NIH). No other authors were fully or partly NIH funded, employed by NIH, or are in receipt of an NIH grant for this work.

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TABLES

Table 1. SISAQOL-IMI Consortium members

Stakeholder Group	Organisations (alphabetical order)	Country
Academic (n=17)		
	Amsterdam UMC	NL
	Clinical Hospital Center Rijeka	HR
	Complejo Hospitalario de Navarra	ES
	Duke University School of Medicine	US
	Institut Hospital del Mar d'Investigacions Mèdiques	ES
	Johns Hopkins University (representing PROTEUS and PRO Data Presentation Stakeholder Group)	US
	Katholieke Universiteit Leuven	BE
	Leiden University Medical Center	NL
	Medical University of Innsbruck	AT
	Oslo University Hospital	NO
	Region Hovedstaden	DK
	The Symptoms Tool Executive Committee of the University of Texas MD Anderson Cancer Center (The Texas Group)	US
	University Health Network	CA
	University of Birmingham	UK
	University of Freiburg	DE
	University of Ghent	BE
	University of Leeds	UK
Industry (n=5)		
	AbbVie	US/DE
	Bayer	US/DE

	Boehringer Ingelheim	DE
	Merck Healthcare KGaA/EMD Serono	DE/US
	Pfizer	US/UK
Non-profit/Cancer organizations (n=8)		
	American Society of Clinical Oncology	US
	Critical Path Institute	US
	European Organisation for Research and Treatment of Cancer	BE
	European Society for Medical Oncology	CH
	National Cancer Center Hospital (Japan Clinical Oncology Group)	JP
	National Cancer Institute	US
	Queen's University at Kingston (CCTG)	CA
	University of Sydney (Sydney Quality of Life Office)	AU
Small to mid-size enterprise (SME)/Contract research organization (CRO) (n=4)		
	Adelphi Values	UK
	Evaluation Software Development	AT
	Modus Outcomes	FR
	Patient Relevant Evidence	US
Regulatory (n=4)		
	European Medicines Agency	EU (NL)
	Health Canada	CA
	Medicines and Healthcare products Regulatory Agency	UK
	US Food and Drug Administration	US
Health technology assessment (HTA) (n=2)		
	Institute for Quality and Efficiency in Health Care	DE
	Norwegian Medicines Agency	NO
Patients’ representative (n=1)		

	Myeloma Patients Europe (on behalf of the Workgroup of European Cancer Advocacy Networks – WECAN consisting of 23 Pan-European cancer patient organisations.)	BE

Table 2.

Results from Priority Setting of PRO Objectives/Endpoints for RCTs (n = 41)

	Randomized controlled trial			Initial views from different SISAQOL-IMI members
"Would you or your organisation consider using…"	Yes, n	No, n	Yes, %*	
Clinical benefit/treatment efficacy objective (confirmatory: superiority) *Definition:* to demonstrate that based on a PRO domain, the treatment group is superior to (or better than) the reference group by a clinically relevant treatment effect size	40	1	98	• Superiority PRO objective can be used for a primary or secondary endpoint but its assessment and interpretation in conjunction with other clinical endpoints should be considered. Justification should be provided. For example: PROs can be used to differentiate treatments (demonstrate superiority) in a non-inferiority RCT where the primary endpoint is progression free survival. • No significant difference in a superiority objective does not imply equivalence or non-inferiority. • Standards for PRO design and analyses should be treated in the same standard as other survival or response endpoints (e.g., should indicate potential sources of biases and how this is minimized, define what a validated endpoint is, pre-planned in the Statistical Analysis Plan [hierarchical testing], be objectively measured [validated PRO measure for the patient population]). • Scores and differences from the PRO endpoints should be interpretable (e.g., what does a 10 point difference mean?). Both statistical significance and clinically meaningful difference is critical for drawing comparative conclusions on PROs (control for type 1 error should be considered, implications for sample size calculation, what is a clinically meaningful difference?).
Clinical benefit/treatment efficacy objective (confirmatory: equivalence/non-inferiority) *Definition:* to demonstrate that based on a PRO domain, the treatment group is similar (equivalent) or not worse (non-inferior) than the reference group by a pre-specified clinically relevant margin	38	2	95	• Non-inferiority/equivalence PRO objective can be used for a primary or secondary PRO endpoint but its assessment and interpretation in conjunction with other clinical endpoints should be considered. Justification should be provided. • Ensure that the PRO measure is valid and reliable for the target population and is responsive to change. • Ensure that non-inferiority / equivalence margins are pre-specified.

Descriptive objective (exploratory/descriptive) *Definition:* to present PRO findings but no comparative conclusions between treatment arms will be drawn	32	7	82	• PROs are often used as descriptive objectives with the idea that this can complement primary and secondary clinical objectives. • Descriptive / exploratory objectives lack adequate rigor and does not allow for comparison of PRO results between groups. There are concerns about the robustness of the data generated, lack of pre-defined hypothesis (including validated instruments) and analysis of PRO endpoints. • Improving standards on how PROs are analysed even for descriptive / exploratory is needed to allow better use of this data (e.g., data must be of high quality).
Time to improvement *Definition:* the time it takes before a clinically relevant improvement from a PRO domain is observed within a pre-specified timeframe.	32	5	86	• This objective assumes that if all patients are followed up long enough, they will experience an improvement. Therefore, this can be used if the expected assumption is that patients will improve in that PRO domain (e.g., patients undergoing primary curative therapy with acute toxicity or trials where the goal is to alleviate patients' symptoms). This objective may not be appropriate for early diagnosis with minimal symptoms (where no improvement in symptoms is expected) or for patients with poor prognosis (where an improvement is not expected). • Additional information on sustained improvement will be relevant to describe this endpoint (e.g., duration of the improvement) since PRO concepts and symptoms may be more volatile relative to other clinical endpoints (e.g., death or PFS). The relative proportion of responders would also be important to report for each arm (similar to time to response for other clinical endpoints). • Defining a clinically meaningful event (improvement) is important. • General design and statistical issues for time to event objectives need to be addressed. This endpoint may require relatively frequent assessments over a potentially long period of time.
Time to worsening *Definition:* the time it takes before a clinically relevant worsening from a PRO domain is observed within a pre-specified timeframe	37	3	93	• Time to worsening is a common endpoint in cancer clinical trials since the expectation is that patients tend to worsen over time for various PRO domains and symptoms (e.g., due to toxicity). It is highly relevant for cancers with poor prognosis where maintaining functioning will be the main goal. This endpoint can capture the start of experiencing a (symptom/domain) worsening. • This may also be a more relevant objective because worsening signals the end of the period of sufficient favourable effects [of a medicine] for a patient. It is therefore closely related to important favourable effects that determine the magnitude of benefits of a medicine (e.g., duration of response). • Additional information on sustained worsening will be relevant to describe this endpoint (e.g., duration of the worsening) since PRO domains and symptoms may be more volatile relative to other clinical endpoints (e.g., death or PFS). • Defining a clinically meaningful event (worsening) is important.

				• General design and statistical issues for time to event objectives need to be addressed. This endpoint may require relatively frequent assessments over a potentially long period of time.
Time to stable state *Definition:* After observing a clinically relevant change from baseline (either worsening or improvement) from a PRO domain, the time it takes before the PRO domain returns to its baseline value (i.e., no change from baseline or as change from baseline within the predefined baseline margin)	21	11	66	• Time to stable state is not often seen as an endpoint in cancer clinical trials. However, this may be relevant in contexts where patients may experience a deterioration from their baseline state, but it will be temporary (e.g., if patients have good functioning at baseline, or minimal symptoms; and the expectation is that patients will experience a temporary deterioration, and they will go back to baseline after the deterioration). • Currently the definition will measure the stable state after patients have improved or worsened, which will be hard to interpret. • If time to stable state is used, this may no longer be a comparison of randomized groups because this endpoint assumes that patients have to experience a change (e.g., worsen) before one can measure the event, "time to stable state". Non responders (those who do not change) will be excluded from analyses. • Defining a clinically meaningful event (stable state) is important. • General design and statistical issues for time to event objectives need to be addressed. This endpoint may require relatively frequent assessments over a potentially long period of time.
Time to end of stable state *Definition:* The time it takes until the stable state ends or time until a clinically relevant improvement or worsening from a PRO domain is observed.	14	12	54	• Currently, the definition implies ending the stable state by both improvement and worsening, which will be hard to interpret. • This endpoint may be difficult to implement in cancers with poor prognosis because of the short disease duration (less frequent assessments). • Time to improvement and time to worsening could also address this objective. • Additional information on sustained "end of stable state" will be relevant to describe this endpoint (e.g., duration of the worsening) since PRO concepts and symptoms may be more volatile relative to other clinical endpoints (e.g., death or PFS). • Defining a clinically meaningful event (end of stable state) is important. • General design and statistical issues for time to event objectives need to be addressed. This endpoint may require relatively frequent assessments over a potentially long period of time.
Magnitude of change at specific time point(s) *Definition:* The actual value or change from baseline value for a PRO domain at pre-defined time points	37	3	93	• Defining the relevant timepoint would imply making an assumption on when an improvement or worsening will happen across patients. • Defining a clinically relevant change/difference for both superiority and non-inferiority objectives will be critical (e.g., MID) for this endpoint. • Whether the absolute value or change scores will be used as data needs to be taken into account.

