The Lancet Oncology

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

--Manuscript Draft--

Manuscript Number:	THELANCETONCOLOGY-D-25-00580R1
Article Type:	Policy Review (Invited)
Keywords:	patient-reported outcomes; quality of life; statistical analysis; recommendations; cancer clinical trials; consensus
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Abstract:	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 implementation of PRO in randomised controlled trials and single arm trials, terminology, definitions and selection of PRO score interpretation thresholds, and

	visualising PRO results for different audiences. To facilitate the implementation of these standards, in addition to this publication, four key outputs are available: an interactive table, a guidebook, plain language materials and a glossary.

Reviewers' comments (note that reviewer numbers are issue when reviewers are invited; missing numbers do not necessarily indicate missing reviews):

We thank all the reviewers for their comments to help improve this manuscript further. We have responded to each comment and referred to the relevant page numbers in the document with track changes.

Reviewer #1:

This is very important work that will really propel this PRO work forwards and this is a clearly a culmination of a lot of consensus building on a very large scale. This means that the work has a lot of value for clinicians and researchers. There are some aspects that will help improve the paper in terms of readability and clarity of methods and results:

RESPONSE: We highly appreciate this feedback, thank you.

INTRODUCTION:

1. I think the introduction could include a bit more justification for the need for the work. The authors have set this out but should be stronger in their details about what is currently not working and how this will really solve these problems. This especially for readers who are not experts in this field, but should care about the details of this.

RESPONSE: We thank the reviewer for this thoughtful comment. We have now added a sentence in the introduction to clarify the current state of PROs/HRQOL in oncology trials (see p. 8 – track changes document).

"Previous reviews have consistently demonstrated that vague PRO research objectives, lack of well-defined PRO endpoints, including unclear definitions a of clinically meaningful change or difference, and lack of transparency in the reporting of PRO findings have raised concerns about their reliability"

2. The authors have set out that there are guidelines about how to include PROs in protocols, but then go on to indicate that we need more guidance on how to design studies also. Is that lacking in the current guidance?

RESPONSE: Reporting guidelines inform trialists on what to report in protocols or clinical trial reports, but it does not provide information on the methodological standards that need to be included in these sections of the protocols/reports. We have now clarified this on p. 8.

"… they do not provide information on an agreed methodological standard for the design, analysis, interpretation, and reporting of PRO data that would be acceptable for various decision-makers."

3. The authors should explain what ICH E9 is.

RESPONSE: We have added this explanation on p. 8.

"… which offer guidance on statistical principles for clinical trials aiming for pharmaceutical product registration"

4. When the justification for the work is clearer, the aims will flow more naturally from that.

RESPONSE: Thank you for this comment. We have now updated the introduction based on the comments above and agree that the flow is better with these suggestions.

5. There should be more explanation as to why there would be a difference between RCTs and SATs when it comes to design and analysis etc. I am sure it is quite obvious but that clarity should be spelled out. In addition, would these differences influence the way the study was designed, the study that is described in this paper?

RESPONSE: Thank you for this comment. We have now included this in the introduction and provided a cautionary note about the difference in the level of evidence from a RCT vs single-arm study (see p. 9).

"Despite many design and analysis considerations being similar between SATs and RCTs, the absence of randomisation in SATs implies that more care is needed to reduce bias and avoid misleading interpretations."

6. Explain what the 'interactive table' is about.

RESPONSE: We have explained this further on p. 9

"… a webtool that allows users to easily navigate through the recommendations and get a tailored set of recommendations based on their PRO research objective and variable of interest."

METHODOLOGY:

7. The methodology is quite difficult to follow. I think this section could benefit from a Design section, outlining the methods that were used to gather this information. Currently it talks about WPs but not about the underlying methods that were applied to get to the results that are needed. And what is therefore the process that was followed.

RESPONSE: Thank you for this comment. We have now updated and reorganized this part to make it easier to follow. A section on design, outlining the methods, is included (see pp. 10-14). This five-year consensus project was designed with repetitive consensus processes including the yearly GA consensus meetings addressing a specific milestone each year as outlined in Table 1. The overall framework of each of these consensus processes is described in Figure 1.

8. The description of the WPs is very complex and I am not sure that adds anything. The WPs link to the overall study, which is fine, but the description of the paper is about 4 WPs. I found I lost the thread quite quickly with this and wonder whether it would be better to just describe the four WPs and what they did.

RESPONSE: The methods used in the four scientific WPs is quite similar and would imply a lot of repetition if described separately. We have now rewritten and reorganised the methods section and hopefully, it is now less complex. Details about the methods used in the WPs are available online in the Guidebook appendix 5 and this can be found in the SISAQOL website: www. sisaqol-imi.org, please see pp 11-12 in the method section for details.

9. One of the important things is the make-up of the consortium and how this was curated. Given that these were the people making the decisions and working towards consensus it would be important to understand how they were chosen and what the thinking was behind the make-up of the consortium. This because the choices here influence the final decisions.

RESPONSE: We have updated this section and have now included a rationale for the make-up of the consortium (p.10).

"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 effectively in decision-making. The SISAQOL-IMI Consortium was established to address these gaps by bringing together relevant stakeholders who rely on PROs, including international regulatory agencies, health technology assessment bodies, industry, academic and professional societies alongside experts in statistics, PRO measurement, clinical oncology, and patient advocacy. This collaboration ensures that the resulting recommendations are both methodologically robust and accessible to both technical and non-technical audiences. More information on the Consortium has been reported in a previous publication."

10. There is quite a lot of referring to Figures that are not very easy to understand, so perhaps more explanation in the text is helpful. Much of the description is not easy to understand without understanding the figures.

RESPONSE: Thank you for this comment. The order and content of the Figures have been changed as described below, and we have included more explanation in the manuscript.

The numbering of figures has been changed according to the revised presentation in the manuscript text:

- *The original Figure 2 "Overview of the consensus process" has been renamed and changed to Figure 1 "Framework of each of the consensus processes"*
- *The original Figure 4 "Consensus process" has changed to Figure 3 "Development and evolution of statements"*
- *The original Figure 1 has changed number to Figure 2, but the title is unchanged.*
- *The original Figure 3 has changed number to Figure 4*

11. The section refers to 'statements' without explaining what they are how they were developed. Where did these come from and what was their purpose and what was the ask of participants?

RESPONSE: Statements are now defined as follows (see pp. 10-11): 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 and the corresponding examples and explanation.

A more detailed description of the development process of the statements has been included. We created a separate heading called "The methods used to develop statements in the work packages" (see page 11).

12. Why would a statement that did not reach consensus be revised? Why not rejected? A bit more explanation would help. And to this point, perhaps more upfront understanding of the process and decision rules would make this clearer.

RESPONSE: Thank you for pointing this out. We have now elaborated the text to explain why, please see page 13.

"Statements that did not reach the two-thirds majority but received at least half of the votes; and/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. This was an important consideration since some votes may be a result of misinterpretation of a concept or statement and needed further discussions or elaboration with the rest of the Consortium."

13. What is the difference between a statement and a recommendation, and how were the recommendations developed and by whom?

RESPONSE: Thank you for pointing this out, we have now included a definition of both statement and recommendation on p 11. 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 including statements with examples and explanation.

14. In the INDEPENDENT VALIDATION section the first sentence is difficult to understand. What process? And what does integrity refer to? and how is a recommendation validated? What would the methods be for that?

RESPONSE: We agree that the first sentence is difficult to understand and have now revised the text. The recommendations were validated by two external sources: the ISAB and by external experts that participated in the WP5 led validation process with 1) expert interviews and 2) pilot testing of the statements. The text has been modified to explain this better, please see pp 15-16 under the section Independent Validation.

15. The development of a glossary should be justified: given the complexity of the subject matter for many clinicians, and given the purpose of the work is to make things clearer, this might be quite a cumbersome way to transfer knowledge?

RESPONSE: In the final outputs the glossary is integrated in the interactive table, the guidebook and the patient material as popup boxes that we believe will facilitate transfer of knowledge, contrary to being cumbersome. The text is now revised to better reflect this point on page 14.

"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 harmonization across WP statements and was important for external participants during the independent validation process."

Once these aspects are clearer it will be easier to assess the quality of discussion.

Reviewer #4:

This paper reports the process used to establish consensus-based guidelines for designing, analysing, interpreting and presenting PROs in cancer clinical trials, and the outputs of that process. The process was designed and implemented by a large international multidisciplinary consortium (SISAQOL-IMI), and included the involvement of a wide range of relevant stakeholders, perspectives and expertise, including clinical trialists, statisticians, clinician-researchers, representing academia, industry, regulatory/HTA bodies, and non-profit cancer organisations - plus patient representatives. This initiative was meticulously organised and implemented, and this same ethos is apparent this paper, which is clear and thorough, and makes an important contribution to the literature.

RESPONSE: We highly appreciate this feedback, thank you

MAJOR:

1. Page 9 - The Methods section headed 'Development of the recommendations' describes a 4 key steps in the development process: 'a) to evaluate current standards and address the gaps in the

literature, b) to develop ways to improve the standards through expert discussions and surveys within WPs, c) to achieve consensus regarding the harmonised way of moving forward, and d) to validate the feasibility of implementing the recommendations'.

The next Methods sections address Steps c and d under headings 'The consensus process' and 'Independent validation'. So one wonders what methods were used to address Steps a and b. Figure 1 indicates that Step a was addressed with literature reviews of cancer clinical trials and existing guidelines to describe the current state of practice in the design, analysis, reporting and presentation of PRO data. Such a literature review must have been a mammoth task. However, there are no specific methods described for that literature review such as search terms, screening process, etc. This is an important point that should be addressed. Similarly, Figure 1 indicates that Step b was addressed with expert discussions and surveys within work packages and methodological evaluation of results, but no specific methods are described for this step. Again, this is a critical gap in the paper that needs to be filled.

RESPONSE: Thank you for this comment. We agree and have now included more information about the methods used in the WPs on pp. 11-12 under the heading: The methods used to develop statements in the work packages.

MINOR:

2. Page 10 - These statements were made available online for comments from the Consortium. Suggest you add '(via Sharepoint)' here to provide an explicit link to the relevant box in Fig 2.

