SISAQOL-IMI consensus-based guidelines to design, analyse, interpret, and present patient-reported outcomes in cancer clinical trials

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Standardising the implementation of patient-reported outcomes (PROs) in clinical trials is crucial for evaluating the benefits and risks of cancer treatments. The Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative (SISAQOL-IMI) has developed 146 consensus-based recommendations for designing, analysing, interpreting, and presenting PROs in cancer clinical trials. This initiative, undertaken from 2021 to 2025, involved experts, including statisticians, PRO measurement experts, clinicians, and patient representatives from 41 organisations representing regulatory agencies, academia, the pharmaceutical industry, health–technology assessment bodies, and patient advocates. SISAQOL-IMI provides guidance on the implementation of PROs in randomised controlled trials and single-arm trials, terminology, definitions and the selection of PRO score interpretation thresholds, and for visualising PRO results for different audiences. To facilitate the implementation of these standards, in addition to this Policy Review, four key outputs are available: an interactive table, a guidebook, plain language materials, and a glossary.

Lancet Oncol 2025; 26: e683–93

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Introduction

Health-related quality of life and other patient-reported outcomes (PROs) are recognised as important for evaluating the benefits and risks of cancer treatments. These outcomes are important to a broad range of stakeholders, including clinicians, academics,[1–4] patient advocates,[5] drug developers, international regulatory agencies, and health technology assessment (HTA) bodies.[6–8] Although guidelines exist on how to include PROs in protocols,[9] how to report them in trial publications,[10] and how to create graphical presentations,[11] these guidelines do not provide information on agreed methodological standards for the design, analysis, interpretation, and reporting of PRO data that would be acceptable for various decision makers. Previous reviews have consistently shown that vague PRO research objectives, poorly defined PRO endpoints (including unclear definitions of clinically meaningful change or difference), and a lack of transparency in the reporting of PRO findings have raised concerns about the reliability of such studies.[12] This lack of consistency in PRO reporting could affect the comparative evaluation of cancer clinical trials and hinder the optimal use of PRO data in the decision making of various stakeholders. A common framework is essential across different clinical trial environments (eg, academic and industry-sponsored trials) to ensure that trials generate high-quality PRO data that meet the needs of various stakeholders and for less experienced researchers to access a best-case methodology. To establish consensus recommendations, it was necessary to bring together different stakeholders to develop guidelines that accomplish these needs.

Expanding the Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials (SISAQOL) work[12] into the SISAQOL-Innovative Medicines Initiative (SISAQOL-IMI) was a logical step forward. SISAQOL-IMI aimed to consider various stakeholder needs and adopt recent developments in the methodological literature (eg, the estimands framework from the International Council for Harmonisation [ICH] E9 [R1], which offers guidance on statistical principles for clinical trials aiming for pharmaceutical product registration).[13,14] SISAQOL-IMI involved expert statisticians and other PRO measurement experts to develop practical tools that support the implementation of these the recommendations.[15] The goal of the SISAQOL-IMI was to establish consensus-based guidelines for designing, analysing, interpreting, and presenting PROs in cancer clinical trials.

Four key scientific priority areas were identified, the first being randomised controlled trials (RCTs), where PROs can be used to evaluate the clinical benefit of an intervention or describe the patient perspective, for instance, to complement clinician-reported adverse event data. The second priority is single-arm trials (SATs), where PROs often are used to describe the patient perspective; for example, to support generation of future PRO related hypotheses in an RCT setting or to complement clinician-reported adverse events. In

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settings where an RCT is not feasible to evaluate clinical outcomes,[16] results from SATs are sometimes accepted by regulatory authorities.[17] Recommendations are needed on how to analyse and interpret PROs in such studies[18] to leverage their potential for decision making. The third area of focus is presenting and visualising PRO results in trials, where graphic displays are commonly used to visualise results. Recommendations are required for optimally presenting data for different audiences. The last priority area is defining clinically relevant thresholds for differences and changes in PRO scores. Interpretation of the clinical relevance or meaningfulness of differences and changes in PRO scores is necessary but challenging due to heterogeneity in the definition of these concepts and inconsistencies in both terminology and the methodology on which they are based.[19–21] Despite many design and analysis considerations being similar between SATs and RCTs, the absence of randomisation in SATs means that more care is needed to reduce bias and avoid misleading interpretations.

To support the dissemination and implementation of the recommendations among various expert and stakeholder groups, SISAQOL-IMI has generated scientific and plain language versions of the recommendations, supported by an online, interactive glossary. This Policy Review provides an overview of the consensus process, the methods used, and the project outcomes, including key recommendations and the final outputs: the interactive table (ie, a webtool that allows users to easily navigate the recommendations, and get a tailored set of recommendations based on their PRO research objective and variable of interest), the guidebook, plain language recommendations, and the glossary. We conclude with the lessons learned and outline the plan for implementation and sustainability.

Methods

Implementing the vision: organising workstreams to harmonise PRO standards

Individual researchers and organisations often follow their own procedures and standards for the design, analysis, and interpretation of PRO data. This lack of consistency had led to varying analytical approaches and, at times, confusing or non-comparable findings, making it difficult for stakeholders to use PRO data to effectively inform decision making. The SISAQOL-IMI Consortium was established to address these gaps by bringing together relevant stakeholders who use PROs in the evaluation of cancer treatments, including international regulatory bodies, health technology assessment bodies, the pharmaceutical industry, and academic and professional societies alongside experts in statistics, PRO measurement, clinical oncology, and patient advocacy. This collaboration ensured that the resulting recommendations were both methodologically robust and accessible to both technical and non-technical audiences, which has been reported previously.[15]

The work was organised in eight different work packages (WPs), as illustrated in the appendix (p 1), with international, multidisciplinary participation, including patient representatives, in all WPs. The steering committee, composed of WP leaders and a management team, met bimonthly to address issues, adjust work plans, initiate actions, and ensure alignment across WPs. The general assembly, with the 41 participating organisations, acted as the decision-making body. The consortium included over 180 members from 15 countries, representing 33 funded organisations and eight with other agreements. Details on the SISAQOL-IMI Consortium's organisation are available on the Innovative Health Initiatives website.