Responder with improvement at specific time point(s) *Definition:* Whether the value (or change from baseline value) from a PRO domain at a specific time point reaches a pre-defined improvement threshold or not	34	4	89	• Defining the relevant timepoint would imply making an assumption on when an improvement or worsening will happen across patients. • Defining a clinically meaningful responder (improvement) is important. • This can be used for supportive information for a clinical finding and support interpretation for other PRO endpoints (e.g., magnitude of change or time to event endpoints). • Is there a possibility to include stable state in the definition of improvement (i.e., patients who did not worsen)?
Responder with worsening at specific time point(s) *Definition:* Whether the value (or change from baseline value) from a PRO domain at a specific time point reaches a pre-defined worsening threshold or not.	31	6	84	• Defining the relevant timepoint would imply making an assumption on when an improvement or worsening will happen across patients. • Defining a clinically meaningful responder (worsening) is important. • This can be used for supportive information for a clinical finding and support interpretation for other PRO endpoints (e.g., magnitude of change or time to event endpoints).
Responder with stable state at specific time point(s) *Definition:* Whether the value (or change from baseline value) from a PRO domain at a specific time point remains within a pre-defined baseline margin or not.	19	12	61	• This may be relevant for trials where the goal is "maintenance of a specific PRO domain". • Defining the relevant timepoint would imply making an assumption on when stable state will happen across patients. • Defining a meaningful responder (stable state) is important. • This can be used for supportive information for a clinical finding and support interpretation for other PRO endpoints (e.g., magnitude of change or time to event endpoints). • When interpreting results for stable state alone (responder) this will imply merging patients who improved and worsened into one category (non-responders). • It may be more meaningful to report descriptively improved/stable/worsened by time point (rather than just stable state). • The focus of interpretation is usually the number of patients who improved or worsened, rather than those who remained stable. • Is there a possibility to include stable state in the definition of improvement (i.e., patients who did not worsen)?
Overall average or median over a specified timeframe *Definition:* The average or median score of all available	27	7	79	• This definition needs to be clarified as overall average or median over time for an individual (and not group). • The advantage of this endpoint is that it allows the assessment of PROs over an entire time frame, making full use of the information that was collected.

scores from a PRO domain over a pre-specified timeframe.				• The concern for this endpoint lies on the interpretation since averages over time wash out changes at specific time points. It then puts into question how the resulting estimate can be understandable and interpretable by patients. • This has been suggested as a useful approach if the planned assessments differ between trial participants (e.g., stopped assessments due to death and progression). However, there are concerns that this may not be an appropriate approach to handle these "missing data" since they are usually missing not at random.
Area under the curve over a specified timeframe *Definition:* The area under the curve value of all available scores from a PRO domain over a pre-specified timeframe.	32	3	91	• This endpoint requires the timeframe specified to be meaningful and comparable between the two arms. • There are concerns over interpretation of an area under the curve result (i.e., different patterns of observed assessment that reflects different clinical realities may lead to similar AUC). • This endpoint has strong missing data assumptions.
Best score over a specified time frame *Definition:* The best score of all available scores from a PRO domain over a pre-specified timeframe	12	17	41	• Best / worst score over a time frame is prone to bias (and measurement error). For example, one assessment point can have a high score and rest is low, and the interpretation of the results will be biased towards showing benefit (high score). • Timing of best score will also differ for each patient. • One assessment of a best score and not knowing the duration of that (e.g., if temporary or sustained) is not useful in terms of clinical relevance. • There is a need to determine whether the best score is clinically meaningful. • There is a need to find a context where this endpoint will be relevant.
Worst score over a specified time frame *Definition:* The worst score of all available scores from a PRO domain over a pre-specified timeframe	15	18	45	• Best / worst score over a time frame is prone to bias (and measurement error). For example, one assessment point can have a low score and rest is high, and the interpretation of the results will be biased towards showing risks/harm (low score). • This is similar to how CTCAE / safety data is reported and makes the PRO reporting similar to the clinician reporting. • There is a need to determine whether the worst score is clinically meaningful.
Response patterns/profiles over a specified time frame *Definition:* The longitudinal pattern of all available scores from a PRO domain over a pre-specified timeframe	31	3	91	• It will be difficult to develop a pre-defined hypothesis for comparability and efficacy for this PRO endpoint. • This is more useful for descriptive rather than confirmatory objectives (superiority / non-inferiority).

Note: Definitions for PRO objectives are based on the SISAQOL recommendations[15].

For each PRO objective, organization representatives were asked whether they or their organization would consider using the specified objective in cancer randomized controlled trials (RCTs) or single-arm studies. Organizations could respond “yes”, “no” or “don’t know” to each item. If organizations replied no to a PRO objective, they were encouraged to state their reasons. An open-ended question was also included to capture additional PRO objectives.
A PRO research objective was identified as high priority if at least two-thirds of the organization representatives responded “yes”. An objective was identified as low priority if less than half of the representatives responded “yes” on the PRO objective. A statement was “for discussion” if it did not meet the high or low priority criteria. Organization representatives who responded “don’t know” for a specific objective were not included in the total number of responses. Initial views from different SISAQOL-IMI members are summarized by qualitative comments from the survey, which can guide further discussions for each objective or endpoint.
The cells with white background show the PRO objectives that reached the high priority threshold (>2/3). Yes (%) is calculated as the number of “yes” votes divided by the total number of “yes” and “no” votes (don’t know or missing is excluded).
Reaching 100% agreement among the Consortium members was not always possible and individual organizations might have different views on specific recommendations given their institutional or stakeholder standpoint. Therefore, we encourage readers to read this table together with Tables 4 and 5 to consider the positions of relevant stakeholder groups.

Table 3.

Results from Priority Setting of PRO Objectives/Endpoints for Single-arm studies (n = 41)

	Single-arm studies			Initial views from different SISAQOL-IMI members
“Would you or your organisation consider using…”	Yes, n	No, n	Yes, %*	
Clinical benefit/treatment efficacy objective (confirmatory: superiority) *Definition:* to demonstrate that based on a PRO domain, the treatment group is superior to (or better than) the reference group by a clinically relevant treatment effect size	23	13	64	• The importance of using PROs in single-arm trials can support the assessment of PROs in rare cancers where RCTs would not be feasible. This is a key area to explore given the number of single-arm trials that are being done in oncology. • There are significant concerns in concluding superiority in single-arm trials based on PRO data. In general, single-arm trials are sensitive to selection bias. Without a comparator arm, the impact of treatment on PROs cannot be disentangled from baseline prognostic factors, making it difficult to contextualize the benefit or impact of treatment for the patient population of interest. • The lack of comparator arm can be addressed by the use of external control groups, historical data (reference data). However, there are questions on the quality of the reference data, and whether the patient population and treatment are comparable between the trial data and the reference data. There is a need to better define the reference population and ensure that the external control group/historical data are true comparators for the specific trial.

				• Even if good reference data is used for a single-arm trial, a confirmatory study using an RCT would still need to be explored.
Clinical benefit/treatment efficacy objective (confirmatory: equivalence/non-inferiority) *Definition:* to demonstrate that based on a PRO domain, the treatment group is similar (equivalent) or not worse (non-inferior) than the reference group by a pre-specified clinically relevant margin	19	19	50	• All comments on superiority objective in single-arm studies apply. • An added concern is the usefulness of a non-inferiority / equivalence objective in a single-arm trial, even if the endpoint was not a PRO.
Descriptive objective (exploratory/descriptive) *Definition:* to present PRO findings but no comparative conclusions between treatment arms will be drawn	36	5	88	• Currently, the use of PROs in single-arm trials would usually be limited to descriptive/exploratory objectives. This can be due to the limited number of patients. The results from a single-arm trial (e.g., phase II) can be used to inform the PRO hypothesis at a later phase. • Standards for descriptive objective need to be better defined, including the use of a validated instrument and PRO data being collected reliably so that this objective can be useful as supportive information.
Time to improvement *Definition:* the time it takes before a clinically relevant improvement from a PRO domain is observed within a pre-specified timeframe.	30	9	77	• This objective can be used if the expected assumption is that patients will improve in that PRO domain (e.g., patients undergoing primary curative therapy with acute toxicity or trials where the goal is to alleviate patients' symptoms). This objective may not be appropriate for early diagnosis with minimal symptoms (where no improvement in symptoms is expected) or for patients with poor prognosis (where an improvement is not expected). • This endpoint can be relevant as a descriptive objective (since reference data are not available). This can also be used in Phase II to guide the analysis planned for Phase III. • Defining a clinically meaningful event (improvement) is important. • General design and statistical issues for time to event objectives need to be addressed. This endpoint may require relatively frequent assessments over a potentially long period of time.
Time to worsening *Definition:* the time it takes before a clinically relevant worsening from a PRO domain is observed within a pre-specified timeframe	31	7	82	• This objective may be appropriate for patients with poor prognosis (where a worsening is expected). • This endpoint can be relevant as a descriptive objective (since reference data are not available). This can also be used in Phase II to guide the analysis planned for Phase III. • Defining a clinically meaningful event (worsening) is important.