RESPONSE: Thank you. This is now included in the text on page 13.

3. Page 10 - 'Unresolved statements were either withdrawn or revised for inclusion in the following year's survey (third round of voting).' It is not clear to me whether this step is covered in Figure 2. Can you please clarify? If not, would it be useful to modify Fig 2 to include this step for completeness? If it is included already, that is not clear to me and perhaps not to eventual readers. Can you modify Fig 2 to make this clearer? E.g. is an additional recurrent looping arrow required?

RESPONSE: Thank you, we have now revised the Figure (which is now Figure 1). We have included an additional box for unresolved statements and a footnote to explain what happened to these statements. In the manuscript, page 13, the text has been elaborated:

"Unresolved statements (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".

4. Page 10 - five additional attributes. It would be helpful here to list the 5 attributes and indicate how these relate to the goals stated in the intro: design, analyse, present/visualise and interpret.

RESPONSE: Thank you, the five additional attributes are now listed: (PRO score interpretation thresholds, study design considerations, external comparison (for single-arm studies only), *analyses considerations and results visualisation and presentation), see p. 15.*

5. Page 12, Figures 2 vs 4 - I'd like to see a more explicit connection between Figures 2 and 4 regarding Consensus Processes 2, 3 and 4. See also my comment above re 3rd round of voting. Please revise the text here and above (paragraph about Figure 2) to provide full clarity on the number consensus processes and their placement in the overall scheme. Making this clear in

the text may suffice, but you might also think about whether any of the process terms in Figures 2 and 4 could harmonised to make the connection between Figures 2 and 4 regarding Consensus Processes 2, 3 and 4 more explicit.

RESPONSE: Figure 2 (changed to Figure 1) is the framework applied for each consensus process. Figure 4 (changed to Figure 3) describes the development and evolvement of the statements throughout consensus processes 2, 3 and 4. We have now included a paragraph to clarify the number and content of the consensus processes (pp 13-14). Hopefully this will make the connection between the Figures easier to follow.

"The first consensus process focused on prioritising concepts. Statements were not developed at this point. Consensus process two and three focused on statements related to RCTs (WP2), SATs (WP3) and PRO score interpretation thresholds (WP6) (Figure 3). The third process also included statements on how to present PRO results (WP4). The fourth consensus process included one statement related to patient involvement and the final updates of statements for RCT, SATS, and PRO score interpretation thresholds."

6. Page 12 - Table 2 -The term 'hypothetical' is used 3 times in Table 2. But I find its use hard to understand, e.g. 'hypothetical strategies are often used'. Synonyms for hypothetical include 'imagined' and 'supposed', and the antonym is 'real'. How can hypothetical strategies be used? Is this the best term? Is it an established term? If you feel it is the best term, perhaps explain what it means somewhere.

RESPONSE: According to the established guideline on statistical principles for clinical trials, ICH E9 (R1), there are different strategies to address death as an intercurrent event of which one of them is named "hypothetical". Thus, we would like to keep the established term as it is in Table 2.

7. Page 12 - Appendix 6 - This page needs to be landscape rather than portrait to make all columns visible.

RESPONSE: We agree, this is now changed to landscape

8. Page 15 - 'scientific community' - Is this term broad enough? Does it implicitly exclude some stakeholders? Consider modifying or adding to it to convey the broad range stakeholders who will hopefully adopt and apply these recommendations, including scientists from academia, industry and government, and non-scientists from both sides of the consulting table (i.e. clinicians and patient advocates), also importantly cancer clinical trials groups. Given the remainder of the paragraph, pergaps the best solution is simply to delete the phrase 'within the scientific community'? Or amend it to make your intended meaning clear.

RESPONSE: Thank you, the sentence has been expanded to include "other stakeholder groups". See p. 20.

9. Page 16 - first sentence of Conclusion ends with 'stakeholders' - I suggest you append this sentence with a phrase such as 'in the production and use of clinical trial evidence' as otherwise the term 'stakeholders' is very generic. Specifying here 'production and use of clinical trial evidence' may be more conceptually embracing than merely listing all the stakeholders, which was done in the previous paragraphs where it served a good purpose.

RESPONSE: Thank you for this suggested edit. We have now modified the first sentence of the Conclusion with: "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

within and across relevant stakeholders in the production and use of clinical trial evidence." (see p. 22).

Editorial comments:

1. Please provide: one preferred degree qualification per author and indicate any full professors; affiliation details (department, institute, city, state, country) for each author; full institutional correspondence address for corresponding author.

RESPONSE: Done, and corresponding author is mentioned in the paper

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Affiliations are updated

2. Please check that all author details and affiliations are correct in both the main text and appendix investigator lists (if applicable). We do not guarantee that we will fix errors or omissions after publication (if your article is accepted).

RESPONSE: Not applicable.

3. Please ensure that your conflict of interest statement matches the submitted ICMJE forms.

RESPONSE: Done.

4. Please ensure that your contributors section matches that in the author statement forms.

RESPONSE: Confirmed.

5. We require written consent from any individuals who are cited in acknowledgments. The following format can be used: "I permit <corresponding author> et al to list my name in the acknowledgments section of their manuscript and I have seen a copy of the paper <full article title>"

RESPONSE: The final draft of the paper was shared and the consent of all acknowledged people were obtained via email.

6. We require confirmation that the paper has not been submitted to another journal and has not been published in whole or in part elsewhere previously.

RESPONSE: We confirm that the paper has not been submitted to another journal and has not been published in whole or in part elsewhere previously..

7. For papers listed in references that are "in press" we need to see a galley proof and letter from the publisher stating that it is 'in press' as well as the full expected citation (ie, publication date/volume/issue etc).

RESPONSE: No such references were used in this paper

8. Please ensure that you provide your figures in editable formats. For trial profiles (clinical trials) and study selection diagrams (systematic reviews and meta-analyses), figures must be provided

as Word files (.doc or .docx) or powerpoint files (.ppt or .pptx) and made of boxes with editable text. For any statistical images such as histograms, survival or time-to-event curves, line graphs, scatter graphs, and forest plots you should provide editable vector files (ie, the original artwork generated by the statistical package used to make the image, typically by using "Export" or "Print to file" commands); our preferred formats for these files are .eps, .pdf, or .ai. Photographic images must be provided at a minimum of 300 dpi at 107 mm wide. We cannot guarantee accurate reproduction of images without these files. For more information, see our artwork guidelines here.

RESPONSE: Revised accordingly

9. References should be in the Vancouver style and numbered in the order in which they first appear in the manuscript. If the references "move" from the body text into tables or figures, please maintain the sequence of citation. Please ensure tables and figures are cited correctly in the body text to prevent the need for renumbering of references should the table and figure citations subsequently move. Please ensure that reference numbering throughout the manuscript is not inserted with electronic referencing software, such as Endnote.

RESPONSE: References checked.

10. Please supply a section entitled "Search strategy and selection criteria". This should state clearly the sources (databases, journals, or book reference lists, etc) of the material covered and the criteria used to include or exclude studies. Please state which search terms, languages and date ranges were used.

RESPONSE: This has been added to the manuscript.

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 final reference list was generated based on originality and relevance to the broad scope of this Review.

11. Please supply tables as separate Word files (not excel or fdf/pdf). Each row of data should be in a separate line. Please ensure that rows and columns are not tabbed; data should be entered in cell form.

RESPONSE: Tables are merged in a separate Word file and tabs and paragraph marks are removed.

12. Please supply the webappendix as a single PDF file, with the pages paginated - when you refer to an item in the appendix, please refer to the page number on which it appears, not the table or section. Please note that we will be unable to correct any errors in the webappendix, including errors or omissions in author names or affiliations, following publication; as such, please check carefully when submitting.

RESPONSE: Revised as PDF file, page numbers are inserted in the main text where Appendices are referenced.

13. Please ensure ICMJE and Author Statement forms have been submitted for all authors.

RESPONSE: We confirm that all ICMJE and Author Statement forms have been submitted

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

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Summary

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 implementation of PRO in randomised controlled trials and single arm trials, terminology, definitions and selection of PRO score interpretation thresholds, and visualising PRO results for different audiences. To facilitate the implementation of these standards, in addition to this publication, four key outputs are available: an interactive table, a guidebook, plain language materials and a glossary (www.sisaqol-imi.org).

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 final reference list was generated based on originality and relevance to the broad scope of this Review.

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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: 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], ~~there~~ they do not provide information on ~~an~~ agreed methodological~~are limited~~ ~~agreed~~ standard~~s~~ ~~on how to~~for the design, ~~analyse~~analysis, interpretation, and reporting of PRO data ~~across all parties involved in clinical trials~~that would be acceptable for various decision-makers. Previous reviews have consistently demonstrated that vague PRO research objectives, ~~lack of well-~~poorly defined PRO endpoints, ~~-~~ including unclear ~~defining~~definitions ~~a~~ of clinically meaningful change or difference~~—~~, and lack of transparency in the reporting of PRO findings have raised concerns about their reliability~~put into question the reliability of these findings~~[12]. This gap may impact the comparative evaluation of cancer clinical trials and hinder the optimal use of PRO~~these~~ data in the decision-making of various stakeholders. A common framework is essential across different clinical trial environments (e.g., academic and industry-sponsored) 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 SISAQOL "Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials" work [12] into the SISAQOL-Innovative Medicines Initiative (SISAQOL-IMI) was a logical step forward. SISAQOL-IMI aimed to consider various stakeholder needs, adopt recent developments in the methodological literature (e.g., the estimands framework from 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.

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Four key scientific priority areas were identified:

a) Randomised controlled trials (RCTs), where PROs can be used to evaluate the clinical benefit of an intervention and/or describe the patient perspective, for instance, to complement clinician-reported adverse event data.
b) 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 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.
c) 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.
d) 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 implies 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 manuscript provides an overview of the consensus process, ~~detailing~~ the methods used and the project outcomes, including key recommendations and the final outputs: the interactive table (a webtool that allows users to easily navigate through the recommendations, and get a tailored set of recommendations based on their PRO research objective and variable of interest), the guidebook, the plain language recommendations, and the glossary. It concludes with lessons learned and outlines the plan for implementation and sustainability.