Design of the consensus process

The consensus-building process used in this project employed a modified Delphi method. Although the traditional Delphi approach relies on anonymous individual expert surveys conducted in multiple rounds where individual experts review the results and reconsider their votes based on the additional information provided, our method used anonymous surveys at the organisational level, combined with in-person or hybrid meetings and active engagement with diverse stakeholders, including patient partners. This approach enabled real-time discussion, iterative refinement of recommendation statements, and a more inclusive and transparent decision-making process.

There were five yearly meetings and the first consensus process focused on prioritising concepts (table 1). Statements were not developed at this point. Consensus processes 2 and 3 focused on statements related to RCTs (WP2), SATs (WP3), and PRO score interpretation thresholds (WP6). The third process also included statements on how to present PRO results (WP4). Consensus process 4 included one statement related to patient involvement and incorporated the final updates of statements for RCTs, SATs, and PRO score interpretation thresholds. Consensus process 5 focused on the final ratification of the consensus

	Year	Milestones
1	2021	Defined the goals, PRO objectives, and identified expectations
2	2022	Ratification of the first set of recommendations for cancer RCTs, SATs, and clinical meaningful change and PRO score interpretation thresholds
3	2023	Ratification of the updated and expanded version of recommendations for cancer RCTs, SATs, visualisation and presentation of PRO results, and for clinical meaningful change and PRO score interpretation thresholds
4	2024	Ratifications of the final version of recommendations for cancer RCTs, SATs, visualisation and presentation of PRO results, and for clinical meaningful change and PRO score interpretation thresholds
5	2025	Ratification of the final output and sustainability plan

PRO=patient-reported outcome. RCT=randomised controlled trial. SAT=single-arm trial.

Table 1: **Milestones set at the five general assemblies**

recommendations developed in the previous years and sustainability plan.

The overall framework of the consensus process for the development of the recommendations is described in more detail later (see also figure 1). Each process was initiated by the ongoing work within each WP, followed by the consensus process in the SISAQOL-IMI Consortium with voting rounds, discussions, revisions, harmonisation, validation, and the final ratification of the recommendations by the general assembly. SISAQOL-IMI defined statements as the specific formulation of each new advice developed and ratified within the Consortium, while recommendations were defined as the final output, which included statements with the corresponding examples and explanations.

Development of statements for voting

To develop the statements for each of the four priority areas (ie, RCTs, SATs, visualisation and presentation of PRO results, and interpretation of PRO results), the work was divided among four scientific WPs. These WPs used a multistep process to gather the information needed to develop the statements (figure 1).

The initial step involved conducting comprehensive literature reviews. These reviews collated relevant information, evaluated current standard and identified gaps in the literature, while highlighting areas of similarities and divergence. The methods used to select and extract relevant data were described in research protocols, with details provided in appendix 5 of the online guidebook.[22] Each literature review informed the statements within its respective priority area. Harmonisation across WPs took place after the draft statements were developed.

The literature review on RCTs focused on current practices of PRO analysis, existing stakeholder guidelines, and key methodological recommendations for PRO analysis in RCTs.[12] The literature review on SATs centred on current practices and methodological recommendations on design, analysis, reporting, and interpretation of SATs.[16] The literature review on visualisation focused on evidence regarding the graphical representation of PRO data[11] and more general information for the design of PRO visualisations. The literature review on PRO score interpretation thresholds centred on publications regarding clinically meaningful change thresholds between 2009 and 2021. Studies establishing PRO score interpretation thresholds for the most frequently used PRO measures in oncology and methodological articles discussing application of these thresholds were included. Using the information from the literature reviews, expert discussions were conducted within the WPs. Results from these discussions fed into the formulation of the initial set of statements for RCTs, SATs, visualisation and presentation of PRO data, and PRO score interpretation thresholds that were included in the consensus survey.

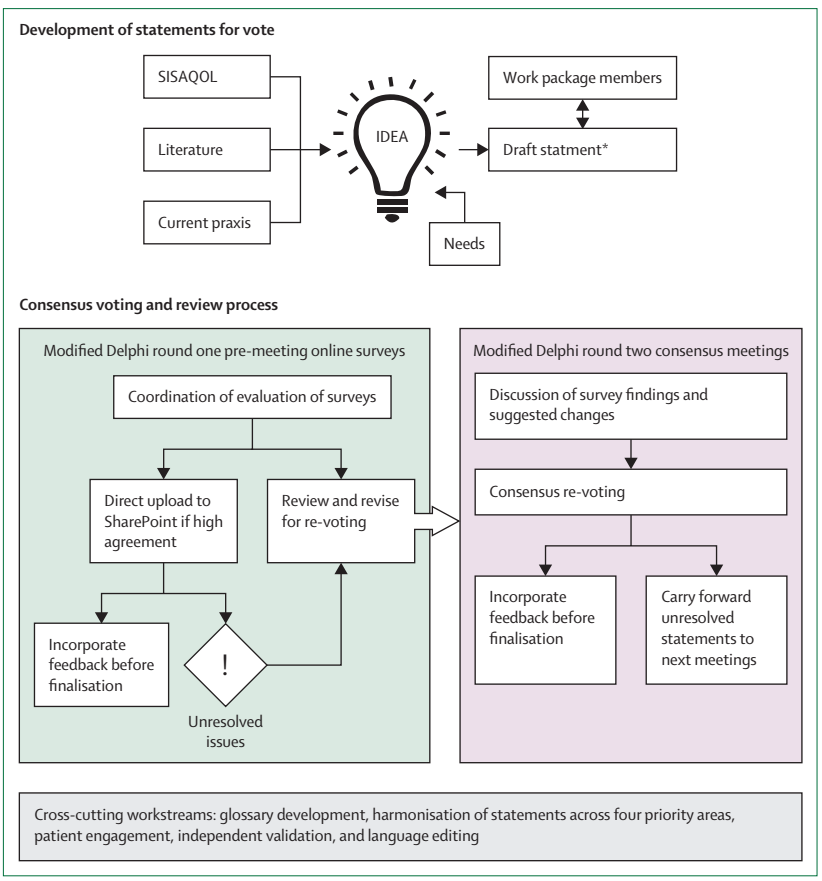

Figure 1: **Framework of each consensus process**
SISAQOL=Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials. *Includes both new proposals and unresolved statements in need of revision.