				• General design and statistical issues for time to event objectives need to be addressed. This endpoint may require relatively frequent assessments over a potentially long period of time.
Time to stable state *Definition:* After observing a clinically relevant change from baseline (either worsening or improvement) from a PRO domain, the time it takes before the PRO domain returns to its baseline value (i.e., no change from baseline or as change from baseline within the predefined baseline margin)	15	19	44	• Time to stable state is not often seen as an endpoint in cancer clinical trials. However, this may be relevant in contexts where patients may experience a deterioration from their baseline state, but it will be temporary (e.g., if patients have good functioning at baseline, or minimal symptoms; and the expectation is that patients will experience a temporary deterioration, and they will go back to baseline after the deterioration). • Currently the definition implies measurement of stable state after patients have improved or worsened. Non responders (those who do not improve or worsen) will be excluded from analyses. This will further aggravate the issue of small sample size from single-arm trials, which may prevent the robust measurement of this endpoint. • Defining a clinically meaningful event (stable state) is important. • General design and statistical issues for time to event objectives need to be addressed. This endpoint may require relatively frequent assessments over a potentially long period of time.
Time to end of stable state *Definition:* The time it takes until the stable state ends or time until a clinically relevant improvement or worsening from a PRO domain is observed.	15	18	45	• Currently the definition implies ending the stable state by both improvement and worsening, which will be hard to interpret. • This endpoint may be difficult to implement in cancers with poor prognosis because of the short disease duration (less frequent assessments). • Time to improvement and time to worsening could also address this objective. • Additional information on sustained "end of stable state" will be relevant to describe this endpoint (e.g., duration of the worsening) since PRO concepts and symptoms may be more volatile relative to other clinical endpoints (e.g., death or PFS). • Defining a clinically meaningful event (end of stable state) is important. • General design and statistical issues for time to event objectives need to be addressed. This endpoint may require relatively frequent assessments over a potentially long period of time.
Magnitude of change at specific time point(s) *Definition:* The actual value or change from baseline value for a PRO domain at pre-defined time points	33	5	87	• Defining the relevant timepoint would imply making an assumption on when an improvement or worsening will happen across patients. • Defining a clinically relevant change/difference for both superiority and non-inferiority objectives will be critical (e.g., MID) for this endpoint. Will these MIDs take into account the baseline scores of the patient or will they differ depending on where the patient starts on the scale? • Whether the absolute value or change scores will be used as data needs to be taken into account.

Responder with improvement at specific time point(s) *Definition:* Whether the value (or change from baseline value) from a PRO domain at a specific time point reaches a pre-defined improvement threshold or not	30	8	79	• Defining the relevant timepoint would imply making an assumption on when an improvement or worsening will happen across patients. • Defining a clinically meaningful responder (improvement) is important. • This can be used for supportive information for a clinical finding and support interpretation for other PRO endpoints (e.g., magnitude of change or time to event endpoints). • Is there a possibility to include stable state in the definition of improvement (i.e., patients who did not worsen)?
Responder with worsening at specific time point(s) *Definition:* Whether the value (or change from baseline value) from a PRO domain at a specific time point reaches a pre-defined worsening threshold or not	26	10	72	• This is a relevant endpoint to descriptively report toxicity or symptoms. • Defining the relevant timepoint would imply making an assumption on when an improvement or worsening will happen across patients. • Defining a clinically meaningful responder (worsening) is important. • This can be used for supportive information for a clinical finding and support interpretation for other PRO endpoints (e.g., magnitude of change or time to event endpoints).
Responder with stable state at specific time point(s) *Definition:* Whether the value (or change from baseline value) from a PRO domain at a specific time point remains within a pre-defined baseline margin or not.	19	17	53	• This may be relevant for trials where the goal is "maintenance of a specific PRO domain". • Defining the relevant timepoint would imply making an assumption on when stable state will happen across patients. • Defining a meaningful responder (stable state) is important. • This can be used for supportive information for a clinical finding and support interpretation for other PRO endpoints (e.g., magnitude of change or time to event endpoints). • When interpreting results for stable state alone (responder) this will imply merging patients who improved and worsened into one category (non-responders). • It may be more meaningful to report descriptively. improved/stable/worsened by time point (rather than just stable state). • The focus of interpretation is usually the number of patients who improved or worsened, rather than those who remained stable. • Is there a possibility to include stable state in the definition of improvement (i.e., patients who did not worsen)?
Overall average or median over a specified timeframe	22	11	67	• This definition needs to be clarified as overall average or median over time for an individual (and not group). • The advantage of this endpoint is that it allows the assessment of PROs over an entire time frame, making full use of the information that was collected.

Definition: The average or median score of all available scores from a PRO domain over a pre-specified timeframe.				• The concern for this endpoint lies on the interpretation since averages over time wash out changes at specific time points. It then puts into question how the resulting estimate can be understandable and interpretable by patients. • This has been a suggested approach if the planned assessments differ between trial participants (e.g., stopped assessments due to death and progression). However, there are concerns that this may not be an appropriate approach to handle these "missing data" since they are usually missing not at random. An added concern is if it is used in single-arm trials, the findings become even more difficult to interpret in the absence of a control group.
Area under the curve over a specified timeframe *Definition:* The area under the curve value of all available scores from a PRO domain over a pre-specified timeframe.	21	14	60	• This endpoint requires the timeframe to be specified to be meaningful. • There are concerns over interpretation of an area under the curve result (i.e., different patterns of observed assessment that reflects different clinical realities may lead to similar AUC). • This endpoint has strong missing data assumptions. • An added concern is if it is used in single-arm trials, it becomes even more difficult to interpret in the absence of a control group.
Best score over a specified time frame *Definition:* The best score of all available scores from a PRO domain over a pre-specified timeframe	12	17	41	• Best / worst score over a time frame is prone to bias (and measurement error). For example, one assessment point can have a high score and rest is low, and the interpretation of the results will be biased towards showing benefit (high score). • Timing of best score will also differ for each patient. • One assessment of a best score and not knowing the duration of that (e.g., if temporary or sustained) is not useful in terms of clinical relevance. • There is a need to determine whether the best score is clinically meaningful. • There is a need to find a context where this endpoint will be relevant.
Worst score over a specified time frame *Definition:* The worst score of all available scores from a PRO domain over a pre-specified timeframe	13	18	42	• Best / worst score over a time frame is prone to bias (and measurement error). For example, one assessment point can have a low score and rest is high, and the interpretation of the results will be biased towards showing risks/harm (low score). • This is similar to how CTCAE / safety data is reported and makes the PRO reporting similar to the clinician reporting. • There is a need to determine whether the worst score is clinically meaningful.
Response patterns/profiles over a specified time frame *Definition:* The longitudinal pattern of all available scores from a PRO domain over a pre-specified timeframe	28	8	78	• It will be difficult to develop a pre-defined hypothesis for comparability and efficacy for this PRO endpoint. • This is more useful for descriptive rather than confirmatory objective (superiority / non-inferiority).

Note: Definitions for PRO objectives are based on the SISAQOL recommendations[15]

For each PRO objective, organization representatives were asked whether they or their organization would consider using the specified objective in cancer randomized controlled trials (RCTs) or single-arm studies. Organizations could respond “yes”, “no” or “don’t know” to each item. If organizations replied no to a PRO objective, they were encouraged to state their reasons. An open-ended question was also included to capture additional PRO objectives. A PRO research objective was identified as high priority if at least two-thirds of the organization representatives responded “yes”. An objective was identified as low priority if less than half of the representatives responded “yes” on the PRO objective. A statement was “for discussion” if it did not meet the high or low priority criteria. Organization representatives who responded “don’t know” for a specific objective were not included in the total number of responses. Initial views from different SISAQOL-IMI members are summarized by qualitative comments from the survey, which can guide further discussions for each objective or endpoint.

The cells with white background show the PRO objectives that reached the high priority threshold (>2/3). Yes (%) is calculated as the number of “yes” votes divided by the total number of “yes” and “no” votes (don’t know or missing is excluded).

Reaching 100% agreement among the Consortium members was not always possible and individual organizations might have different views on specific recommendations given their institutional or stakeholder standpoint. Therefore, we encourage readers to read this table together with Tables 4 and 5 to consider the positions of relevant stakeholder groups.