Methodology

~~Organisation, leadership and management process~~**The SISAQOL-IMI Consortium and the organisation of its work**

~~The SISAQOL-IMI Consortium was co-chaired by the European Organisation for Research and Treatment of Cancer (EORTC) (representing academia) and Boehringer Ingelheim (representing pharmaceutical companies).~~ 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, industry, academic and professional societies alongside experts in statistics, PRO measurement, clinical oncology, and patient advocacy. This collaboration ensures that the resulting recommendations are both methodologically robust and accessible to both technical and non-technical audiences. More information on the Consortium has been reported in a previous publication[15].~~from a broad range of stakeholder groups representing regulatory agencies, academia, the pharmaceutical industry, HTA bodies, clinicians and patient advocates.~~

The work was organised in eight different work packages (WPs), as illustrated in the Appendix (page 1), with international, multidisciplinary~~, multinational~~ participation, including patient representatives, in all WPs. ~~To address scientific priorities for implementing PROs in cancer clinical trials, four scientific WPs focused on developing recommendations for the four key areas: RCTs (WP2), SATs (WP3), communication tools for PRO findings (WP4), and clinically meaningful changes (WP6). Involving external experts, WP5 independently validated the feasibility of implementing the preliminary recommendations in protocols and statistical analysis plans. Additionally, three cross-cutting WPs managed the overall coordination (WP1), the consensus process and the final deliverables (WP7), and communication of results and patient representation throughout the process (WP8).~~

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 (GA), 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: (Innovative Health Initiative | IHI Innovative Health Initiative)[22].

The ~~consensus process~~project design and definitions

This five-year consensus project was designed with repetitive consensus processes including the yearly GA consensus meetings addressing a specific milestone each year (Table 1). The overall framework of each of these consensus processes is described in 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 GA. 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.

The methods used to develop statements in the work packages

To develop the statements for each of the four priority areas (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 multi-step process to gather the information needed to develop the statements (see Figure 2).

By conducting targeted literature reviews, the WPs collated relevant information, evaluated current standards 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 (www.sisaqol-imi.org).

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 reviews on SATs** focused on current practices and methodological recommendations on design, analysis, reporting and interpretation of SATs[16]. **The literature review on visualisation** focused on -evidence on 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** focused on publications on clinically meaningful

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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. The results of the literature reviews fed into the formulation of the initial set of statements for RCTs, SATs, visualisation and presentation of PRO data, and PRO score interpretation thresholds.

The next step was to conduct surveys and hold expert discussions within the WPs. Specific surveys were performed involving the members of each WP, focusing on topics that were not sufficiently covered by the literature review or topics raised in the previous consensus meeting. Results from these surveys were discussed with all WP members; discussion outcomes were noted and formed the basis to develop new statements for the next consensus process.

Subsequently, the WPs proposed draft statements that wereas included in the consensus survey (see Figure 1).

The involvement of the whole Consortium: the consensus process

The framework for consensus process one to four is displayed in Figure 1. Each- year in December, the consensus process began with the scientific WPs submitteding their proposed statements to the coordinating WP7. Selected consortium members (Ppatient representatives, clinicians and statisticians) reviewed the statements for clarity. Based on their feedback, WP leaders updated the statements as needed before including them in the first round of voting in the consensus survey. Statements achieving consensus by a two-thirds majority across all stakeholder groups, with no concerns raised, did not have to be revoted a (i.e., 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; and/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 may have been a result of misinterpretation of a concept or statement and needed further discussions or elaboration with the rest of the Consortium. Unresolved statements (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.

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Each organisation had one vote. To ensure high consensus, the Consortium agreed upon voting rules, including a two-step voting procedure (Appendix 2 on page 2). Recognising that unanimous agreement was not always achievable, the Consortium developed a "diverging views document" to capture differences in perspectives[15].

The first consensus process focused on prioritising concepts. Statements were not developed at this point. Consensus process two and three focused on statements related to RCTs (WP2), SATs (WP3) and PRO score interpretation thresholds (WP6) (Figure 3). The third process also included statements on how to present PRO results (WP4). The fourth consensus process included one statement related to patient involvement and the final updates of statements for RCTs, SAT
s, and PRO score interpretation thresholds.

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 GA/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 prior to the consensus meetings to address key issues and clarify complex concepts.

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Organisation of final recommendations

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 (confirmatory—superiority and equivalence/non-inferiority—or descriptive), and rows specifying the PRO variable of interest (the PRO endpoint). This structure creates 30 individual 'cells' (18 for RCTs, and 12 for SATs), each representing a unique combination of study design and PRO variable of interest (e.g., an RCT with a confirmatory superiority

objective [column] and time to PRO improvement [row] endpoint). Figure 4 demonstrates the structure for RCTs as displayed in the interactive table. 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 (PRO score interpretation thresholds, study design considerations, external comparison (for single-arm studies only), analyseis considerations and results visualisation and presentation).

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 through discussions with the responsible WP leaders. In addition, one WP (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: statisticians, clinicians, PRO methodologists. These experts represented academia, industry, regulatory/HTA bodies, and non-profit cancer organisations~~.~~. Their aim is 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.

Reconciliation between work packages, development of the glossary, and language review

To ensure harmonisation of recommendations between RCTs and SATs, the two WPs 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 (see Appendix 3, page 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

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actively participate in meaningful discussion and decisions across WPs. In addition, this resource supported terminology harmonization 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.

Key results and outputs of SISAQOL-IMI

Final recommendation statements

SISAQOL-IMI ratified 146 out 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 evolvement 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 (19 from RCTs and 6 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 above 85% (see Appendix, pages 4-7). Forty-two statements reached consensus in the first round of voting, while 22 were adapted with minor wording changes without discussion. Eighty-two statements required discussion during consensus meetings. For five statements, divergent views among the stakeholder groups (see Appendix, pages 8-9) were included as "considerations" along with the final recommendation.

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The key results for each of the four scientific priority areas from the WPs are presented in Table 2.

a) For RCTs, the recommendations emphasise the need to align estimands with research objectives, an area identified as lacking in current practice[23]. 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 supplementary and sensitivity analyses. They also address specific issues dependent on the type of analytic metrics used (e.g., time to event, responder analyses) including how to account for repeated measures.

b) 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 taking 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[24].

c) 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, tailored to specific contexts. For example, graphs presenting PRO data should be consistent with the pre-specified domains and time frames of the trial, with exploratory or descriptive results clearly labelled. They should also include details on 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. 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 (e.g., asterisks) rather than p-values.

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

d) 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- 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. Finally, the recommendations encourage reporting how thresholds were chosen and applied in the analysis and interpretation of PRO data.

SISAQOL-IMI outputs

To support and encourage the implementation of the final recommendations, the Consortium produced five key outputs, which will be available on the SISAQOL-IMI website [https://www.sisaqol-imi.org/].

Field Code Changed

1. ***The current SISAQOL-IMI publication***

This publication aims to enhance transparency and implementation by presenting the SISAQOL-IMI consensus process and final results. Sharing lessons learned and outlining sustainability plans supports the long-term impact of the SISAQOL-IMI recommendations.

2. ***An interactive table***

This table presents the recommendations organised according to the study objective and PRO variable of interest to give researchers easy access to recommendations relevant to their specific study design. Each recommendation was evaluated and assigned to the applicable cells of the web tool (Appendix, page 10) and the corresponding attribute of the analytical framework. Ideally, the recommendations should be used in the planning phase of a (cancer) clinical trial and applied throughout the process.

3. ***A guidebook***

The guidebook outlines the development process of the SISAQOL-IMI recommendations, applied methods, lessons learned, and the sustainability plan. It provides instructions for using SISAQOL-IMI outputs (interactive table, glossary, plain language checklist), and also covers the SISAQOL-IMI recommendations, with explanations and examples in two different formats: On the one hand, the tabular format as used in the interactive table and, on the other hand, according to the analytical framework applied. The Guidebook is designed for a wide audience, including statisticians, clinicians, regulatory bodies, industry, academics, and patient advocates.

4. ***Plain language materials***

Plain language checklists and tutorial videos are intended to make the recommendations more accessible to patient representatives, patients and the general public. Different plain language checklists are available to assist non-scientists in the review of study protocols and reports. A plain language version of the glossary is included in the guidebook and the interactive table to clarify technical terms.

5. A glossary

The final consensus-based glossary contains 227 terms with scientific and plain language definitions. The glossary is a standalone document, as well as being integrated into the interactive table and the guidebook. Pop-up boxes providing scientific and plain language definitions, when used within text, facilitate the knowledge transfer to the end users and foster understanding. It promotes consistent interpretation of terms used in the statements, explanations and examples and all future SISAQOL-IMI documents.

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Discussion and lessons learned

The success of the SISAQOL-IMI project stems from consensus among diverse stakeholders and this was achieved through 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 ~~in~~ 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 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 proliferation of multiple smaller guidelines. It

bridges a 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/consensus meetings proved invaluable, as informal discussions during breaks helped clarify issues and resolve disagreements, fostering stronger consensus. Patient involvement was crucial. Over time, special meetings and dialogues were arranged in order 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 significant impact on the field of PROs and their application in cancer clinical trials. It has been cited in the Food and Drug Administration Guidance "Submitting Patient-Reported Outcome Data in Cancer Clinical Trials"[25] and received the American Statistical Association's Statistical Partnership Among Academia, Industry and Government (SPAIG) Award for collaboration among academia, industry, and government[26]. The recommendations have been recognised as an important solution to advance the PRO field at the European Medicines Agency/EORTC workshop[7] on PRO data in regulatory decision-making. Additionally, a collaboration with ESMO-Magnitude of Clinical Benefit Scale (ESMO/MCBS) 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.

Implementation and sustainability plan

The SISAQOL-IMI final outputs (interactive table, guidebook, plain language material, and glossary) will be freely available on the website [https://www.sisaqol-imi.org/], 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 demonstrate 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 be freely accessible on the project website.

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 within and across 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 and make the results more transferable to clinical care and individual patient well-being. The training activities and sustainability plan are essential to ensure the long-term impact of our efforts.