Consensus voting and review process

The proposed statements were evaluated by the full SISAQOL-IMI Consortium of 41 organisations, each of which cast one vote. Initial votes were collected via pre-meeting online surveys using a 5-point Likert scale (ranging from strongly agree to strongly disagree), with options for "don't know" and "not applicable" along with qualitative comments. WP leads reviewed survey feedback, addressed comments, and revised statements in collaboration with the experts within their WPs. Statements achieving consensus by a two-thirds majority across all stakeholder groups, with no concerns raised, did not have to be re-voted (ie, second vote) during the in-person consensus meeting but were made available online via SharePoint for additional comments from the Consortium. Statements that did not reach the two-thirds majority but received at least half of the votes or statements that reached two-thirds majority but raised concerns in some stakeholder groups were discussed, revised if necessary, and re-voted on during the second round of voting at the consensus meeting. The second round of voting was an important step since some votes might have been a result of misinterpretation of a

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See Online for appendix

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concept or statement and needed further discussions or elaboration with the rest of the Consortium. Unresolved statements (ie, those that received less than one-half of the votes or did not reach sufficient consensus) were either withdrawn or revised for inclusion in the following year's consensus process.

The Consortium agreed upon these voting rules, including the two-step voting procedure (appendix p 2). Recognising that unanimous agreement was not always achievable, the Consortium developed a diverging views document to capture differences in perspectives.[15]

Cross-cutting workstreams

Participation and patient engagement

WP7 coordinated the consensus-building process, actively encouraging timely engagement from all participating organisations. All SISAQOL-IMI organisations participated in all consensus surveys, except for one organisation that opted-out of voting in consensus survey 4 due to time constraints. Each general assembly or consensus meeting was attended by approximately 80 attendees representing all stakeholder groups. Between seven and 12 patient representatives participated in pre-survey discussions and surveys, and between four and six attended the consensus meetings. To encourage input from patient representatives, four workshops were arranged before the consensus meetings to address key issues and clarify complex concepts.

Independent validation

Different initiatives ensured transparency of the consensus process and evaluated whether the statements were accurate, easy to understand, and feasible to be implemented in clinical research. The independent scientific advisory board provided continuous critical review of statements developed by the scientific WPs, clarifying any concerns with discussions involving the responsible WP leaders. In addition, WP 5 performed a two-step independent validation of the preliminary statements, involving interviews with experts and pilot testing of the statements. First, they conducted interviews with 17 individuals with various expertise within oncology, such as statisticians, clinicians, and PRO methodologists. These experts represented academia, industry, regulatory and HTA bodies, and non-profit cancer organisations. Their aim was to evaluate the clarity of the statements. While most statements were interpreted as intended, some confusion arose from unfamiliar terminology or concepts. The WPs used the feedback to revise their statements as needed. Thereafter, 12 experts tested the preliminary statements by applying them to a study protocol with a defined PRO objective, setting up a statistical analysis plan, and outlining how the PRO results would be presented.

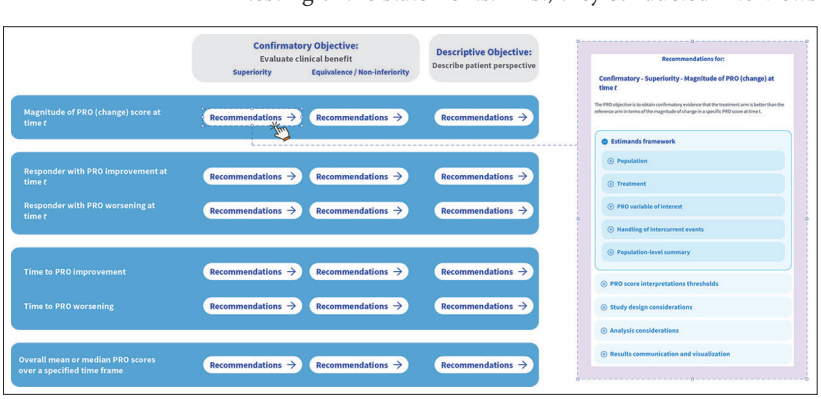

Figure 2: **Screenshot of the interactive table using the analytical framework for organisation of statements as an example**
PRO=patient-reported outcomes.

Harmonisation across WPs, language review, and development of the glossary

To ensure harmonisation of recommendations between RCTs and SATs, the two WP2 and WP3 reviewed each other's recommendations. Recommendations developed for RCTs or SATs that could also be applicable for the other WP were either adopted by the other WP without changes, or adapted with minor changes to the statements, explanations, or examples. To ensure a common understanding and consistent terminology both in scientific and plain language, a glossary was created.[15] A dedicated team developed scientific and plain language versions using a hierarchy of recognised dictionaries (appendix p 3). The Consortium reviewed and agreed upon all the proposed terms. The glossary enabled multiple stakeholders with diverse backgrounds and training, including patient representatives, to actively participate in meaningful discussion and decisions across WPs. In addition, this resource supported terminology harmonisation across WP statements and was important for external participants during the independent validation process. Once all recommendations were available, a professional language editor reviewed all the recommendations in close collaboration with WP leaders, statisticians and PRO methodologists, clinicians, and patient representatives to ensure they were unambiguous, easy to understand, and consistent across WPs. The language editor then reviewed all final output documents to harmonise the language.

Presentation of final recommendations

Given the breadth of over 140 recommendations, the guidance was designed to be intuitive and easy to navigate. The table format allows users to directly access the cell that aligns with their specific PRO objective and endpoint, streamlining the process of identifying relevant guidance. This structure also encourages users to approach their study planning with clearly defined PRO endpoints.