Table 4: Results from Priority Setting of PRO Objectives/Endpoints for RCTs by stakeholder group

“Would you or your organisation consider using…”	**Academic (N=17)**	**Industry (N=5)**	**Non-profit/ Cancer org. (N=8)**	**SME/ CRO (N=4)**	**Regulatory (N=4)**	**HTA (N=2)**	**Patient repr. (N=1)**	**Total (N=41)**
	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)
Clinical benefit/treatment efficacy objective (confirmatory: superiority)	17/17 (100)	5/5 (100)	7/8 (88)	4/4 (100)	4/4 (100)	2/2 (100)	1/1 (100)	40/41 (98)
Clinical benefit/treatment efficacy objective (confirmatory: equivalence/non-inferiority)	17/17 (100)	5/5 (100)	7/8 (88)	4/4 (100)	2/3 (67)	2/2 (100)	1/1 (100)	38/40 (95)
Descriptive objective (exploratory/descriptive)	14/16 (88)	5/5 (100)	7/8 (88)	2/3 (67)	2/4 (50	1/2 (50)	1/1 (100)	32/39 (82)
Time to improvement	15/17 (88)	5/5 (100)	6/7 (86)	3/4 (75)	1/2 (50)	1/1 (100)	1/1 (100)	32/37 (86)
Time to worsening	16/17 (94)	5/5 (100)	8/8 (100)	4/4 (100)	2/3 (67)	1/2 (50)	1/1 (100)	37/40 (93)
Time to stable state	11/14 (79)	3/4 (75)	3/8 (38)	2/2 (100	0/2 (0)	1/1 (100)	1/1 (100)	21/32 (66)
Time to end of stable state	9/13 (69)	2/4 (50)	2/6 (33)	0/1 (0)	0/1 (0)	0/0[1] (-)	1/1 (100)	14/26 (54)
Magnitude of change at specific time point(s)	15/16 (94)	5/5 (100)	7/8 (88)	4/4 (100)	4/4 (100)	1/2 (50)	1/1 (100)	37/40 (93)
Responder with improvement at specific time point(s)	14/16 (88)	5/5 (100)	6/6 (100)	3/4 (75)	4/4 (100)	1/2 (50)	1/1 (100)	34/38 (89)
Responder with worsening at specific time point(s)	15/16 (94)	3/4 (75)	6/7 (86)	3/4 (75)	2/3 (67)	1/2 (50)	1/1 (100)	31/37 (84)
Responder with stable state at specific time point(s)	9/13 (69)	3/3 (100)	3/8 (38)	1/3 (33)	1/1 (100)	1/2 (50)	1/1 (100)	19/31 (61)
Overall average or median over a specified timeframe	11/13 (85)	5/5 (100)	4/7 (57)	3/3 (100)	2/3 (67)	1/2 (50)	1/1 (100)	27/34 (79)
Area under the curve over a specified timeframe	16/16 (100)	5/5 (100)	7/7 (100)	1/3 (33)	2/3 (67)	1/1 (100)	0/0[2] (-)	32/35 (91)

Best score over a specified time frame	8/13 (62)	3/5 (60)	0/6 (0)	0/1 (0)	0/1 (0)	0/2 (0)	1/1 (100)	12/29 (41)
Worst score over a specified time frame	9/14 (64)	2/5 (40)	1/7 (14)	1/2 (50)	1/2 (50)	0/2 (0)	1/1 (100)	15/33 (45)
Response patterns or profiles over a specified time frame	13/14 (93)	4/5 (80)	5/6 (83)	3/3 (100)	3/3 (100)	2/2 (100)	1/1 (100)	31/34 (91)

[1] Both HTAs responded don't know to this item

[2] The patient representatives responded don't know to this item

When calculating the proportion of agreement, "don't know", "not applicable" and "missing" were omitted from the denominator (n).

The cells with white background show the PRO objectives that reached the high priority threshold (>2/3 majority).

The patients are represented by WECAN which is an umbrella organisation representing 23 Pan-European cancer patient organisations, and patient input is coordinated by the Myeloma Patients Europe.

Table 5: Results from Priority Setting of PRO Objectives/Endpoints for Single-arm studies by stakeholder group

"Would you or your organisation consider using…"	**Academic (N=17)**	**Industry (N=5)**	**Non-profit/ Cancer org. (N=8)**	**SME/CRO (N=4)**	**Regulatory (N=4)**	**HTA (N=2)**	**Patient repr. (N=1)**	**Total (N=41)**
	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)
Clinical benefit/treatment efficacy objective (confirmatory: superiority)	13/17 (76)	4/4 (100)	2/5 (40)	3/4 (75)	0/3 (0)	0/2 (0)	1/1 (100)	23/36 (64)
Clinical benefit/treatment efficacy objective (confirmatory: equivalence/non-inferiority)	11/16 (69)	3/5 (60)	1/7 (14)	3/4 (75)	0/3 (0)	0/2 (0)	1/1 (100)	19/38 (50)
Descriptive objective (exploratory/descriptive)	17/17 (100)	5/5 (100)	6/8 (75)	4/4 (100)	3/4 (75)	0/2 (0)	1/1 (100)	36/41 (88)
Time to improvement	15/17 (88)	4/5 (80)	6/8 (75)	4/4 (100)	0/2 (0)	0/2 (0)	1/1 (100)	30/39 (77)
Time to worsening	16/17 (94)	3/4 (75)	6/7 (86)	4/4 (100)	1/3 (33)	0/2 (0)	1/1 (100)	31/38 (82)
Time to stable state	9/14 (64)	1/4 (25)	1/7 (14)	3/3 (100)	0/3 (0)	0/2 (0)	1/1 (100)	15/34 (44)
Time to end of stable state	11/14 (79)	1/5 (20)	1/7 (14)	1/2 (50)	0/2 (0)	0/2 (0)	1/1 (100)	15/33 (45)
Magnitude of change at specific time point(s)	16/16 (100)	5/5 (100)	6/8 (75)	4/4 (100)	1/2 (50)	0/2 (0)	1/1 (100)	33/38 (87)
Responder with improvement at specific time point(s)	14/16 (88)	5/5 (100)	6/8 (75)	3/4 (75)	1/2 (50)	0/2 (0)	1/1 (100)	30/38 (79)
Responder with worsening at specific time point(s)	12/14 (86)	3/4 (75)	6/8 (75)	3/4 (75)	1/3 (33)	0/2 (0)	1/1 (100)	26/36 (72)
Responder with stable state at specific time point(s)	10/14 (71)	3/5 (60)	2/7 (29)	2/3 (67)	1/4 (25)	0/2 (0)	1/1 (100)	19/36 (53)
Overall average or median over a specified timeframe	10/12 (83)	4/5 (80)	3/8 (38)	4/4 (100)	0/1 (0)	0/2 (0)	1/1 (100)	22/33 (67)
Area under the curve over a specified timeframe	12/15 (80)	4/5 (80)	4/7 (57)	0/3 (0)	0/2 (0)	0/2 (0)	1/1 (100)	21/35 (60)
Best score over a specified time frame	8/13 (62)	2/4 (50)	1/6 (17)	0/2 (0)	0/1 (0)	0/2 (0)	1/1 (100)	12/29 (41)

Worst score over a specified time frame	7/13 (54)	2/4 (50)	1/7 (14)	1/2 (50)	1/2 (50)	0/2 (0)	1/1 (100)	13/31 (42)
Response patterns or profiles over a specified time frame	13/15 (87)	5/5 (100)	4/7 (57)	3/3 (100)	2/3 (67)	0/2 (0)	1/1 (100)	28/36 (78)

When calculating the proportion of agreement, “don’t know”, “not applicable” and “missing" were omitted from the denominator (n).
The cells with white background show the PRO objectives that reached the high priority threshold (>2/3 majority).
The patients are represented by WECAN which is an umbrella organisation representing 23 Pan-European cancer patient organisations, and patient input is coordinated by the Myeloma Patients Europe.

SISAQOL-IMI Consortium participants

First Name	Family Name
Cat	Bui
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Rajesh	Kamalakar
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Barbara	Peil
Maarten	Voorhaar
Brendon	Wong
Gracia	Dekanic Arbanas
Karin	Kuljanic
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Gerhard	Rumpold
Felix	Schoepf
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Jennifer	Black
Maxime	Sasseville
Katherine	Soltys
Montserrat	Ferrer
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Stefanie	Thomas

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Anja	Schiel
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Michael	Brundage
Dongsheng	Tu
Mogens	Groenvold
Morten	Petersen
Charlie	Cleeland
Lori	Williams
Xin	Shelley Wang
Jolie	Ringash
Melanie	Calvert
Samantha	Cruz Rivera
Olalekan Lee	Aiyegbusi
Els	Goetghebeur
Limin	Liu
Kelly	Van Lancker
Florien	Boele
Alexandra	Gilbert
Rosemary	Peacock
Ethan	Basch
Madeleine	King
Claudia	Rutherford
Vishal	Bhatnagar
Mallorie	Fiero
Erica	Horodniceanu
Laura Lee	Johnson
Paul	Kluetz
Lisa	Rodriguez

Appendix 1

SISAQOL-IMI: Pre-kick off meeting survey questionnaire

Dear SISAQOL-IMI member,

This survey aims to understand your or your organisation's perspective on relevant PRO objectives for cancer randomized controlled trials (RCTs) and single-arm studies. Suggestions for key references on PROs will also be asked. The survey is split into three parts.