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Figures legends

Contributors

All authors are members of the SISAQOL-IMI Consortium and were involved in the conceptualization of this Policy Review. CDA led in the drafting of the manuscript with support from AA, RSF, KB and MP. MS, SR, VB, LMV, AR were all part of the core writing committee. MP, AI, AA CC, MS, SR, SLC, BH, LMW, JC, MT, PC, JMG, JCC, KB, VP, StS, EJP are all work package leaders and contributed to the collection and analysis of the SISAQOL-IMI recommendations. All authors representing the 41 organizations in SISAQOL-IMI collected and provided the data in the development of the SISAQOL-IMI 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

- KBJ, JG, BH, GR, reports receiving funding paid to their institution from the SISAQOL-IMI grant to conduct this work.
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- AC reports being an employee of Genentech from 2011 to 2019 and then AZ from year 2020 to 2024. However the current work was done as part of PRE LLC and on external time. AC reports patent unrelated to this work, AZ ownership. AC reports stocks, leadership roles, receipt of equipment and other services, and other financial / non-financial interest from AZ.
- PC, JC, SR reports being an employee of Pfizer and receives stocks and stock options as part of his employment.
- MC reports receiving grants paid to her institution from NIHR Birmingham Biomedical Research center, Health data research UK, Innovate UK, Macmillan Cancer Support, GSK, Research England, European Commission and EFPIA, Brain Tumour Charity, Gilead, Janssen, NIHR, UKRI, Merck. She also reports receiving revenue from commercial license of the symptom burden questionnaire – long COVID; She receives consulting fees from Aparito Ltd, Boehringer Ingelheim, CIS Oncology, Merck, Genentech, GSK, Pfizer, Vertex Pharmaceuticals, ICON, Halfloop,

University of Michigan, Northwestern University, EuroQoL, Shionogi, Cell and Gene Therapy Catapult. She also received payment or honoraria from University of Maastricht, Sount-Eastern Norway Regional Health Authority, Cochrane Portugal, Singapore National Medical Research Council. She reports leadership role in PROTEUS Consortium which she receives a consultancy fee. She reports a family member has stocks in GSK.

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- StS reports that her employer Myeloma Patients Europe receives grant and sponsorship from various pharmaceutical companies, which are listed here: https://www.mpeurope.org/about-mpe/our-funding/

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Acknowledgements

The SISAQOL-IMI project 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).

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 Medical Products Agency (NOMA), the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) or any other institution, organisation, or entity. This project received no funding from the US National Institutes of Health (NIH). Neither IMI nor the EU, nor EFPIA are responsible for any use that may be made of the information contained therein.

We would like to express our sincere appreciation to former WP leaders Carla Mamolo, Jinma Ren, Jayne Galinsky, Linda Dirven as well as former SISAQOL-IMI Steering Committee members Daniel O'Connor and Kathy Oliver, for their invaluable efforts and dedication. We are also grateful to Rosa Abruzzese for her extensive review and harmonisation of the language in the final deliverables of the project.

References

1. Booth CM, Sengar M, Goodman A, Wilson B, Aggarwal A, Berry S, et al. Common Sense Oncology: outcomes that matter. *Lancet Oncol.* 2023;24(8):833-5.
2. Oosting SF, Barriuso J, Bottomley A, Galotti M, Gyawali B, Kiesewetter B, et al. Methodological and reporting standards for quality-of-life data eligible for European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) credit. *Ann Oncol.* 2023;34(4):431-9.
3. Lacombe D, Bean J, Bogaerts J, Bottomley A, Collette L, Gilotay C, et al. 50 years of the EORTC and the central role of the EORTC Headquarters. *European Journal of Cancer Supplements.* 2012;10(1):3-12.
4. ~~Friends of Cancer Research. Supporting Patient-Centric Approach to dose optimization in Oncology: patient-reported outcomes (PROs).2022.~~ Friends of Cancer Research. Supporting patient-centric approach to dose optimization in oncology: patient-reported outcomes (PROs). 2022. Available from: https://friendsofcancerresearch.org/wp-content/uploads/Supporting_Patient-entric_Approach_Dose_Optimization_Oncology-PROs.pdf; 2022.
5. WECAN (Work group of European Cancer Patient Advocacy network). Patient-reported outcomes, and other patient-relevant measures and endpoints. ~~Access:11.12.2024~~ Accessed Dec 11, 2024. Available from: https://wecanadvocate.eu/academy/patient-reported-outcomes-and-other-patient-relevant-measures-and-endpoints/
6. ~~U.S. Department of Health and Human Services, Food and Drug Administration, Core patient-reported outcomes in cancer clinical trials. www.fda.gov/regulatory; 2024 October 2024.~~ U.S. Food and Drug Administration. Core patient-reported outcomes in cancer clinical trials. October 2024. Available from: www.fda.gov/regulatory
7. EMA and European Organisation for Research and Treatment of Cancer (EORTC) workshop: How can patient-reported outcomes (PRO) and health-related quality of life (HRQoL) data inform regulatory decisions? | European Medicines Agency (EMA). 29.02.2024. Available from: https://www.ema.europa.eu
8. Directorate-General for Health and Food Safety, EU. Guidance on reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses in joint clinical assessments. 2024. Available from: https://health.ec.europa.eu/
9. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *JAMA.* 2018;319(5):483-94.
10. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. ~~*Jama*~~*JAMA.* 2013;309(8):814-22.
11. Snyder C, Smith K, Holzner B, Rivera YM, Bantug E, Brundage M. Making a picture worth a thousand numbers: recommendations for graphically displaying patient-reported outcomes data. *Qual Life Res.* 2019;28(2):345-56.
12. Coens C, Pe M, Dueck AC, Sloan J, Basch E, Calvert M, et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer

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randomised controlled trials: recommendations of the SISAQOL Consortium. *Lancet Oncol*. 2020;21(2):e83-e96.

13. ICH Expert Working Group. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conferenceon Harmonisation E9 Expert Working Group. Stat Med. 1999;18:1905-42.

14. ICH Expert Working Group.. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. www.ema.europa.eu: European Medicine Agency; 2017. 17 February 2020. ICH Expert Working Group. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. European Medicines Agency; 2017. Published Feb 17, 2020. Available from: www.ema.europa.eu

15. Pe M, Alanya A, Falk RS, Amdal CD, Bjordal K, Chang J, et al. 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. *Lancet Oncol* –2023;24(6): e270-e83.

16. Liu L, Choi J, Musoro JZ, Sauerbrei W, Amdal CD, Alanya A, et al. Single-arm studies involving patient-reported outcome data in oncology: a literature review on current practice. *Lancet Oncol*. 2023;24(5): e197-e206.

17. Agrawal S, Arora S, Amiri-Kordestani L, de Claro RA, Fashoyin-Aje L, Gormley N, et al. Use of Single-Arm Trials for US Food and Drug Administration Drug Approval in Oncology, 2002-2021. *JAMA Oncol*. 2023;9(2): e266-72.

18. Di Maio M. The Value of Patient-Reported Outcomes in Single-Arm Cancer Trials. *Cancer Invest*. 2023;41(5): e491-4.

19. Cappelleri JC, Bushmakin AG. Interpretation of patient-reported outcomes. Stat *Methods Med Res*. 2014;23(5): e460-83.

20. Coon CD, Cappelleri JC. Interpreting Change in Scores on Patient-Reported Outcome Instruments. *Ther Innov Regul Sci*. 2016;50(1):22-9.

21. Bushmakin AG, Cappelleri JC. A Practical Approach to Quantitative Validation of Patient-Reported Outcomes: A Simulation-Based Guide Using SAS. . Sons JW, editor. Hoboken, NJew Jersey: John Wiley & Sons; 2022. 30 November 2022.

22. Initiative IH. SISAQOL-IMI Establishing international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials. 2021. †Available from: https://www.ihi.europa.eu/.

23 Machingura A, Coens C, Pe M, Alanya A, Regnault A, Mazerolla F. Methodological work and use of Patient-Reported Outcomes data in randomised controlled trials (RCTs) in cancer: Literature reviews on current practices and guidelines. 2024.

24. Thomassen D, Roychoudhury S, Amdal CD, Reynders D, Musoro JZ, Sauerbrei W, et al. The role of the estimand framework in the analysis of patient-reported outcomes in single-arm trials: a case study in oncology. *BMC Med Res Methodol*. 2024;24(1): e290.

25. US. Food and Drug Adminstration. Submitting Patient Reported Outcome Data in Cancer Clinical Trials, Guidance for Industry, Technical Specifications Document. 2023. Contract No.: FDA-2018-D-1216.

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26. American Statistical Association. Statistical Partnerships Among Academe, Industry, and Government (SPAIG) award. ~~https://www.amstat.org2024 |~~Available from: https://www.amstat.org/your-career/awards/statistical-partnerships-among-academe-industry-and-government-(spaig)-award.

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

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Summary

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 implementation of PRO in randomised controlled trials and single arm trials, terminology, definitions and selection of PRO score interpretation thresholds, and visualising PRO results for different audiences. To facilitate the implementation of these standards, in addition to this publication, four key outputs are available: an interactive table, a guidebook, plain language materials and a glossary (www.sisaqol-imi.org).

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 final reference list was generated based on originality and relevance to the broad scope of this Review.

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: 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], they do not provide information on agreed methodological standard for the design, analysis, interpretation, and reporting of PRO data that would be acceptable for various decision-makers. Previous reviews have consistently demonstrated that vague PRO research objectives, poorly defined PRO endpoints, including unclear definitions of clinically meaningful change or difference, and lack of transparency in the reporting of PRO findings have raised concerns about their reliability[12]. This gap may impact 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 (e.g., academic and industry-sponsored) 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 SISAQOL "Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials" work [12] into the SISAQOL-Innovative Medicines Initiative (SISAQOL-IMI) was a logical step forward. SISAQOL-IMI aimed to consider various stakeholder needs, adopt recent developments in the methodological literature (e.g., the estimands framework from 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:

a) Randomised controlled trials (RCTs), where PROs can be used to evaluate the clinical benefit of an intervention and/or describe the patient perspective, for instance, to complement clinician-reported adverse event data.
b) 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 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.
c) 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.
d) 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 implies 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 manuscript provides an overview of the consensus process, the methods used and the project outcomes, including key recommendations and the final outputs: the interactive table (a webtool that allows users to easily navigate through the recommendations, and get a tailored set of recommendations based on their PRO research objective and variable of interest), the guidebook, the plain language recommendations, and the glossary. It concludes with lessons learned and outlines the plan for implementation and sustainability.