The recommendations were structured as concise statements accompanied by explanations and examples, presented by study design (RCTs or SATs). To facilitate navigation, the recommendations are arranged in a tabular format, with columns specifying the study

objective (eg, confirmatory—superiority and equivalence or non-inferiority—or descriptive), and rows specifying the PRO variable of interest (ie, the PRO endpoint). This structure creates 30 individual cells (ie, 18 for RCTs and 12 for SATs), each representing a unique combination of study design and PRO variable of interest (eg, an RCT with a confirmatory superiority objective [column] and time to PRO improvement [row] endpoint). Figure 2 shows the structure for RCTs as displayed in the interactive table.[23] Within each cell, recommendations are structured based on an analytical framework, consisting of the estimands framework of ICH E9 (R1)[14] and five additional attributes (eg, PRO score interpretation thresholds, study design considerations, external comparison—for single-arm studies only—analysis considerations, and results visualisation and presentation).

Key results and outputs of SISAQOL-IMI

SISAQOL-IMI ratified 146 (98·0%) of the 149 proposed statements related to RCTs (WP2, n=50), SATs (WP3, n=43), visualisation and presentation of PRO results (WP4, n=25), PRO score interpretation thresholds (umbrella term replacing clinically meaningful change; WP6, n=27), and patient involvement (WP8, n=1). Figure 3 describes the development and evolution of the statements throughout consensus processes 2, 3, and 4. During the process, nine statements required re-voting after revision. Due to the substantial overlap between statements for RCTs and SATs, 25 shared recommendations were further harmonised across the WPs (ie, 19 from RCTs and six from SATs) and adopted either identically or adapted with minor wording changes.

Among the 146 accepted statements, the level of agreement was high, ranging from 70% to 100%, and 82% of the statements had agreement greater than 85% (appendix, pp 4–7). 42 statements reached consensus in the first round of voting, while 22 were adapted with minor wording changes without discussion. 82 statements required discussion during consensus meetings. For five statements, divergent views among the stakeholder groups (appendix pp 8–9) were included as "considerations" along with the final recommendation.

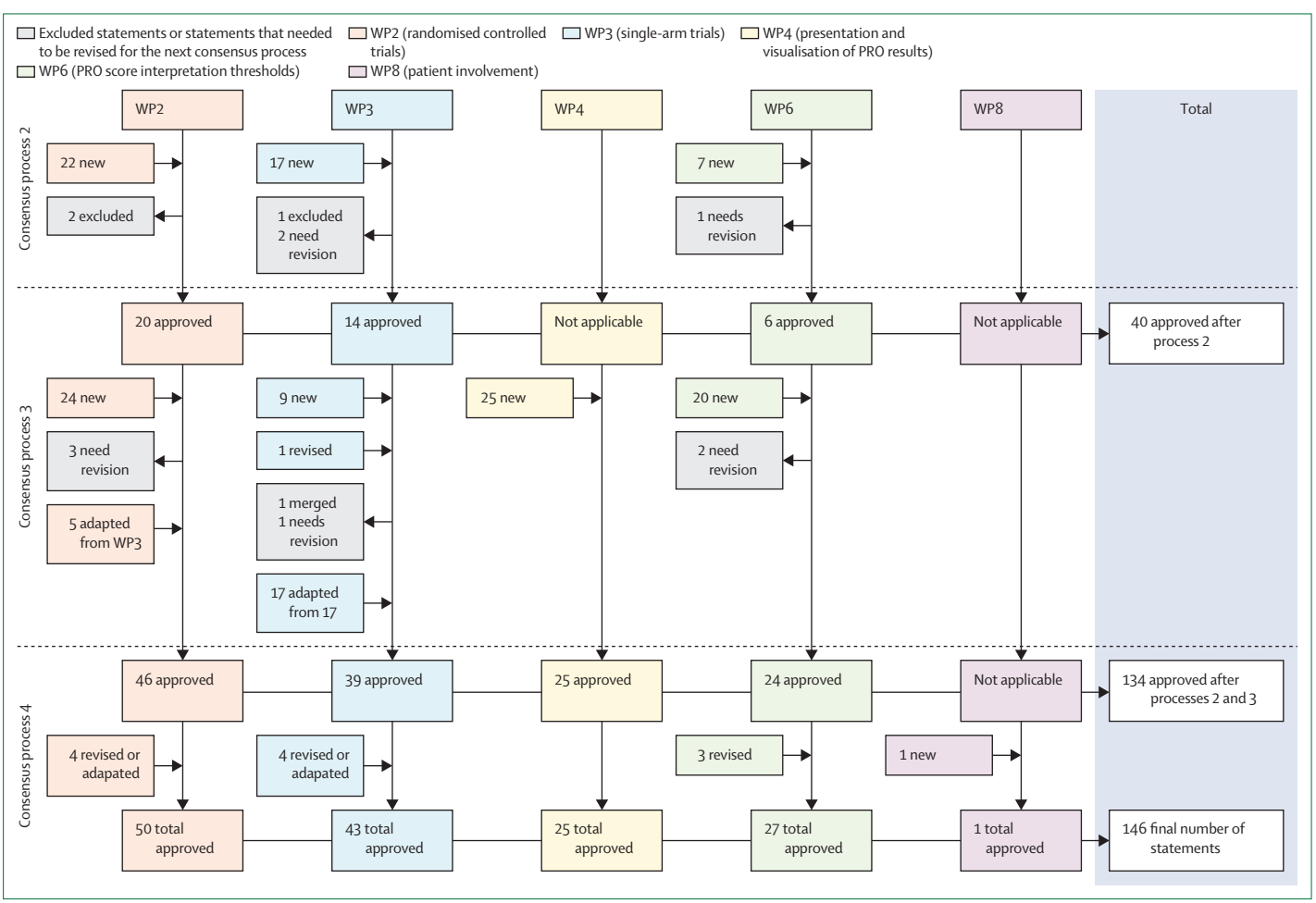

Figure 3: **Development and evolution of statements within each WP**
PRO=patient-reported outcome. WP=work package.