In Parts I and II of this survey, your opinion will be asked about PRO objectives that you or your organization would consider using in cancer randomized controlled trials (RCTs) or single arm cancer trials, respectively. These PRO objectives are based on the SISAQOL research objectives framework (1).

Your response to this survey will be used to identify which PRO research objectives are initially considered relevant for different organizations or experts.

This will allow the SISAQOL-IMI work packages to prioritize the PRO objectives and evaluate the appropriate methodologies to respond to each of these objectives.

Please note that the questions for RCTs and single arm studies are similar to each other, but they are separated into two parts to clearly differentiate PRO objectives that will be used for an RCT and a single-arm context.

In Part III of this survey, you will be asked to provide key references that you and your organization use related to four of the scientific SISAQOL-IMI WPs:

- WP 2: randomized controlled trials
- WP 3: single-arm trials
- WP 4: communication tools for PRO findings
- WP 6: terminology and definitions of clinically meaningful change

We encourage you to provide a comprehensive list of key references (e.g., published reports, official guidelines, grey literature, internal organizational documents) since this will allow the individual work packages to identify areas of agreement and disagreement across these various key documents.

Only one response per organization is needed. We encourage you to discuss your responses with your team so you can combine your responses before submitting the survey. Please set aside enough time to discuss all parts of the survey before responding. The responses to this survey will take approximately 15 minutes to complete.

Your organizational information is collected to keep track of the participation in the survey. EORTC and the SISAQOL-IMI Consortium will only use your organizational information in the scope of the SISAQOL-IMI project.

In order to collect your replies to this survey, EORTC and the SISAQOL-IMI Consortium are using the service of ESD, a processor which will process your personal data according to xxxxx (privacy notice of ESD). EORTC will act as data controller for processing your personal data. For any information on how EORTC protects your data: https://www.eortc.org/privacy-policy/.

The findings of this survey will be presented and discussed at the SISAQOL-IMI meeting as part of the development of the SISAQOL-IMI consensus recommendations.

Thank you for your cooperation, your responses to this survey are very much valued.

(1) International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomized controlled trials: recommendations of the SISAQOL Consortium. The Lancet Oncology 21, no. 2 (2020): e83-e96.

ORGANIZATION INFORMATION

Your information is collected to keep track of the participation in the survey.
Please identify the contact person who will be responsible for submitting your organization's response to this survey.

P1. Name of Organization

P2. Name of contact person

P3. Email of contact person

P4. What are the primary areas of experience of the individuals from your organization who participated in completing this survey? [Checkbox, multiple options possible]

- Clinician
- Clinical professor
- Data manager/coordinator
- Expert advisor on HRQOL/PROs
- Ethicist
- Funder
- Health economist
- Health psychologist
- Industry representative
- Journal editor
- Linguistic validator
- Patient representative
- Policy maker
- Psychometrician
- Regulator
- Research nurse/therapist
- Researcher/health related academic
- Reviewer
- Statistician
- Trial manager/coordinator
- Trials methodologist
- Other [**Please specify other primary area of experience**]

PART I: IDENTIFYING RELEVANT PRO OBJECTIVES IN RANDOMIZED CONTROLLED CANCER CLINICAL TRIALS

Instructions: SISAQOL-IMI aims to identify PRO research objectives that can be aligned to statistical methods. To achieve this goal, it is important to identify which PRO research objectives in **randomized controlled cancer clinical trials** would be considered relevant for you or your organization. For each objective, you can provide comments to explain or support your responses. The identified PRO objectives below are based on the SISAQOL research objectives framework.

Q1.1. Would you or your organisation consider using **treatment efficacy / clinical benefit (confirmatory: superiority objective) in a randomized controlled trial**, with the goal to demonstrate that based on a **PRO domain,** the treatment group is **superior** to (or better than) the reference group by a clinically relevant treatment effect size

- Yes
- No
- Don't know

Q1.1c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.2. Would you or your organization consider using **treatment efficacy / clinical benefit (confirmatory: equivalence/non-inferiority objective) in a randomized controlled trial**, with the goal to demonstrate that based on a **PRO domain,** the treatment group is **similar** (equivalent) **or not worse** (non-inferior) than the reference group by a pre-specified clinically relevant margin

- Yes
- No
- Don't know

Q1.2c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.3. Would you or your organization consider using a **descriptive objective (exploratory/descriptive objective) in a randomized controlled trial,** with the goal to present **PRO findings** but no comparative conclusions between treatment arms will be drawn.

- Yes
- No
- Don't know

Q1.3c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.a. Would you or your organization consider **time to improvement** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?
Time to improvement: The time it takes before a clinically relevant improvement from a PRO domain is observed within a pre-specified timeframe.

- Yes
- No
- Don't know

Q1.a/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q1.a/b, otherwise go to Q1.a/c]

Q1.a/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q1.a/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.b. Would you or your organization consider **time to worsening** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?
Time to worsening: The time it takes before a clinically relevant worsening from a PRO domain is observed within a pre-specified timeframe.

- Yes
- No
- Don't know

Q1.b/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q1.b/b, otherwise go to Q1.b/c]

Q1.b/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]

- Don't know

Q1.b/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.c. Would you or your organization consider **time to stable state** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?
Time to stable state: After observing a clinically relevant change from baseline (either worsening or improvement) from a PRO domain, the time it takes before the PRO domain returns to its baseline value (i.e., no change from baseline or as change from baseline within the predefined baseline margin).

- Yes
- No
- Don't know

Q1.c/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q1.c/b, otherwise go to Q1.c/c]

Q1.c/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q1.c/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.d. Would you or your organization consider **time to end of stable state** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?
Time to end of stable state: The time it takes until the stable state ends or time until a clinically relevant improvement or worsening from a PRO domain is observed.

- Yes
- No
- Don't know

Q1.d/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q1.d/b, otherwise go to Q1.d/c]

Q1.d/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q1.d/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.e. Would you or your organization consider **magnitude of change (improvement or worsening) at specific time point(s)** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?

Magnitude of change (improvement or worsening) at specific time point(s): The actual value or change from baseline value for a PRO domain at pre-defined time points.

- Yes
- No
- Don't know

Q1.e/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q1.8b, otherwise go to Q1.8c]

Q1.e/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q1.e/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.f. Would you or your organization consider **responder with improvement at specific time point(s)** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?

Responder with improvement at specific time point(s): Whether the value (or change from baseline value) from a PRO domain at a specific time point reaches a pre-defined improvement threshold or not.

- Yes
- No
- Don't know

Q1.f/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q1.f/b, otherwise go to Q1.f/c]

Q1.f/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q1.f/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.g. Would you or your organization consider **responder with worsening at specific time point(s)** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?
Responder with worsening at specific time point(s): Whether the value (or change from baseline value) from a PRO domain at a specific time point reaches a pre-defined worsening threshold or not.

- Yes
- No
- Don't know

Q1.g/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q1.g/b, otherwise go to Q1.g/c]

Q1.g/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q1.g/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.h. Would you or your organization consider **responder with stable state at specific time point(s)** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?
Responder with stable state at specific time point(s): Whether the value (or change from baseline value) from a PRO domain at a specific time point remains within a pre-defined baseline margin or not.

- Yes
- No
- Don't know

Q1.h/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q1.h/b, otherwise go to Q1.h/c]

Q1.h/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q1.h/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.i. Would you or your organization consider **overall average or median over a specified timeframe** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?
Overall average or median over a specified timeframe: The average or median score of all available scores from a PRO domain over a pre-specified timeframe.

- Yes
- No
- Don't know

Q1.i/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q1.i/b, otherwise go to Q1.i/c]

Q1.i/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- o Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- o Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- o Descriptive / exploratory objective
- o Other [open text box]
- o Don't know

Q1.i/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.j. Would you or your organization consider **area under the curve over a specified timeframe** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?
Area under the curve over a specified timeframe: The area under the curve value of all available scores from a PRO domain over a pre-specified timeframe.

- o Yes
- o No
- o Don't know

Q1.j/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- o Yes
- o No
- o Don't know
- o Not applicable

[If yes, see Q1.j/b, otherwise go to Q1.j/c]

Q1.j/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- o Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- o Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- o Descriptive / exploratory objective
- o Other [open text box]
- o Don't know

Q1.j/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.k. Would you or your organization consider **best score over a specified time frame** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?
Best score over a specified time frame: The best score of all available scores from a PRO domain over a pre-specified timeframe.