Methodology

The SISAQOL-IMI Consortium and the organisation of its work

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, industry, academic and professional societies alongside experts in statistics, PRO measurement, clinical oncology, and patient advocacy. This collaboration ensures that the resulting recommendations are both methodologically robust and accessible to both technical and non-technical audiences. More information on the Consortium has been reported in a previous publication[15].

The work was organised in eight different work packages (WPs), as illustrated in the Appendix (page 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 (GA), 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: (Innovative Health Initiative | IHI Innovative Health Initiative)[22].

The project design and definitions

This five-year consensus project was designed with repetitive consensus processes including the yearly GA consensus meetings addressing a specific milestone each year (Table 1). The overall framework of each of these consensus processes is described in 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 GA. 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.

The methods used to develop statements in the work packages

To develop the statements for each of the four priority areas (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 multi-step process to gather the information needed to develop the statements (see Figure 2).By conducting targeted literature reviews, the WPs collated relevant information, evaluated current standards 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 (www.sisaqol-imi.org).

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** focused on current practices and methodological recommendations on design, analysis, reporting and interpretation of SATs[16]. **The literature review on visualisation** focused on evidence on 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** focused on publications on 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. The results of the literature reviews fed into the formulation of the initial set of statements for RCTs, SATs, visualisation and presentation of PRO data, and PRO score interpretation thresholds.

The next step was to conduct surveys and hold expert discussions within the WPs. Specific surveys were performed involving the members of each WP, focusing on topics that were not sufficiently covered by the literature review or topics raised in the previous consensus meeting. Results from these surveys were discussed with all WP members; discussion outcomes were noted and formed the basis to develop new statements for the next consensus process. Subsequently, the WPs proposed draft statements that were included in the consensus survey (see Figure 1).

The involvement of the whole Consortium: the consensus process

The framework for consensus process one to four is displayed in Figure 1. Each year in December, the consensus process began with the scientific WPs submitting their proposed statements to the coordinating WP7. Selected consortium members (patient representatives, clinicians and statisticians) reviewed the statements for clarity. Based on their feedback, WP leaders updated the statements as needed before including them in the first round of voting in the consensus survey. Statements achieving consensus by a two-thirds majority across all stakeholder groups, with no concerns raised, did not have to be revoted (i.e., 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; and/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 may have been a result of misinterpretation of a concept or statement and needed further discussions or elaboration with the rest of the Consortium. Unresolved statements (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.

Each organisation had one vote. To ensure high consensus, the Consortium agreed upon voting rules, including a two-step voting procedure (Appendix 2 on page 2). Recognising that unanimous agreement was not always achievable, the Consortium developed a "diverging views document" to capture differences in perspectives[15].

The first consensus process focused on prioritising concepts. Statements were not developed at this point. Consensus process two and three focused on statements related to RCTs (WP2), SATs (WP3) and PRO score interpretation thresholds (WP6) (Figure 3). The third process also included statements on how to present PRO results (WP4). The fourth consensus process included one statement related to patient involvement and the final updates of statements for RCTs, SATs, and PRO score interpretation thresholds.

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 GA/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 prior to the consensus meetings to address key issues and clarify complex concepts.

Organisation of final recommendations

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 (confirmatory—superiority and equivalence/non-inferiority—or descriptive), and rows specifying the PRO variable of interest (the PRO endpoint). This structure creates 30 individual 'cells' (18 for RCTs, and 12 for SATs), each representing a unique combination of study design and PRO variable of interest (e.g., an RCT with a confirmatory superiority objective [column] and time to PRO improvement [row] endpoint). Figure 4 demonstrates the structure for RCTs as displayed in the interactive table. 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 (PRO score interpretation thresholds, study design considerations, external comparison (for single-arm studies only), analysis considerations and results visualisation and presentation).

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 through discussions with the responsible WP leaders. In addition, one WP (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: statisticians, clinicians, PRO methodologists. These experts represented academia, industry, regulatory/HTA bodies, and non-profit cancer organisations. Their aim is 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.

Reconciliation between work packages, development of the glossary, and language review

To ensure harmonisation of recommendations between RCTs and SATs, the two WPs 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 (see Appendix 3, page 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 harmonization 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.

Key results and outputs of SISAQOL-IMI

Final recommendation statements

SISAQOL-IMI ratified 146 out 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 evolvement 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 (19 from RCTs and 6 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 above 85% (see Appendix, pages 4-7). Forty-two statements reached consensus in the first round of voting, while 22 were adapted with minor wording changes without discussion. Eighty-two statements required discussion during consensus meetings. For five statements, divergent views among the stakeholder groups (see Appendix, pages 8-9) were included as "considerations" along with the final recommendation.

The key results for each of the four scientific priority areas from the WPs are presented in Table 2.

a) For RCTs, the recommendations emphasise the need to align estimands with research objectives, an area identified as lacking in current practice[23]. 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 supplementary and sensitivity analyses. They also address specific issues dependent on the type of analytic metrics used (e.g., time to event, responder analyses) including how to account for repeated measures.
b) 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 taking 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[24].
c) 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, tailored to specific contexts. For example, graphs presenting PRO data should be consistent with the pre-specified domains and time frames of the trial, with exploratory or descriptive results clearly labelled. They should also include details on 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. 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 (e.g., asterisks) rather than p-values.

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

d) 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- 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. Finally, the recommendations encourage reporting how thresholds were chosen and applied in the analysis and interpretation of PRO data.

SISAQOL-IMI outputs

To support and encourage the implementation of the final recommendations, the Consortium produced five key outputs, which will be available on the SISAQOL-IMI website [https://www.sisaqol-imi.org/].

1. The current SISAQOL-IMI publication

This publication aims to enhance transparency and implementation by presenting the SISAQOL-IMI consensus process and final results. Sharing lessons learned and outlining sustainability plans supports the long-term impact of the SISAQOL-IMI recommendations.

2. An interactive table

This table presents the recommendations organised according to the study objective and PRO variable of interest to give researchers easy access to recommendations relevant to their specific study design. Each recommendation was evaluated and assigned to the applicable cells of the web tool (Appendix, page 10) and the corresponding attribute of the analytical

framework. Ideally, the recommendations should be used in the planning phase of a (cancer) clinical trial and applied throughout the process.

3. A guidebook

The guidebook outlines the development process of the SISAQOL-IMI recommendations, applied methods, lessons learned, and the sustainability plan. It provides instructions for using SISAQOL-IMI outputs (interactive table, glossary, plain language checklist), and also covers the SISAQOL-IMI recommendations, with explanations and examples in two different formats: On the one hand, the tabular format as used in the interactive table and, on the other hand, according to the analytical framework applied. The Guidebook is designed for a wide audience, including statisticians, clinicians, regulatory bodies, industry, academics, and patient advocates.

4. Plain language materials

Plain language checklists and tutorial videos are intended to make the recommendations more accessible to patient representatives, patients and the general public. Different plain language checklists are available to assist non-scientists in the review of study protocols and reports. A plain language version of the glossary is included in the guidebook and the interactive table to clarify technical terms.

5. A glossary

The final consensus-based glossary contains 227 terms with scientific and plain language definitions. The glossary is a standalone document, as well as being integrated into the interactive table and the guidebook. Pop-up boxes providing scientific and plain language definitions, when used within text, facilitate the knowledge transfer to the end users and foster understanding. It promotes consistent interpretation of terms used in the statements, explanations and examples and all future SISAQOL-IMI documents.

Discussion and lessons learned

The success of the SISAQOL-IMI project stems from consensus among diverse stakeholders and this was achieved through 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 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 proliferation of multiple smaller guidelines. It bridges a 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/consensus meetings proved invaluable, as informal discussions during breaks helped clarify issues and resolve disagreements, fostering stronger consensus. Patient involvement was crucial. Over time, special meetings and dialogues were arranged in order 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 significant impact on the field of PROs and their application in cancer clinical trials. It has been cited in the Food and Drug Administration Guidance "Submitting Patient-Reported Outcome Data in Cancer Clinical Trials"[25] and received the American Statistical Association's Statistical Partnership Among Academia, Industry and Government (SPAIG) Award for collaboration among academia, industry, and government[26]. The recommendations have been recognised as an important solution to

advance the PRO field at the European Medicines Agency/EORTC workshop[7] on PRO data in regulatory decision-making. Additionally, a collaboration with ESMO-Magnitude of Clinical Benefit Scale (ESMO/MCBS) 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.

Implementation and sustainability plan

The SISAQOL-IMI final outputs (interactive table, guidebook, plain language material, and glossary) will be freely available on the website [https://www.sisaqol-imi.org/], 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 demonstrate 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 be freely accessible on the project website.

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 within and across 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 and make the results more transferable to clinical care and

individual patient well-being. The training activities and sustainability plan are essential to ensure the long-term impact of our efforts.