The key results for each of the four scientific priority areas from the WPs are presented in table 2. For RCTs, the recommendations emphasise the need to align estimands with research objectives, an area identified as lacking in current practice.[24] The recommendations provide guidance on both general issues, such as strategies for intercurrent events, handling missing data, and overall PRO analysis strategy, including the need for

	Current standards	SISAQOL-IMI standards	Rationale for change
RCTs (WP2)			
Addressing death in PRO analysis	There is no standard method for addressing death in PRO analysis for RCTs. Hypothetical strategies are often used without specifying the underlying assumptions. According to the established guideline on statistical principles for clinical trials, ICH E9 (R1),[34] a hypothetical strategy is a method used to estimate the treatment effect by assuming a hypothetical scenario: what if the intercurrent event (eg, death) did not occur. Commonly used methods often do not reflect the intended estimand or objective.	There are different strategies to address death, as an intercurrent event in RCTs (eg, hypothetical, composite, while alive, and principal stratum). The choice of strategy will have an influence on the treatment effect estimate and its interpretation. Protocols should define and justify a clear strategy in line with the assumptions based on the pre-defined PRO objective and discussed with relevant stakeholder groups.	Four main strategies for addressing death as an intercurrent event can be considered. For each strategy, the underlying assumptions and resulting interpretation need to be considered in the selection of the best-suited strategy that fits the context of PRO objectives, disease setting, and study constraints.
Missing data versus intercurrent event	Many statistical analyses assume the same number of observations per patient. Unobserved data are often considered as missing and addressed without consideration of underlying causes. No distinction is made between intercurrent events and missing data.	The overall PRO analysis strategy should include a main PRO analysis supported by sensitivity analyses (accounting for missing data) or supplementary analyses (accounting for intercurrent events). It is recommended to report an overview of relevant intercurrent events and reasons and frequencies for missing data.	Intercurrent events can cause relevant PRO data to be unavailable for the analysis (eg, after death). However, the way an intercurrent event is addressed in the analysis is linked to its interpretation, and therefore, to the objective. Missing data are unobserved data (eg, questionnaire lost) and its effects on the results should be handled via sensitivity analyses. Missing data can bias results and affect uncertainty if not handled properly.
Completion rates and available data rates	PRO data might be unavailable for different reasons. The data used in analyses are often insufficiently reported. There is no standard measure addressing data quality nor consistent terminology.	Completion rates and available data rates should be reported for each assessment timepoint. For both, the numerator is set to the number of patients that completed the PRO assessment at that timepoint. For the completion rate, the denominator is set as the number of patients with a scheduled PRO assessment at that timepoint. This denominator can change with time to account for deaths, as an example. For the available data rate, the denominator equals the number of patients randomly assigned in the trial. This denominator will not change with time.	For the calculation of completion rates, a distinction should be made between failure to collect relevant data (leading to missing data) and the choice not to collect or use data due to an intercurrent event, such as treatment discontinuation or progression of disease.
Handling missing data	Simple techniques, such as single imputation, complete case analysis (only including patients with no missing data), or available case analysis (only including patients with no missing data at the timepoint of interest), are often used as they are easily understood.	Single imputation, complete case analysis, or available case analysis to handle missing data are generally not recommended. A justification should be given if these approaches are used. As an alternative, multiple imputation techniques can be considered.	In many RCTs, attrition bias can occur when participants with specific attributes (eg, worse physical status) are more likely to drop out than others. Simple techniques tend to be biased. Moreover, these techniques often ignore the uncertainty resulting from missing data, which can lead to a biased estimate.
Repeating cross-sectional analyses are not recommended in longitudinal analyses	Cross-sectional treatment effect estimates consider data from only a single specific timepoint, which is not an efficient use of the PRO dataset. Moreover, such repeated estimates at consecutive timepoints are often presented as a longitudinal series. Time trends are then inferred but these can result in misleading interpretation.	It is not recommended to analyse data at each timepoint separately using multiple cross-sectional analyses. Longitudinal modelling is preferred.	There is a considerable loss of information by using cross-sectional analyses instead of modelling the full longitudinal profiles. Repeated cross-sectional testing results in multiple testing and does not consider data selection with time (due to patient attrition or missing data), or the correlation between different observations of the same patient.
SATs (WP3)			
Research objectives and estimands	In SATs, PRO objectives are often unclear or not mentioned at all.	SATs should have prespecified PRO objectives that should be translated into key clinical questions using the estimand framework.	Unclear or missing PRO objectives can lead to inappropriate analysis and ambiguous interpretation of results. A clearly specified objective is needed to define the research question and the corresponding estimand.
PRO objectives and the absence of a randomised control group	PRO objectives in SATs are usually descriptive. Naive numerical comparisons are often made with external control data without considering the differences between data sources.	PRO objectives can be descriptive or confirmatory. The analysis strategy should be aligned with the research question using the estimand framework to address the question of interest. Comparisons can be made using changes from baseline or a suitable external control. Appropriate steps should be taken in the design and conduct to reduce bias and avoid misleading interpretations. The absence of random assignment of patients should be addressed.	It is crucial to align the analysis strategy with the research question of interest using the estimand framework question. In some situations, comparing PROs from a SAT to an external control can serve as confirmatory. However, without appropriate design and analysis considerations, comparison with external control data can lead to erroneous conclusions.

(Table 2 continues on next page)

supplementary and sensitivity analyses. The recommendations also address specific issues dependent on the type of analytical metrics used (eg, time to event or responder analyses), including how to account for repeated measures.

For SATs, gaps in the current practice for addressing research questions related to PROs were identified.[16] The recommendations focus on what to consider when including PROs in SATs; providing guidance on formulating research questions that take into account the attributes of the estimands framework; and addressing challenges, such as the absence of a randomised control group, handling of intercurrent events, and missing data, which are quite distinct from absence of data following death. These recommendations are illustrated in a SAT case study with and without an external control group.[25] With regards to visualisation and presentation of PRO results, the recommendations consider both scientific audiences and non-specialist readers. In addition to recommendations on graph types based on previous evidence,[11] advice is provided on the information to include in visualisations that is tailored to specific contexts. For example, graphs presenting PRO data should be consistent with the prespecified domains and timeframes of the trial, with exploratory or descriptive results clearly labelled. Graphs should also include details of sample size, intercurrent events, and missing data to clarify the basis for estimates. Statistical significance should be reported mainly for confirmatory objectives or labelled as exploratory when applicable.