- o Yes
- o No
- o Don't know

Q1.k/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q1.k/b, otherwise go to Q1.k/c]

Q1.k/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q1.k/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.l. Would you or your organization consider **worst score over a specified time frame** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?
Worst score over a specified time frame: The worst score of all available scores from a PRO domain over a pre-specified timeframe.

- Yes
- No
- Don't know

Q1.l/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q1.l/b, otherwise go to Q1.l/c]

Q1.l/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q1.l/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.m. Would you or your organization consider **response patterns or profiles over a specified timeframe** a relevant PRO endpoint to assess in **randomized controlled cancer clinical trials**?
Response patterns or profiles over a specified time frame: The longitudinal pattern of all available scores from a PRO domain over a pre-specified timeframe.

- o Yes
- o No
- o Don't know

Q1.m/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- o Yes
- o No
- o Don't know
- o Not applicable

[If yes, see Q1.m/b, otherwise go to Q1.m/c]

Q1.m/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- o Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- o Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- o Descriptive / exploratory objective
- o Other [open text box]
- o Don't know

Q1.m/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q1.n. Please specify other relevant PRO endpoints; [Open text box; optional]

Q1.n/a. Have you used this PRO endpoint **previously** for a **randomized controlled cancer clinical trial** in your organization?

- o Yes
- o No
- o Don't know
- o Not applicable

[If yes, see Q1.n/b, otherwise go to Q1.n/c]

Q1.n/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- o Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- o Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- o Descriptive / exploratory objective
- o Other [open text box]
- o Don't know

Q1.n/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

PART II: IDENTIFYING RELEVANT PRO OBJECTIVES IN SINGLE-ARM CANCER CLINICAL TRIALS

SISAQOL-IMI aims to identify PRO research objectives that can be aligned to statistical methods. To achieve this goal, it is important to identify which PRO research objectives in **single-arm cancer clinical trials** would be considered relevant for you or your organization. For each objective, you can provide comments to explain or support your responses. The identified PRO objectives below are based on the SISAQOL research objectives framework.

Q2.1. Would you or your organization consider using **treatment efficacy / clinical benefit (confirmatory: superiority objective) in a single-arm trial**, with the goal to demonstrate that based on a **PRO domain,** the treatment group is **superior** to (or better than) a reference value by a clinically relevant treatment effect size

- Yes
- No
- Don't know

Q2.1/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.2. Would you or your organization consider using **treatment efficacy / clinical benefit (confirmatory: equivalence/non-inferiority objective) in a single-arm trial**, with the goal to demonstrate that based on a **PRO domain,** the treatment group is **similar** (equivalent) **or not worse** (non-inferior) than a reference value.by a pre-specified clinically relevant margin

- Yes
- No
- Don't know

Q2.2/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.3. Would you or your organization consider using a **descriptive objective (exploratory/descriptive objective) in a single-arm trial,** with the goal to present **PRO findings** but no comparative conclusions will be drawn.

- Yes
- No
- Don't know

Q2.3/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.a. Would you or your organization consider **time to improvement** a relevant PRO endpoint to assess in **single-arm cancer clinical trials**?
Time to improvement: The time it takes before a clinically relevant improvement from a PRO domain is observed within a pre-specified timeframe.

- Yes

- No
- Don't know

Q2.a/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q2.a/b, otherwise go to Q2.a/c]

Q2.a/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.a/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.b. Would you or your organization consider **time to worsening** a relevant PRO endpoint to assess in **single-arm cancer clinical trials**?
Time to worsening: The time it takes before a clinically relevant worsening from a PRO domain is observed within a pre-specified timeframe.

- Yes
- No
- Don't know

Q2.b/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q2.b/b, otherwise go to Q2.b/c]

Q2.b/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.b/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.c. Would you or your organization consider **time to stable state** a relevant PRO endpoint to assess in **single-arm cancer clinical trials**?
Time to stable state: After observing a clinically relevant change from baseline (either worsening or improvement) from a PRO domain, the time it takes before the PRO domain returns to its baseline value (i.e., no change from baseline or as change from baseline within the predefined baseline margin).

- o Yes
- o No
- o Don't know

Q2.c/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- o Yes
- o No
- o Don't know
- o Not applicable

[If yes, see Q2.c/b, otherwise go to Q2.c/c]

Q2.c/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- o Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- o Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- o Descriptive / exploratory objective
- o Other [open text box]
- o Don't know

Q2.c/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.d. Would you or your organization consider **time to end of stable state** a relevant PRO endpoint to assess in **single-arm cancer clinical trials**?
Time to end of stable state: The time it takes until the stable state ends or time until a clinically relevant improvement or worsening from a PRO domain is observed.

- o Yes
- o No
- o Don't know

Q2.d/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- o Yes
- o No
- o Don't know
- o Not applicable

[If yes, see Q2.d/b, otherwise go to Q2.d/c]

Q2.d/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- o Treatment efficacy / clinical benefit (confirmatory: superiority objective)

- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.d/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.e. Would you or your organization consider **magnitude of change (improvement or worsening) at specific time point(s)** a relevant PRO endpoint to assess in **single-arm cancer clinical trials**?
Magnitude of change (improvement or worsening) at specific time point(s): The actual value or change from baseline value for a PRO domain at pre-defined time points.

- Yes
- No
- Don't know

Q2.e/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q2.e/b, otherwise go to Q2.e/c]

Q2.e/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.e/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.f. Would you or your organization consider **responder with improvement at specific time point(s)** a relevant PRO endpoint to assess in **single-arm cancer clinical trials**?
Responder with improvement at specific time point(s): Whether the value (or change from baseline value) from a PRO domain at a specific time point reaches a pre-defined improvement threshold or not.

- Yes
- No
- Don't know

Q2.f/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- Yes
- No

- Don't know
- Not applicable

[If yes, see Q2.f/b, otherwise go to Q2.f/c]

Q2.f/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.f/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.g. Would you or your organization consider **responder with worsening at specific time point(s)** a relevant PRO endpoint to assess in **single-arm cancer clinical trials**?
Responder with worsening at specific time point(s): Whether the value (or change from baseline value) from a PRO domain at a specific time point reaches a pre-defined worsening threshold or not.

- Yes
- No
- Don't know

Q2.g/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q2.g/b, otherwise go to Q2.g/c]

Q2.g/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.g/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.h. Would you or your organization consider **responder with stable state at specific time point(s)** a relevant PRO endpointto assess in **single-arm cancer clinical trials**?
Responder with stable state at specific time point(s): Whether the value (or change from baseline value) from a PRO domain at a specific time point remains within a pre-defined baseline margin or not.

- Yes

- No
- Don't know

Q2.h/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q2.h/b, otherwise go to Q2.h/c]

Q2.h/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.h/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.i. Would you or your organization consider **overall average or median over a specified timeframe** a relevant PRO endpointto assess in **single-arm cancer clinical trials**?
Overall average or median over a specified timeframe: The average or median score of all available scores from a PRO domain over a pre-specified timeframe.

- Yes
- No
- Don't know

Q2.i/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q2.i/b, otherwise go to Q2.i/c]

Q2.i/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.i/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.j. Would you or your organization consider **area under the curve over a specified timeframe** a relevant PRO endpoint to assess in **single-arm cancer clinical trials**?
Area under the curve over a specified timeframe: The area under the curve value of all available scores from a PRO domain over a pre-specified timeframe.

- o Yes
- o No
- o Don't know

Q2.j/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- o Yes
- o No
- o Don't know
- o Not applicable

[If yes, see Q2.j/b, otherwise go to Q2.j/c]

Q2.j/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- o Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- o Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- o Descriptive / exploratory objective
- o Other [open text box]
- o Don't know

Q2.j/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.k. Would you or your organization consider **best score over a specified time frame** a relevant PRO endpoint to assess in **single-arm cancer clinical trials**?
Best score over a specified time frame: The best score of all available scores from a PRO domain over a pre-specified timeframe.

- o Yes
- o No
- o Don't know

Q2.k/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- o Yes
- o No
- o Don't know
- o Not applicable

[If yes, see Q2.k/b, otherwise go to Q2.k/c]

Q2.k/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.k/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.l. Would you or your organization consider **worst score over a specified time frame** a relevant PRO endpoint to assess in **single-arm cancer clinical trials**?
Worst score over a specified time frame: The worst score of all available scores from a PRO domain over a pre-specified timeframe.

- Yes
- No
- Don't know

Q2.l/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q2.l/b, otherwise go to Q2.l/c]

Q2.l/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.l/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.m Would you or your organization consider **response patterns or profiles over a specified timeframe** a relevant PRO endpoint to assess in **single-arm cancer clinical trials**?
Response patterns or profiles over a specified time frame: The longitudinal pattern of all available scores from a PRO domain over a pre-specified timeframe.