Figures legends

Figure 1 Framework of each of the consensus processes

Figure 2 Development of statements, a multi-step process

Figure 3 Development and evolvement of statements within each work package

Figure 4 Screenshot of the interactive table using the analytical framework for organisation of statements for one example

Contributors

All authors are members of the SISAQOL-IMI Consortium and were involved in the conceptualization of this Policy Review. CDA led in the drafting of the manuscript with support from AA, RSF, KB and MP. MS, SR, VB, LMV, AR were all part of the core writing committee. MP, AI, AA CC, MS, SR, SLC, BH, LMW, JC, MT, PC, JMG, JCC, KB, VP, StS, EJP are all work package leaders and contributed to the collection and analysis of the SISAQOL-IMI recommendations. All authors representing the 41 organizations in SISAQOL-IMI collected and provided the data in the development of the SISAQOL-IMI 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

- KBJ, JG, BH, GR, reports receiving funding paid to their institution from the SISAQOL-IMI grant to conduct this work.
- ABe, CQ, NC, MF, received travel grants from SISAQOL-IMI to participate in the annual meeting.
- EB reports receiving consulting fees as a scientific advisor for AZ, Navigating Cancer, Verily, N-Power Medicine, Savor, Thyme Care and Resilience Health
- AC reports being an employee of Genentech from 2011 to 2019 and then AZ from year 2020 to 2024. However the current work was done as part of PRE LLC and on external time. AC reports patent unrelated to this work, AZ ownership. AC reports stocks, leadership roles, receipt of equipment and other services, and other financial / non-financial interest from AZ.
- PC, JC, SR reports being an employee of Pfizer and receives stocks and stock options as part of his employment.
- MC reports receiving grants paid to her institution from NIHR Birmingham Biomedical Research center, Health data research UK, Innovate UK, Macmillan Cancer Support, GSK, Research England, European Commission and EFPIA, Brain Tumour Charity, Gilead, Janssen, NIHR, UKRI, Merck. She also reports receiving revenue from commercial license of the symptom burden questionnaire – long COVID; She receives consulting fees from Aparito Ltd, Boehringer Ingelheim, CIS Oncology, Merck, Genentech, GSK, Pfizer, Vertex Pharmaceuticals, ICON, Halfloop,

University of Michigan, Northwestern University, EuroQoL, Shionogi, Cell and Gene Therapy Catapult. She also received payment or honoraria from University of Maastricht, Sount-Eastern Norway Regional Health Authority, Cochrane Portugal, Singapore National Medical Research Council. She reports leadership role in PROTEUS Consortium which she receives a consultancy fee. She reports a family member has stocks in GSK.

- OLA reports receiving grants and contracts paid to University of Birmingham from NIHR BRC, ARC, NIHR Blood and Transplant Research Unit in Precision Transplant and Cellular Therapeutics, Anthony Nolan, Sarcoma UK, Merck. OLA also reports personal consulting fees paid through University of Birmingham from Merck, GSK, Gilead, BI, and Innovate UK
- MB reports receiving an unrestricted research grant paid to his institution from Pfizer
- KC received travel grants from SISAQOL-IMI to attend the annual meeting. She reports consultancy fees from pharmaceutical and medical devices companies for statistical services.
- SE reports membership fees paid by PRO Consortium member firms to CPATH to support staff time to participate in the Consortium. She reports CPATH receiving grants and broad agency announcement contract payments from the US FDA. She reports receiving travel funds to participate in the American College of Neuropsychopharmacology 2022 Annual meeting. She reports receiving travel grants to attend the SISAQOL-IMI meeting.
- CG reports being an employee of Bayer and holds stock options as part of his employment.
- MS reports being an employee of Merck KGAa and receiving stocks/stock options as part of his employment.
- EP reports being an employee of AbbVie and this work was done as part of her employment at AbbVie
- JR is the Chair of the EORTC quality of life group (unpaid) and is the member of scientific advisory board of EpilepsieNL (unpaid). He 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 here: https://www.mpeurope.org/about-mpe/our-funding/

- CS reports receiving research funding from Pfizer and Genentech to her institution. She received personal consulting fees from Shionogi and Movember, and travel costs were covered by Shionogi to present on a panel at the CPATH COA Consortium meeting
- GV reports receiving grants from NIHR, Pfizer and Yorkshire Cancer Research – all paid to her institution. She reports receiving consulting fees paid to her from Pfizer, Roche, Seagen. She also reports payments and honorarias paid to her from Pfizer, Roche, Novartis, Eisai and Sanofi. She reports receiving support from Pfizer and Roche to attend meetings and travel. She reports receiving payment as part of her participation on a data safety monitoring board or advisory board from Roche, Seagen and AZ. She holds leadership roles as part of the EORTC board of directors and NCRI Chair of Living with and beyond cancer group.

Acknowledgements

The SISAQOL-IMI project 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).

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 Medical Products Agency (NOMA), the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) or any other institution, organisation, or entity. This project received no funding from the US National Institutes of Health (NIH). Neither IMI nor the EU, nor EFPIA are responsible for any use that may be made of the information contained therein.

We would like to express our sincere appreciation to former WP leaders Carla Mamolo, Jinma Ren, Jayne Galinsky, Linda Dirven as well as former SISAQOL-IMI Steering Committee members Daniel O'Connor and Kathy Oliver, for their invaluable efforts and dedication. We are also grateful to Rosa Abruzzese for her extensive review and harmonisation of the language in the final deliverables of the project.

References

1. Booth CM, Sengar M, Goodman A, Wilson B, Aggarwal A, Berry S, et al. Common Sense Oncology: outcomes that matter. *Lancet Oncol.* 2023;24(8):833-5.
2. Oosting SF, Barriuso J, Bottomley A, Galotti M, Gyawali B, Kiesewetter B, et al. Methodological and reporting standards for quality-of-life data eligible for European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) credit. *Ann Oncol.* 2023;34(4):431-9.
3. Lacombe D, Bean J, Bogaerts J, Bottomley A, Collette L, Gilotay C, et al. 50 years of the EORTC and the central role of the EORTC Headquarters. *European Journal of Cancer Supplements.* 2012;10(1):3-12.
4. Friends of Cancer Research. Supporting patient-centric approach to dose optimization in oncology: patient-reported outcomes (PROs). 2022. Available from: https://friendsofcancerresearch.org/wp-content/uploads/Supporting_Patient-entric_Approach_Dose_Optimization_Oncology-PROs.pdf; 2022.
5. WECAN (Work group of European Cancer Patient Advocacy network). Patient-reported outcomes, and other patient-relevant measures and endpoints. Accessed Dec 11, 2024. Available from: https://wecanadvocate.eu/academy/patient-reported-outcomes-and-other-patient-relevant-measures-and-endpoints/
6. file:///C:/Users/mpe/OneDrive - EORTC/Desktop/SISAQOL-IMI final manuscript/www.fda.gov/regulatoryU.S. Food and Drug Administration. Core patient-reported outcomes in cancer clinical trials. October 2024. Available from: www.fda.gov/regulatory
7. EMA and European Organisation for Research and Treatment of Cancer (EORTC) workshop: How can patient-reported outcomes (PRO) and health-related quality of life (HRQoL) data inform regulatory decisions? | European Medicines Agency (EMA). 29.02.2024. Available from: https://www.ema.europa.eu
8. Directorate-General for Health and Food Safety, EU. Guidance on reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses in joint clinical assessments. 2024. Available from: https://health.ec.europa.eu/
9. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *JAMA* 2018;319(5):483-94.
10. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013;309(8):814-22.
11. Snyder C, Smith K, Holzner B, Rivera YM, Bantug E, Brundage M. Making a picture worth a thousand numbers: recommendations for graphically displaying patient-reported outcomes data. *Qual Life Res* 2019;28(2):345-56.
12. Coens C, Pe M, Dueck AC, Sloan J, Basch E, Calvert M, 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(2):e83-e96.
13. ICH Expert Working Group. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conferenceon Harmonisation E9 Expert Working Group. Stat Med. 1999;18:1905-42.

14. ICH Expert Working Group. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. European Medicines Agency; 2017. Published Feb 17, 2020. Available from: www.ema.europa.eu

15. Pe M, Alanya A, Falk RS, Amdal CD, Bjordal K, Chang J, et al. 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. *Lancet Oncol* 2023;24(6): e270-83.

16. Liu L, Choi J, Musoro JZ, Sauerbrei W, Amdal CD, Alanya A, et al. Single-arm studies involving patient-reported outcome data in oncology: a literature review on current practice. *Lancet Oncol* 2023;24(5): e197-206.

17. Agrawal S, Arora S, Amiri-Kordestani L, de Claro RA, Fashoyin-Aje L, Gormley N, et al. Use of Single-Arm Trials for US Food and Drug Administration Drug Approval in Oncology, 2002-2021. *JAMA Oncol* 2023;9(2): e266-72.

18. Di Maio M. The Value of Patient-Reported Outcomes in Single-Arm Cancer Trials. *Cancer Invest* 2023;41(5): e491-4.

19. Cappelleri JC, Bushmakin AG. Interpretation of patient-reported outcomes. Stat *Methods Med Res* 2014;23(5): e460-83.

20. Coon CD, Cappelleri JC. Interpreting Change in Scores on Patient-Reported Outcome Instruments. *Ther Innov Regul Sci* 2016;50(1):22-9.

21. Bushmakin AG, Cappelleri JC. A Practical Approach to Quantitative Validation of Patient-Reported Outcomes: A Simulation-Based Guide Using SAS. Hoboken, NJ: John Wiley & Sons; 2022.

22. Initiative IH. SISAQOL-IMI Establishing international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials. 2021.Available from: https://www.ihi.europa.eu/.

23 Machingura A, Coens C, Pe M, Alanya A, Regnault A, Mazerolla F. Methodological work and use of Patient-Reported Outcomes data in randomised controlled trials (RCTs) in cancer: Literature reviews on current practices and guidelines. 2024.

24. Thomassen D, Roychoudhury S, Amdal CD, Reynders D, Musoro JZ, Sauerbrei W, et al. The role of the estimand framework in the analysis of patient-reported outcomes in single-arm trials: a case study in oncology. *BMC Med Res Methodol* 2024;24(1): e290.

25. US. Food and Drug Adminstration. Submitting Patient Reported Outcome Data in Cancer Clinical Trials, Guidance for Industry, Technical Specifications Document. 2023. Contract No: FDA-2018-D-1216.

26. American Statistical Association. Statistical Partnerships Among Academe, Industry, and Government (SPAIG) award. Available from: https://www.amstat.org/your-career/awards/statistical-partnerships-among-academe-industry-and-government-(spaig)-award.