	Current standards	SISAQOL-IMI standards	Rationale for change
(Continued from previous page)			
Handling death in SATs	Currently, there are no well-defined strategies for handling death in PRO analysis in SATs.	There are different strategies to handle death in SATs. The chosen strategy should be defined before analysis in line with the predefined PRO objective. For example, when describing PROs over time, the while-alive strategy is generally preferred. The population-level summary for this approach includes the PRO score of participants alive and descriptive statistics about death, such as the proportion of patients still alive at the timepoint of assessment.	Different strategies can be considered for handling death. For each strategy, the underlying assumptions and resulting interpretation need to be considered. Using a while-alive strategy in SATs aligns with a descriptive research objective (ie, the intention to inform clinicians and patients about expected PROs after the start of treatment). To provide a comprehensive understanding, the expected PRO score at a specific timepoint should be accompanied by the estimated probability of survival at that same time.
Handling missing data versus intercurrent events	The distinction between missing data and data after intercurrent events is frequently overlooked, and assumptions made when handling them are not specified.	Researchers should clearly specify which strategies of the estimand framework are used for the intercurrent events and how missing values are handled. The plausibility of the underlying assumptions on which the analysis method relies and whether the result is still in line with the intended estimand should be examined.	It is crucial to understand the underlying assumptions associated with each method. Sensitivity analyses should be conducted to assess the effect of assumptions made about missing data mechanisms and supplementary analyses accounting for handling intercurrent events. For example, methods such as linear mixed models or generalised linear mixed models implicitly impute values for expected outcomes after death when, in reality, PRO values cease to exist after death. These methods correspond to a hypothetical strategy, which might not align with the research question.
Communication of PRO findings using visualisation (WP4)			
Figures of the main results	The PRO results presented in figures might not correspond to the prespecified research objective and statistical analysis plan of the trial.	The figures should reflect the prespecified PRO objectives and statistical analyses of the trial, particularly regarding the PRO domains and timepoints and frames presented. If figures are presented for additional exploratory or descriptive results, their purpose should be clearly indicated.	(1) To enable immediate differentiation as to whether figures depict the main results of a confirmatory analysis or additional exploratory or descriptive results. (2) To avoid selective presentation (cherry-picking) of results, such as certain PRO domains and timepoints.
Statistical significance	Figures representing results of exploratory or descriptive analyses should include information on statistical significance without clearly identifying them as exploratory or descriptive.	Figures representing results of confirmatory analyses with predefined hypotheses should be the only ones to include information on statistical significance; or, if figures depict results from statistical tests for exploratory or descriptive purposes, this should be clearly indicated and a rationale given.	(1) To promote targeted and transparent reporting of statistical test results. (2) To prevent readers from concluding that exploratory or descriptive results from statistical tests provide the same level of evidence as confirmatory results.
Scaling in graphs	Inconsistencies can exist in the scaling applied to graphs within and across trial reports and publications.	Use consistent scaling reflecting the full PRO score range whenever possible, particularly in graphs based on the same PRO score.	To promote distortion-free and comparable representations of PRO results within and across trial reports and publications.
Sample size, intercurrent events, and missing data	Inconsistencies can exist in the inclusion of numbers of observed patients in figures presenting PRO results.	Graphs should include the number of observed patients, missing data, and intercurrent events at each assessment point.	Enhances transparency on (1) the number of patients on which PRO results are based, and (2) how these numbers compare to the original sample size.
Directionalities of PRO scores	Despite existing standards on this topic, there are inconsistencies in whether labels are provided to support interpretation.	Graphs should include labels to support interpretation (eg, which direction indicates a good or bad PRO score or which direction indicates an improvement or worsening).	Existing standards require emphasis to facilitate the interpretation of results.

(Table 2 continues on next page)

	Current standards	SISAQOL-IMI standards	Rationale for change
(Continued from previous page)			
Interpretation of PRO results (WP6)			
Harmonised terminology for thresholds when interpretating PRO data	Different terms and definitions are used and inconsistently applied for conceptually similar thresholds when interpreting PRO data (eg, minimal clinically important difference and clinically meaningful change).	Harmonised terminology has been established, providing clarification on terms and definitions for various types of PRO score interpretation thresholds.	The currently heterogeneous terminology poses challenges when selecting thresholds for a specific purpose and can lead to inappropriate or misleading application and interpretation.
Differentiation of patient-level and group-level PRO score interpretation thresholds	The literature rarely distinguishes PRO score interpretation thresholds for patient-level scores (eg, for within-patient change) and group-level scores (eg, for between-group differences or within-group change).	Terminology is provided that differentiates patient-level and group-level PRO score interpretation thresholds and different types of thresholds are linked to specific statistical analysis methods for correct implementation and interpretation.	A lack of distinction between patient-level and group-level thresholds compromises interpretation of PRO data and sample size calculation. This confusion can lead to invalid conclusions; for example, when responder thresholds for within-patient change are used for the interpretation of mean differences between groups.
Key criteria for selecting PRO score interpretation thresholds	Different methodological approaches are used to establish PRO score interpretation thresholds for specific PRO measures, with anchor-based and distribution-based methods being the most common.	Key criteria for selecting appropriate thresholds are provided.	The various methods used could result in threshold values that are not fit-for-purpose for specific settings. The established key criteria aim to support the application of valid, relevant thresholds as a cornerstone of PRO data analysis and interpretation.
How to report PRO score interpretation thresholds	Reporting PRO score interpretation thresholds (eg, in clinical trial publications and protocols) is frequently insufficient and does not allow for an understanding and a critical evaluation of their appropriate implementation.	Reporting crucial aspects of how thresholds are selected and applied in the analysis and interpretation of PRO data are encouraged.	Detailed reporting increases the clarity of PRO objectives and provides transparency for evaluating the selection of thresholds, their use in statistical analysis, and for appropriate interpretation of PRO results.

ICH=International Council for Harmonisation. PRO=patient-reported outcome. RCT=randomised controlled trial. SAT=single-arm trial. SISAQOL-IMI=Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative. WP=work package.

Table 2: **Key scientific results for each WP**

For **SISAQOL-IMI** see www.sisaqol-imi.org

Scales in figures should reflect the full range of PRO scores and the directionality of results should be clearly stated. For non-specialist readers, statistical significance is best indicated by symbols (eg, asterisks) rather than p values.