- Yes
- No
- Don't know

Q2.m/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q2.m/b, otherwise go to Q2.m/c]

Q2.m/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.m/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

Q2.n. Please specify other relevant PRO endpoints; [Open text box]

Q2.n/a. Have you used this PRO endpoint **previously** for a **single-arm cancer clinical trial** in your organization?

- Yes
- No
- Don't know
- Not applicable

[If yes, see Q2.n/b, otherwise go to Q2.n/c]

Q2.n/b. For which broad PRO objective did you **previously** use this PRO endpoint? Select all that apply. [multiple options possible]

- Treatment efficacy / clinical benefit (confirmatory: superiority objective)
- Treatment efficacy / clinical benefit (confirmatory: non-inferiority/equivalence objective)
- Descriptive / exploratory objective
- Other [open text box]
- Don't know

Q2.n/c. If your response was no to the question "would you consider using this PRO objective", please provide a rationale below. You can also provide any additional comments about this specific PRO objective below.

PART III: IDENTIFYING KEY REFERENCE DOCUMENTS

SISAQOL-IMI aims to provide a comprehensive report on current standards on PRO design, analyses, presentation of results and interpretation in cancer clinical trials. One important way to address to this goal is to collect key references and guidance documents that your organization use when assessing or evaluating PRO data in cancer clinical trials for the following topics. This will allow the individual scientific work packages (WPs) to identify areas of agreement and disagreement across these various documents.

Please indicate **key references** your organization uses for **each topic** below (this may include published papers, official guidelines, grey literature or internal organization documents; indicate the doi if feasible):

Q3. WP 2: Designing, analyzing and interpreting of PROs in randomized controlled cancer clinical trials [Open text box]

Q4. WP 3: Designing, analyzing and interpreting of PROs in single-arm cancer clinical trials [Open text box]

Q5. WP 4: Presentation and visualization of PRO findings [Open text box]

Q6: WP 6: Clinically relevant change or clinically relevant difference of PROs [Open text box]

Thank you!

You have come to the end of this survey.

Q7. If you have any comments or additional suggestions, please fill in the text box below. [Open text box]

Appendix 2

Principles for handling divergent views in SISAQOL-IMI Consortium

Background

According to the rules agreed by SISAQOL-IMI consortium, a proposed statement is accepted if at least two-thirds of the voters agreed on the statement. A statement is rejected if less than half of the voters agreed on the statement. A statement is postponed or noted for discussion if it does not meet the agreement or rejection criteria, or if it is agreed by the consortium that more discussion is needed.

When developing recommendations, reaching 100% agreement among the Consortium members is not always possible. Even if there is high level of agreement and a statement is accepted by two-thirds majority, there might be stakeholders with substantive concerns or different views. This is acknowledged as normal within a large constituent group. We would like to consistently address these various views whilst maintaining the notion of consensus and avoiding formal individual organization disclaimers for specific recommendation statements which could affect the future utility and implementation of the SISAQOL-IMI recommendations.

Proposal

The aim of the SISAQOL-IMI Consortium is to provide clear and credible recommendations on the design, analysis, presentation and interpretation of PRO data in cancer clinical trials. It is crucial to speak with one voice to make our message powerful, consistent, and executable. Therefore, the Steering Committee proposes the following principles to address divergent views within the Consortium.

Specific individual organisation disclaimers will not be included in the individual recommendations. However, the following will apply in order to help reflect when different views arise and the needs of consortium organisations:

- In publications the following general disclaimer will continue to be applied: '*This publication reflects the views of the individual authors and should not be construed to represent official views or policies of the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the US National Cancer Institute (NCI), the Medicines and Healthcare products Regulatory Agency (MHRA), the Institute for Quality and Efficiency in Health Care (IQWiG), Health Canada or the Norwegian Medicines Agency (NOMA), the American Society of Clinical Oncology (ASCO) or the European Society for Medical Oncology (ESMO) or any other institution, organization, or entity."*

- We will include a preamble to the SISAQOL-IMI recommendations stating that reaching 100% agreement among the Consortium members was not always possible. Therefore, readers should take into consideration that individual organizations might have different views on specific recommendations given their institutional or stakeholder standpoint. We recommend readers consult with the relevant organizations or stakeholders when developing their clinical program.

- For each *accepted* recommendation statement that had concerns or alternative views raised by individual organizations, a similar approach will be taken as to the former SISAQOL paper published in 2020[1]: it will be noted that while consensus was reached (with the percentage agreement reported), there were other views, and relevant views will be included under "considerations" along with the accepted recommendation statement. For example:

93%	RS9. Overall effect is defined as summarising all available scores over time for each patient on a specific PRO domain or item.	Disagreement among consortium members (during discussion) arose on whether overall effect endpoints can be used with a treatment efficacy or clinical benefit PRO objective. The recommendation is that overall effects can be used alongside a treatment efficacy or clinical benefit PRO objective. Since information is lost with this type of endpoint, relative to improvement, worsening, and stable state (e.g., an overall PRO score over time will not capture the direction and timing of an effect), caution should be taken when planning to use overall effect endpoints.

- In addition, a table showing percentage agreement by stakeholder group will be presented to inform users about which stakeholder might have held a different position on a given recommendation statement at this point in time. For example:

Table: Level of agreement on SISAQOL-IMI Consensus recommendation statements by stakeholder group

Statement	Academic	Industry	Non-profit/ Cancer org.	SME/CRO	Regulatory	HTA	Patient repr.	Total
	(N=17)	(N=5)	(N=8)	(N=4)	(N=4)	(N=2)	(N=1)	(N=41)
	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)	#agreed/n (%)
1	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)
2	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)
3	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)
4	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)
5	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)

Note: When calculating the proportion of agreement, "don't know", "not applicable" and "missing" were omitted from the denominator (n).

Implementation

Before applying these principles to the SISAQOL-IMI recommendations, we will first evaluate whether the recommendation statements are understandable and feasible during the

[1] Coens C, Pe M, Dueck AC. et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. *Lancet Oncol* 2020; **21**: e83-96.

independent validation study (WP 5) in Year 3. If necessary, we will revise the recommendation statements based on the independent validation study with the future users in mind. If there are still substantive concerns that remain, they will be noted under “considerations”. The text for the considerations that will be listed for each recommendation statement should be reviewed and approved by all organizations.

Appendix 3

Figure 1: Development from SISAQOL to SISAQOL-IMI, and workflow towards developing the final SISAQOL-IMI recommendations

The recommendations are developed through 5 consensus meetings. The consensus reports after each consensus meeting document the process by which the consensus is reached and present the final version of the recommendation statements. The SISAQOL, Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data, refers to the former Consortium that published the first set of recommendation statements. The SISAQOL-IMI, Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials - Innovative Medicines Initiative, refers the current Consortium that is working towards extending the work of SISAQOL.

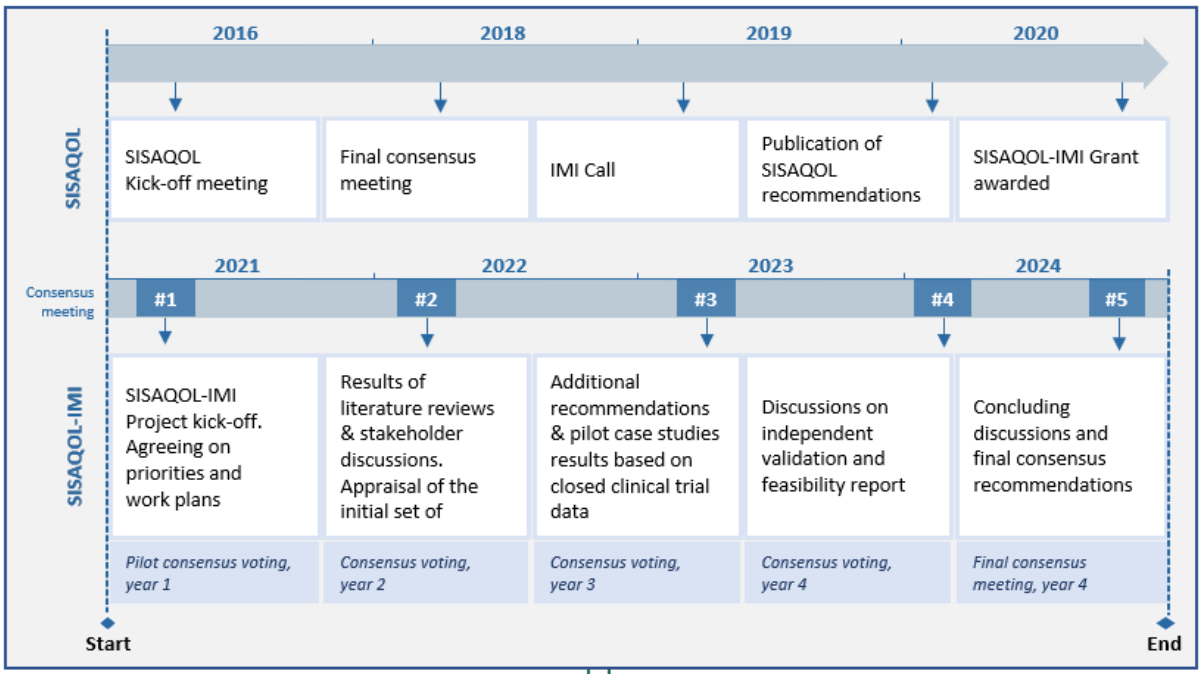
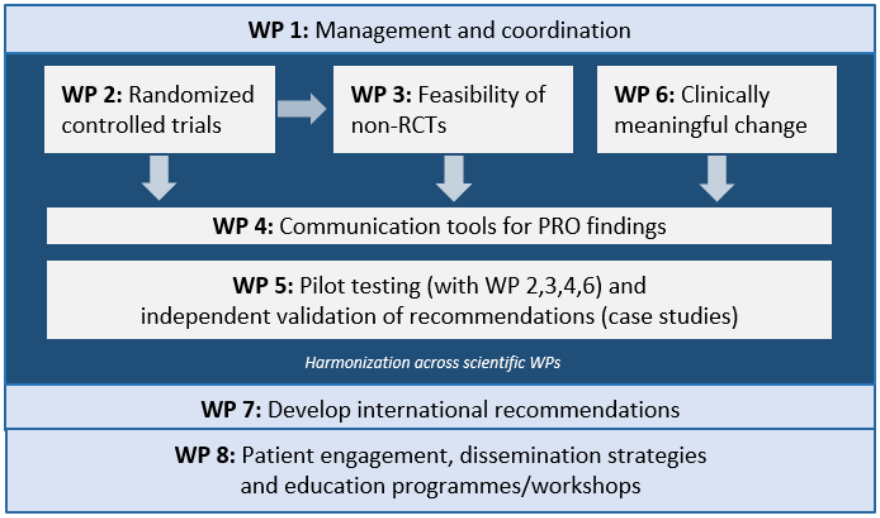