Table

Table 1 Milestones for the general assemblies (GAs)

General Assembly meetings	Year	Milestones
1	2021	Defined the goals, priority of patient-reported (PRO) objectives and identified expectations
2	2022	Ratification of the first set of recommendations for cancer randomised controlled trials, single arm trials and clinical meaningful change/ PRO score interpretation thresholds
3	2023	Ratification of the updated and expanded version of recommendations for cancer randomised controlled trials, single arm trials, visualisation and presentation of PRO results and for clinical meaningful change/ PRO score interpretation thresholds
4	2024	Ratifications of the final version of recommendations for cancer randomised controlled trials, single arm trials, visualisation and presentation of PRO results and for clinical meaningful change/ PRO score interpretation thresholds
5	2025	Ratification of the final output and sustainability plan

Table 2. Scientific key results for each work package

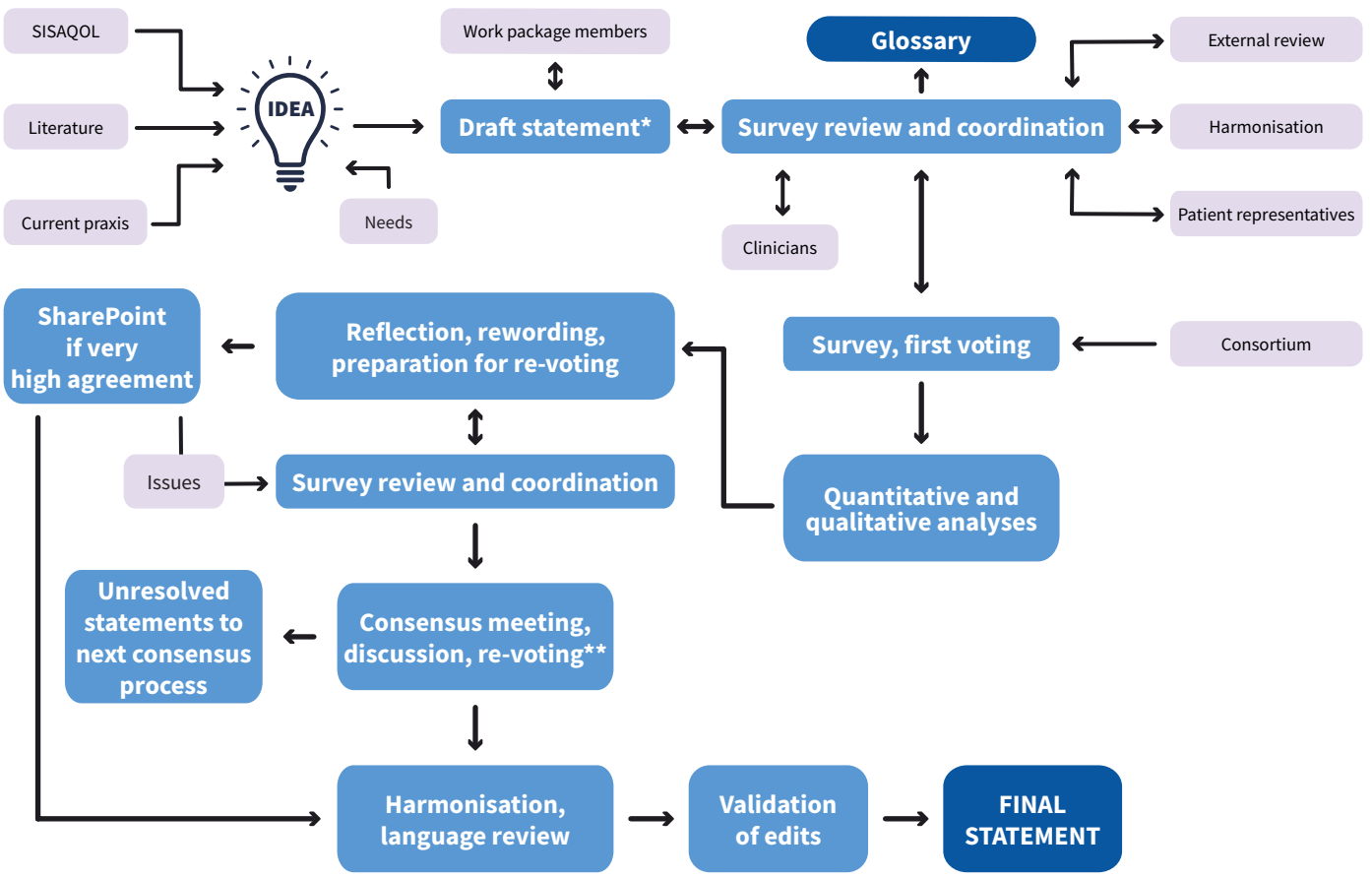
Randomised controlled trials (WP2)	Current standards	SISAQOL-IMI standards	Rationale for change
Addressing death in patient-reported outcome (PRO) analysis	There is no standard method for addressing death in PRO analysis for RCTs. Hypothetical strategies are often used without specifying the underlying assumptions. Commonly used methods often do not reflect the intended estimand/objective.	There are different strategies to address death, as an intercurrent event in RCTs (hypothetical, composite, while alive, principal stratum). The choice of strategy will have an impact 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 cause. No distinction is made between intercurrent events and missing data.	The overall PRO analysis strategy should include a main PRO analysis supported by sensitivity (accounting for missing data) and/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 (e.g. 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 (e.g. questionnaire lost) and its impact on the results should be handled via sensitivity analyses. Missing data may bias results and affect uncertainty if not handled properly.
Completion rates and available data rates	PRO data may be unavailable for different reasons. The data actually 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 time point. For both, **the numerator** is set to the number of patients that completed the PRO assessment at that time point. **For the completion rate** the denominator is set as the number of patients with a scheduled PRO assessment at that time point. This denominator can change over time to account for e.g. deaths. **For the available data rate**, the denominator equals the number of patients randomized in the trial. This denominator will not change over 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	Single imputation, complete case analysis, or available case analysis to handle missing	In many RCTs, attrition bias can occur when participants with specific attributes (e.g., worse

	patients with no missing data), or available case analysis (only including patients with no missing data at the time point of interest) are often used as they are easily understood.	data are generally **not recommended.** A justification should be given if these approaches are used. As an alternative, multiple imputation techniques can be considered.	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 may lead to a biased estimate.
Repeating cross-sectional analyses are not recommended in longitudinal analyses	Cross-sectional treatment effect estimates take into account data from only a single specific time point. This is not an efficient use of the PRO dataset. Moreover, such repeated estimates at consecutive time points are often presented as a longitudinal series. Time trends are then inferred but these may result in misleading interpretation.	It is **not recommended** to analyse data at each time point 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. It does not take into account data selection over time (due to patient attrition or missing data), or correlation between different observations of the same patient.
Single arm trials (WP3)	**Current standards**	**SISAQOL-IMI standards**	**Rationale for change**
Research objectives and estimands	In single-arm trials, PRO objectives are often unclear or not mentioned at all.	Single-arm trials should have pre-specified PRO objectives that should be translated into key clinical questions using the estimand framework.	Unclear or missing PRO objectives may 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 single arm trials are usually descriptive. Naïve 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 change 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 randomisation should be addressed.	It is critical to align the analysis strategy with the research question of interest using the estimand framework question. In some situations, comparing PROs from a single-arm trial to an external control can serve as confirmatory. However, without appropriate design and analysis considerations comparison with external control data may lead to erroneous conclusions.
Handling death in single-arm trials	Currently, there are no well-defined strategies for handling death in PRO analysis in single-arm trials.	There are different strategies to handle death in single-arm trials. The chosen strategy should be defined prior to analysis in line with the pre-defined 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	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 single-arm trials aligns with a descriptive research objective (i.e., the intention to inform clinicians and patients about expected PRO after the start of treatment). To provide a comprehensive understanding, the expected PRO

		about death such as the proportion of patients still alive at the time point of assessment.	score at a specific time point should be accompanied by the estimated probability of survival at that same time,
Handling missing data vs 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 critical to understand the underlying assumptions associated with each method. Sensitivity analyses should be conducted to assess the impact of assumptions made about missing data mechanisms and supplementary analyses accounting for handling intercurrent events. For example, methods such as linear mixed models or generalized 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 may not align with the research question.
Communication of PRO findings using visualisation (WP4)	**Current standards**	**SISAQOL-IMI standards**	**Rationale for change**
Figures on main results	The PRO results presented in figures may not correspond to the pre-specified research objective and statistical analysis plan of the trial.	The figures should reflect the pre-specified PRO objectives and statistical analyses of the trial, particularly regarding the PRO domains and time points/frames presented. If figures are presented for additional exploratory/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/descriptive results. 2) To avoid selective presentation (cherry picking) of results such as certain PRO domains and time points
Statistical significance	Figures representing results of exploratory/descriptive analyses may include information on statistical significance without clearly identifying them as exploratory/descriptive.	Either 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/ 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/descriptive results from statistical tests provide the same level of evidence as confirmatory results.
Scaling in graphs	Inconsistencies may exist in the scaling applied to graphs within and across trial reports/ publications.	Use consistent scaling reflecting the full PRO score range whenever possible, particularly in graphs based on the same PRO score whenever possible.	To promote distortion-free and comparable representations of PRO results within and across trial reports/publications.