In addition, based on an informal process, general guidelines on creating graphical representations are included. These guidelines focus on effectively using colour, highlights, and figure captions for improving readability, maintaining consistency, and avoiding visual clutter. This general advice was not subject to a formal consensus voting process.

To harmonise terminology for PRO thresholds used for interpretation of clinically meaningful change, the umbrella term "PRO score interpretation threshold" was introduced that refers to both patient-level and group-level data. This umbrella term is complemented with specific terms for patient-level and group-level settings. Recommendations link different types of PRO thresholds to specific statistical analysis methods to ensure the correct interpretation of results. In addition, key criteria are provided for selecting an appropriate PRO score interpretation threshold. For example, the threshold should preferably be anchor-based rather than distribution-based, the threshold should be established in a suitable patient population, and the anchors should be patient-centred. Lastly, the recommendations encourage reporting how thresholds were chosen and applied in the analysis and interpretation of PRO data.

To support and encourage the implementation of the final recommendations, the Consortium has produced five key outputs, all of which will be available on the SISAQOL-IMI website. These outputs include the current SISAQOL-IMI publication; an interactive table that facilitates access to recommendations tailored to specific PRO objectives and endpoints; a guidebook offering detailed background on the development of the recommendations and instructions for using the SISAQOL-IMI outputs; plain language materials, such as checklists and a plain language glossary; and a scientific glossary (appendix pp 12–13).

Discussion

The success of the SISAQOL-IMI project stems from consensus among diverse stakeholders, which was achieved with constructive, open, and results-driven collaboration that led to broadly accepted solutions. High agreement on most statements is expected to promote recognition and implementation of the recommendations within the scientific community and other stakeholder groups. The involvement of a wide range of stakeholders, including statisticians, clinicians, and patient representatives, ensures the relevance of the SISAQOL-IMI content, which in turn supports and facilitates its uptake and application. The clinicians, patient representatives, and patient advocates involved ensure the relevance of this work to patient care.

For SISAQOL-IMI, achieving broad consensus was prioritised over a simple majority vote. Differing perspectives were carefully considered, leading to statements being adjusted during re-voting. Instead of including multiple disclaimers, the diverging views

document was created. As a compromise, statements where the ideal situation was perceived as potentially unfeasible for a specific trial setting included the clause: "any deviation should be justified".

This extensive consensus process produced an agreed set of recommendations reflecting a shared understanding of good practice for PRO endpoints in cancer clinical trials. This comprehensive approach helps prevent the creation of multiple smaller guidelines. The recommendations bridge the gap between PRO-specific guidelines with no analytical focus[9,10] and analytical guidelines,[13,14] which do not specifically address key topics related to PRO endpoints.

Rigorous standards for PROs are needed, similar to those existing for other scientific research areas. SISAQOL-IMI agreed that all consensus recommendations should be methodologically robust and acceptable to the stakeholders. The process was transparent, thorough, and comprehensive, involving parallel and overlapping processes, such as feedback on statements, recommendations, reports, and glossary development. The WP leaders' and Consortium's dedication and tight timelines were key to success.

Unlike other consensus processes, this effort involved organisations as institutional members rather than individuals, requiring internal discussions before reaching consensus. Face-to-face interactions at yearly general assembly or consensus meetings proved invaluable, as informal discussions during breaks helped clarify issues and resolve disagreements, fostering stronger consensus. Patient involvement was crucial. Special meetings and dialogues were arranged to strengthen their involvement. Providing adequate training and support enabled patient representatives to understand the discussions and contribute actively.

The SISAQOL-IMI project has already had a considerable effect on the field of PROs and their application in cancer clinical trials. The recommendations have been cited in the US Food and Drug Administration guidance titled Submitting Patient-Reported Outcome Data in Cancer Clinical Trials.[26] Furthermore, the recommendations have received the American Statistical Association's Statistical Partnership Among Academia, Industry and Government Award for collaboration among academia, industry, and government.[27] The recommendations have been recognised as an important solution to advance the PRO field at the European Medicines Agency and European Organisation for Research and Treatment of Cancer workshop[7] on PRO data in regulatory decision making. Additionally, a collaboration with the European Society for Medical Oncology–Magnitude of Clinical Benefit Scale has begun to provide methodological support for addressing relevant clinical questions.[2]

Although the SISAQOL-IMI recommendations are tailored to cancer clinical research, the methods and concepts are broadly applicable. The Consortium expects they will be relevant for research in disease groups other than cancer, but further studies are needed to validate their relevance and effectiveness across disease populations.

The SISAQOL-IMI final outputs (ie, interactive table, guidebook, plain language material, and glossary) will be freely available on the website, along with an instructional video on how to use the tools effectively. To ensure ongoing progress after the project concludes, SISAQOL-IMI has established an updated steering committee and secretariat, along with a sustainability plan for regular updates and revisions. Digital and in-person courses will be developed and the recommendations will be presented at international conferences. By raising awareness among professionals, the goal is to promote the use of the guidelines to improve PRO design, analyses, interpretation, and visualisation of results of cancer clinical trials. SISAQOL-IMI will develop clinical trial protocol and statistical analysis plan templates to show how the SISAQOL-IMI recommendations can be integrated into these key trial documents. These templates will systematically incorporate PRO elements in a logical sequence, with example text aligned with the SISAQOL-IMI recommendations. The templates will also be freely accessible on the project website.

Search strategy and selection criteria

References for this Policy Review were identified from 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 set. Articles were also identified from searches of the authors' own files and recommendations by the Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative Consortium. Only papers published in English were reviewed. The final reference list was generated based on originality and relevance to the broad scope of this Policy Review.

Conclusion

Aligning statistical approaches, terminology, interpretation, and visualisation of PRO results from cancer clinical trials is crucial to optimise the use of these data in decision making by the relevant stakeholders in the production and use of clinical trial evidence. To facilitate effective implementation in updated guidelines, publications, and future studies, trial results should be presented in a clear and accessible format. The SISAQOL-IMI recommendations will help to achieve this goal and thus standardise inclusion of PROs in clinical trials in the future to make the results more transferable to clinical care and individual patient

wellbeing. The training activities and sustainability plan are essential to ensure the long-term impact of our efforts.