Figure 2: Project structure and interaction between the WPs

SISAQOL-IMI is organised into five scientific work packages (WP 2, 3, 4, 5, 6), and 3 cross-cutting work packages (WP 1, 7, 8).



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imi innovative medicines initiative

efpia

Appendix 4

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Year 1 Executive Summary

Summary for patients and the wider community

Contributors: Silène ten Seldam, Kate Morgan, Katie Joyner, Elektra Papadopoulos, Cecilie Delphin Amdal, Ahu Alanya, Madeline Pe

SISAQOL-IMI

Setting International Standards of Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials – Innovative Medicines Initiative

WHAT IS SISAQOL-IMI?

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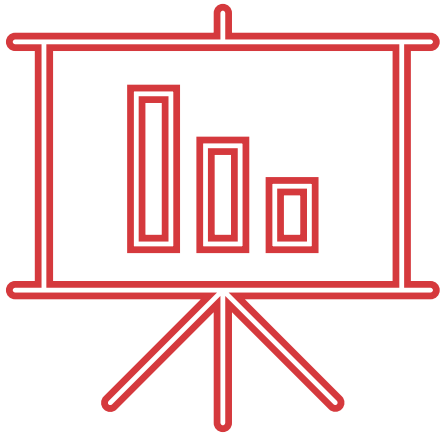
Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints

SISAQOL-IMI has been formed to generate recommendations to standardise the design, analysis, and interpretation of patient-reported outcome (PRO) data in cancer clinical trials



THE CONSORTIUM

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Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints

Duke University School of Medicine

Boehringer Ingelheim

IMIM Parc de Salut MAR Barcelona
Institut Hospital del Mar d'Investigacions Mèdiques

BAYER

IQWiG

Oslo University Hospital

MHRA

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

ES D Evaluation Software Development

Amsterdam UMC
Universitair Medische Centra

Health Canada Santé Canada

Medicines & Healthcare products Regulatory Agency

JCOG
Japan Clinical Oncology Group

PATIENT RELEVANT EVIDENCE
Strategic Advising for Your Patient-Centric Evidence Generation

Adelphi
ADELPHI VALUES

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

UNIVERSITÄTS KLINIKUM FREIBURG

LUMC Leiden University Medical Center

MEDIZINISCHE UNIVERSITÄT INNSBRUCK

KBCRI
KLINIČKI BOLNIČKI CENTAR RIJEKA

Norwegian Medicines Agency

MERCK

KU LEUVEN

NAVARRABIOMED
BIOMEDICAL RESEARCH CENTER

INSTITUT JULES BORDET INSTITUUT

Queen's University

PROTEUS CONSORTIUM

STRATOS INITIATIVE

MODUS OUTCOMES

THE UNIVERSITY OF SYDNEY

Pfizer

abbvie

UNIVERSITY OF BIRMINGHAM | CPROR
CENTRE FOR PATIENT REPORTED OUTCOMES RESEARCH

ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

MPE Myeloma Patients Europe

UNIVERSITY OF LEEDS

CRITICAL PATH INSTITUTE

WHAT ARE THE AIMS OF SISAQOL-IMI?

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Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints

- Recommendations on how to use PRO measures in cancer clinical trials:
  - How to analyse the data
  - How to interpret the data
  - How to present the data
  - Increase the quality of the clinical studies
  - Improve information to patients and clinicians about expected side effects
  - Improve-shared decision-making between patients and physicians and thereby improved patient care

Year 1 Pilot survey

- Broad questions and topics of SISAQOL-IMI organisations identified in survey
  - What PRO objectives are of importance
  - What PRO endpoints are of importance
  - Provide key references and guidelines
- All 41 SISAQOL-IMI organisations responded to the survey

Types of clinical trials

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Randomised control trials: Trials in which the participants are divided by chance into separate groups that compare different treatments or other interventions

Single arm trials: Trials in which everyone enrolled receives the same experimental treatment

PRO objectives

Superiority objective: A treatment-group is better (superior) than the treatment-group it is being compared to (i.e. the control group)

Equivalence/non-inferiority objective: A treatment-group is similar (equivalent) to the treatment-group it is being compared to (i.e. the control group)

Exploratory/descriptive objective: Used to describe the patients' symptoms and functioning without testing them

PRO endpoints

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Endpoint: Outcomes that can be measured objectively to see whether a treatment worked or not

Primary endpoint: The main result to see if a given treatment in a trial worked

Secondary endpoint: Supportive measures that describe whether a treatment works and other effects

Pilot survey results

Overview of main results		Randomised clinical trial			Single-arm trial		
"Would you or your organisation consider using…"		Yes, n	No, n	Yes, %*	Yes, n	No, n	Yes, %*
1	Clinical benefit (**superiority** objective)	40	1	98	23	13	64
2	Clinical benefit (**equivalence/non-inferiority** objective)	38	2	95	19	19	50
3	Descriptive objective (**exploratory/descriptive** objective)	32	7	82	36	5	88
a	Time to improvement	32	5	86	30	9	77
b	Time to worsening	37	3	93	31	7	82
c	Time to stable state	21	11	66	15	19	44
d	Time to end of stable state	14	12	54	15	18	45
e	Magnitude of change at specific time point(s)	37	3	93	33	5	87
f	Responder with improvement at specific time point(s)	34	4	89	30	8	79
g	Responder with worsening at specific time point(s)	31	6	84	26	10	72
h	Responder with stable state at specific time point(s)	19	12	61	19	17	53
i	Overall average or median over a specified timeframe	27	7	79	22	11	67
j	Area under the curve over a specified timeframe	32	3	91	21	14	60
k	Best score over a specified time frame	12	17	41	12	17	41
l	Worst score over a specified time frame	15	18	45	13	18	42
m	Response patterns or profiles over a specified time frame	31	3	91	28	8	78

*Proportion of yes = yes / (yes + no), "don't know" and "missing" is omitted from the denominator
Agreement: Green > 2/3, yellow 1/2 to 2/3, red < 1/2

Consensus meetings

- Recommendations generated throughout the SISAQOL-IMI project will be agreed through consensus and used by all stakeholders involved in PRO data analysis
- Consensus meeting #1 was held 17th-18th March 2021

Consensus meeting #1

- Presentations on pilot survey results, work-packages objectives, work progress and plans for the first year
- Stakeholders shared their perspectives on the current use of PROs and their expectations from the SISAQOL-IMI Consortium
  - Discussions arounds main PRO objectives from the pilot survey
  - All objectives should be kept on the list for evaluation
- The survey results will be used to prioritise the endpoints that are more relevant to the stakeholders when developing the future SISAQOL-IMI recommendations

Next steps

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- Follow-up meeting with the scientific WP leaders to harmonise the work plans
- Harmonisation meetings
- Next consensus survey with proposed recommendation statements
- Next consensus meeting (March 2022)

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This communication reflects the author's view and neither IMI nor the European Union, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained therein. This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 945052. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.