Sample size, intercurrent events and missing data	Inconsistencies may 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 (e.g., which direction indicates a good/bad PRO score, which direction indicates an (improvement/ worsening).	Existing standards require emphasizing to facilitate interpretation of results.
Interpretation of PRO results (WP6)	**Current standards**	**SISAQOL-IMI standards**	**Rationale for change**
Harmonized terminology for thresholds for interpretation of PRO data	Different terms and definitions are used and inconsistently applied for conceptually similar thresholds for interpreting PRO data (e.g., minimal clinically important difference, clinically meaningful change).	A 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 may lead to inappropriate or misleading application and interpretation.
Differentiation of patient- and group-level PRO score interpretation thresholds	The literature rarely distinguishes PRO score interpretation thresholds for patient-level scores (i.e., for within-patient change) and group-level scores (e.g., for between-group differences, within-group change).	Terminology is provided that differentiates patient- and group-level PRO score interpretation thresholds and different types of thresholds are linked to specific statistical analysis methods for correct implementation and interpretation.	Lack of distinction between patient- and group-level thresholds compromises interpretation of PRO data and sample size calculation. This can lead to invalid conclusions, for example, when responder thresholds for within-patient change are used for 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- and distribution-based methods being the most common.	Key criteria for selecting appropriate thresholds are provided.	The various methods used may result in threshold values that are not fit-for-purpose in 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 (e.g., 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 critical 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

Figure 1



* Both new proposals and unresolved statements in need of revision
** Re-voting include both second and third voting

Figure 2

1. Literature reviews of cancer clinical studies and existing guidelines to describe the current state of practice in the design, analysis, reporting and presentation of PRO data
2. Expert discussions and surveys within work packages and methodological evaluation of results
3. Development of draft recommendations within working groups
4. Ratification of the proposed recommendations through the consensus process
5. Independent validation of the preliminary recommendations
6. Adaptation and reconciliation between work packages
7. Harmonisation, language review and development of the glossary
8. Presentation of final consensus recommendations

Figure 3

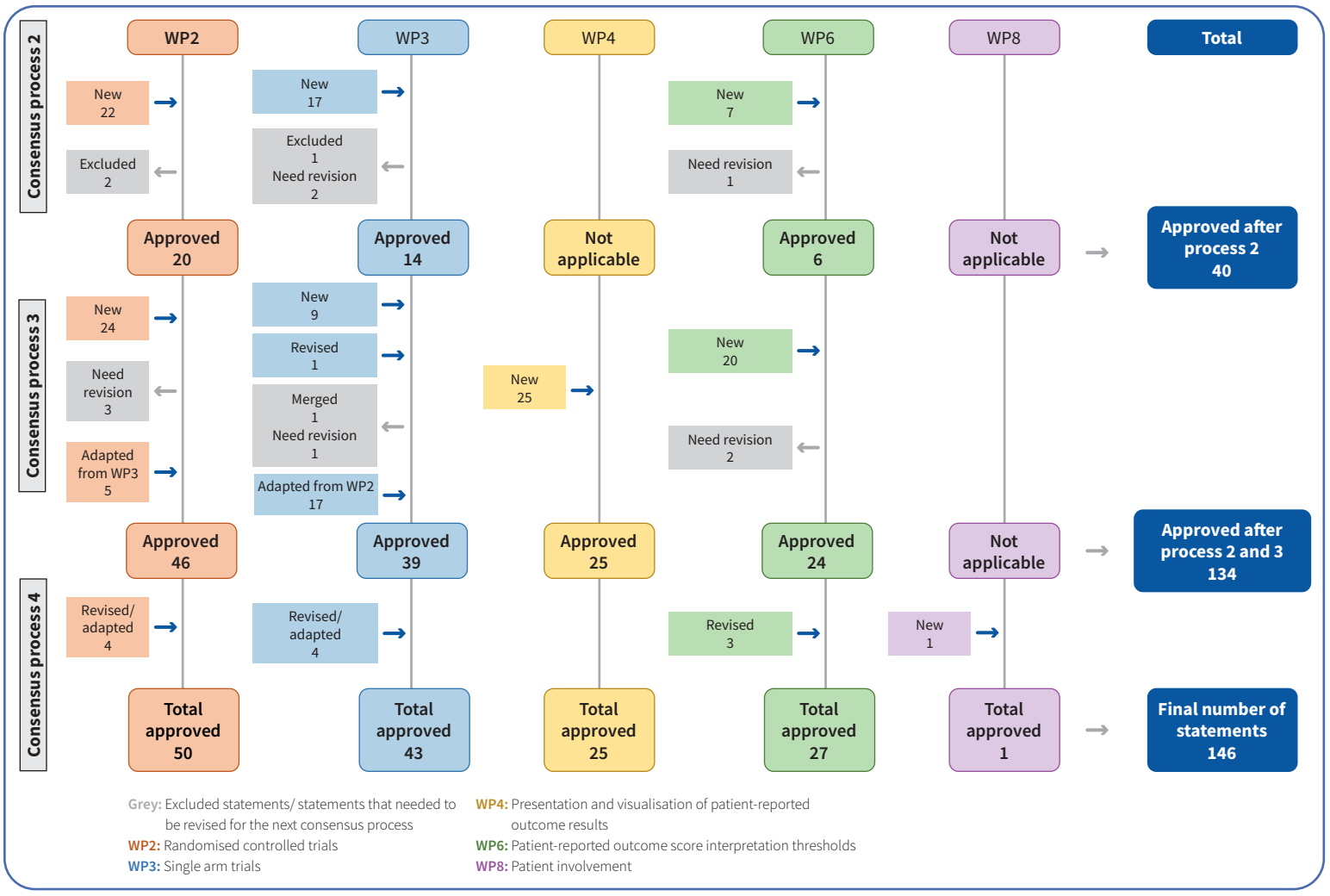
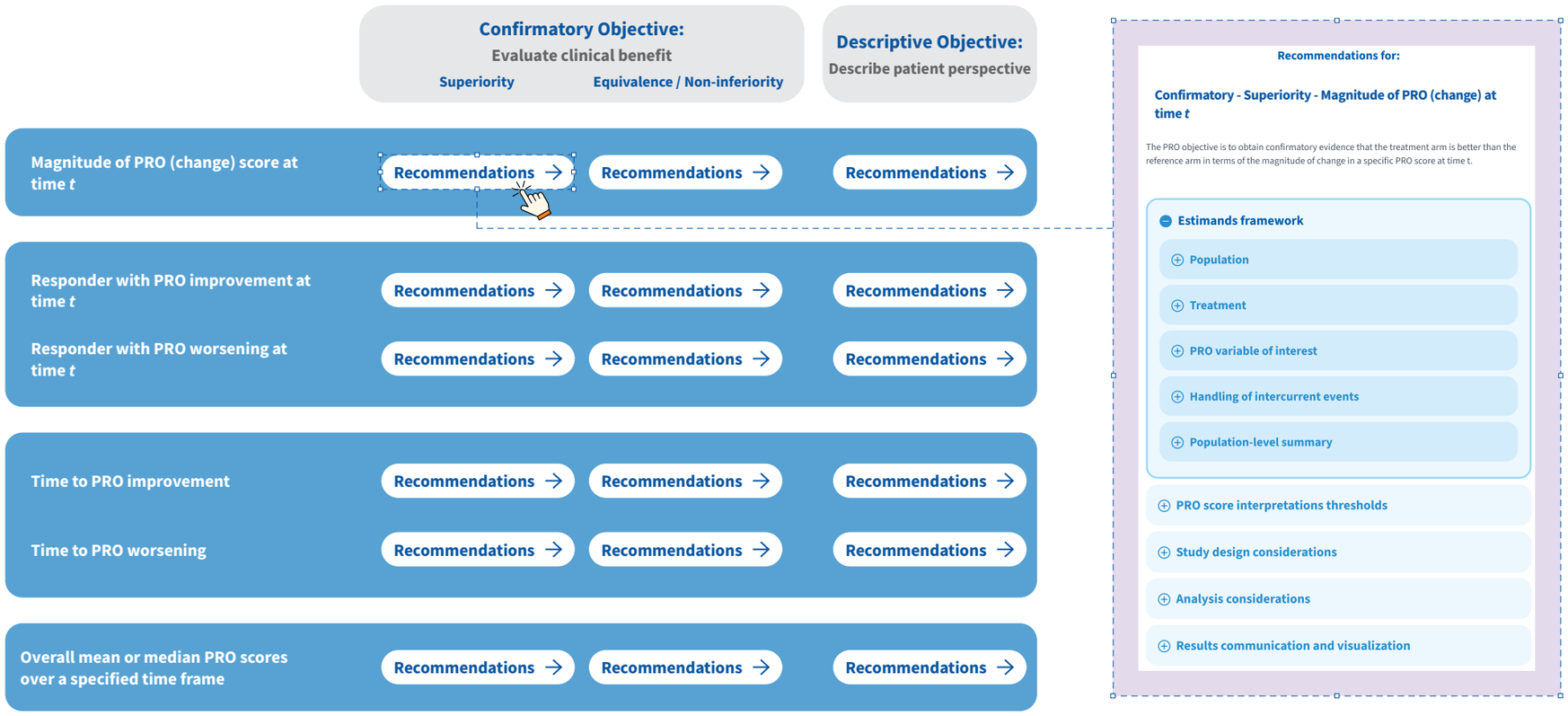

WP2
WP3
WP4
WP6
WP8
Total
Consensus process 2
New 22
Excluded 2
New 17
Excluded 1
Need revision 2
New 7
Need revision 1
Approved 20
Approved 14
Not applicable
Approved 6
Not applicable
Approved after process 2 40
Consensus process 3
New 24
Need revision 3
Adapted from WP3 5
New 9
Revised 1
Merged 1
Need revision 1
Adapted from WP2 17
New 25
New 20
Need revision 2
Approved 46
Approved 39
Approved 25
Approved 24
Not applicable
Approved after process 2 and 3 134
Consensus process 4
Revised/ adapted 4
Revised/ adapted 4
Revised 3
New 1
Total approved 50
Total approved 43
Total approved 25
Total approved 27
Total approved 1
Final number of statements 146
Grey: Excluded statements/ statements that needed to be revised for the next consensus process
WP2: Randomised controlled trials
WP3: Single arm trials
WP4: Presentation and visualisation of patient-reported outcome results
WP6: Patient-reported outcome score interpretation thresholds
WP8: Patient involvement

Figure 4


Confirmatory Objective:
Evaluate clinical benefit
Superiority
Equivalence / Non-inferiority
Descriptive Objective:
Describe patient perspective
Magnitude of PRO (change) score at time t
Recommendations
Recommendations
Recommendations
Responder with PRO improvement at time t
Recommendations
Recommendations
Recommendations
Responder with PRO worsening at time t
Recommendations
Recommendations
Recommendations
Time to PRO improvement
Recommendations
Recommendations
Recommendations
Time to PRO worsening
Recommendations
Recommendations
Recommendations
Overall mean or median PRO scores over a specified time frame
Recommendations
Recommendations
Recommendations
Recommendations for:
Confirmatory - Superiority - Magnitude of PRO (change) at time t
The PRO objective is to obtain confirmatory evidence that the treatment arm is better than the reference arm in terms of the magnitude of change in a specific PRO score at time t.
Estimands framework
Population
Treatment
PRO variable of interest
Handling of intercurrent events
Population-level summary
PRO score interpretations thresholds
Study design considerations
Analysis considerations
Results communication and visualization