Contributors

All authors are members of the Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative (SISAQOL-IMI) Consortium and were involved in the conceptualisation of this Policy Review. CDA led in the drafting of the manuscript with support from AA, RSF, KB, and MP. MSc, SR, VB, LMV, and AR were all part of the core writing committee. MP, AI, AA CC, MSc, SR, SLC, BH, LMW, JC, MT, PC, JMG, JCC, KB, VP, StS, and EJP are all work package leaders and contributed to the collection and analysis of the SISAQOL-IMI recommendations. All authors representing the 41 organisations in SISAQOL-IMI collected and provided the data for the development of the recommendations. All authors interpreted and reviewed the manuscript and the final outputs of the SISAQOL-IMI recommendations. All 41 organisations involved in SISAQOL-IMI reviewed and approved the final version of this Policy Review. All authors had access to data at the stakeholder level. Organisation-level data were processed by MP, AA, and RSF. All authors had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

KB, JMG, BH, and GR received funding paid to their institution from the Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative (SISAQOL-IMI) grant to conduct this work. ABe, CQ, NC, and MF received travel grants from SISAQOL-IMI to participate in the annual meeting. EB received consulting fees as a scientific advisor for AZ, Navigating Cancer, Verily, N-Power Medicine, Savor, Thyme Care, and Resilience Health. AC was an employee of Genentech from 2011 to 2019 and then AZ from 2020 to 2024; however, the current work was done as part of PRE LLC and on external time. AC has a patent unrelated to this work (AZ ownership); and reports stocks, leadership roles, receipt of equipment and other services, and other financial and non-financial interest from AZ. PC, JC, and SR are employees of Pfizer and receive stocks and have stock options. MJC received grants paid to her institution from the National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre, Health Data Research UK, Innovate UK, Macmillan Cancer Support, GSK, Research England, European Commission and the European Federation of Pharmaceutical Industries and Associations, Brain Tumour Charity, Gilead, Janssen, NIHR, UK Research and Innovation, and Merck; revenue from commercial licence of the symptom burden questionnaire–long COVID; consulting fees from Aparito, Boehringer Ingelheim, CIS Oncology, Merck, Genentech, GSK, Pfizer, Vertex Pharmaceuticals, ICON, Halfloop, the University of Michigan, Northwestern University, EuroQoL, Shionogi, and Cell and Gene Therapy Catapult; payment or honoraria from the University of Maastricht, Sount-Eastern Norway Regional Health Authority, Cochrane Portugal, and Singapore National Medical Research Council; has a leadership role in PROTEUS Consortium for which she receives a consultancy fee; and her family member has stocks in GSK. OLA received grants and contracts paid to University of Birmingham from NIHR Biomedical Research Centres, NIHR Applied Research Collaborations, NIHR Blood and Transplant Research Unit in Precision Transplant and Cellular Therapeutics, Anthony Nolan Trust, Sarcoma UK, and Merck; and personal consulting fees paid through the University of Birmingham from Merck, GSK, Gilead, Boehringer Ingelheim, and Innovate UK. MB received an unrestricted research grant paid to his institution from Pfizer. KC received travel grants from SISAQOL-IMI to attend the annual meeting; and is an employee for Adelphi Values who consult with pharmaceutical companies. SE had membership fees paid by PRO Consortium member firms to the Critical Path Institute (CPATH) to support staff time to participate in the Consortium; received grants and broad agency announcement contract payments from the US Food and Drug Administration to CPATH; travel funds to participate in the American College of Neuropsychopharmacology 2022 Annual meeting; and travel grants to attend the SISAQOL-IMI meeting. CG is an employee of Bayer and holds stock options. MSc is an employee of Merck and received stocks and stock options. EJP is an employee of AbbVie. JCR is the Chair of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life group (unpaid); is a member of a scientific advisory board for EpilepsieNL (unpaid); and received travel grants to attend the annual SISAQOL-IMI meeting. StS reports that her employer Myeloma Patients Europe receives grant and sponsorship from various pharmaceutical companies, which are listed on their webpage.[28] CS received funding from Pfizer and Genentech to her institution; personal consulting fees from Shionogi and Movember; and travel costs from Shionogi to present on a panel at the CPATH COA Consortium meeting. GV received grants from NIHR, Pfizer, and Yorkshire Cancer Research all paid to institution; consulting fees paid from Pfizer, Roche, and Seagen; payments and honoraria from Pfizer, Roche, Novartis, Eisai, and Sanofi; travel support from Pfizer and Roche; payment as part of her participation on a data safety monitoring board or advisory board from Roche, Seagen, and AZ; and holds leadership roles as part of the EORTC board of directors and National Cancer Research Institute Chair of Living with and Beyond Cancer group. All other authors declare no competing interests.

Acknowledgments

The Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative (SISAQOL-IMI) project received funding from the IMI 2 Joint Undertaking under grant agreement number 945052. This Joint Undertaking receives support from the EU's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations (EFPIA). This Policy Review reflects the views of the individual authors and should not be construed to represent official views or policies of the European Medicines Agency, the US Food and Drug Administration, US National Cancer Institute, Medicines and Healthcare products Regulatory Agency, Institute for Quality and Efficiency in Health Care, Health Canada, the Norwegian Medical Products Agency, the American Society of Clinical Oncology, the European Society for Medical Oncology, or any other institution, organisation, or entity. This project received no funding from the US National Institutes of Health. Neither the IMI nor the EU, nor EFPIA are responsible for any use that could be made of the information contained therein. We thank former work package leaders Carla Mamolo, Jinma Ren, Jayne Galinsky, Linda Dirven, and former SISAQOL-IMI Steering Committee members Daniel O'Connor and Kathy Oliver, for their invaluable efforts and dedication. We also thank Rosa Abruzzese for her extensive review and harmonisation of the language in the final deliverables of the project. Lastly, we thank Monika Turek for her help with organisational and administrative support during the entire SISAQOL-IMI project, including the submission of this Policy Review.

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