Topic: Establishing international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topic details

Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Patient-centeredness is increasingly identified as a critical component of quality health care [1]. As such, health-related quality of life (HRQOL) and other patient-reported outcomes (PRO) that quantify how a patient feels or functions during treatment are increasingly considered as important endpoints in cancer clinical trials. Data on these endpoints are increasingly used to inform benefit-risk evaluations for regulatory marketing authorisation purposes. These endpoints are also useful in the context of reimbursement decision-making, where they are instrumental in evaluation of added therapeutic benefit and documentation of the value of surrogate endpoints such as progression-free survival (PFS) or overall response rate (RR). Moreover, information on HRQOL and PROs may also be used to enable better communication and shared decision making between patients and their treating physician, improving outcomes, treatment satisfaction and care.

Numerous efforts have been undertaken to standardise the way HRQOL and PRO data are conducted and reported in cancer clinical trials. These include recommendations to standardise reporting and drafting of clinical trials [2][3], translations in clinical trials [4]**Error! Reference source not found.**, and how to develop and standardise measures for use in clinical trials [5]. However, there are no agreed standards on how to analyse HRQOL and PRO data in clinical trials and subsequently, interpret the findings. The various ways data are analysed and interpreted make it difficult to compare results across trials, and hinder the application of research findings to inform physicians, patients, caregivers, policy makers, reimbursement authorities and other stakeholders. Lack of standardisation can lead to variation in the analysis of results and could result in two near-identical trials being analysed in different ways, leading to potential differences in data interpretation.

A number of systematic reviews from randomised controlled trials (RCTs) have highlighted the current lack of standardisation in this field and reported the following key findings [6][7][8]:

- a lack of clear HRQOL and PRO research objectives;
- a lack of standardisation of basic statistical terms such as compliance and completion rates;
- the use of suboptimal statistical practices and a variety of statistical methods not well justified with respect to analysing HRQOL and PRO data;
- the use of a variety of approaches to handling missing data.

There is an urgent need to develop clear standards and guidelines, endorsed by a broad range of stakeholders, to improve how HRQOL and PRO data are analysed in cancer clinical trials. This would also help promote HRQOL and PROs as potential primary or co-primary endpoints (when relevant) in cancer clinical trials. Such standards will support the full use and understanding of HRQOL and PROs in drug development and drug and device approval by regulators and health technology assessment (HTA) bodies, but importantly it will also support better communication of PRO results to clinicians and patients with the potential to inform and improve shared decision-making.

Need and opportunity for public-private collaborative research

This initiative aims to establish a multi-stakeholder consortium with the overall objective to standardise and develop recommendations for the analysis and interpretation of HRQOL and PRO data in cancer clinical trials. The focus of this topic is to achieve a consensus on the analysis methods of HRQOL and PRO data in RCTs. However, as other study designs (e.g. single arm studies, basket trials) are also starting to play an important and innovative role in cancer drug development, there is general agreement that guidelines and best practices also need to be developed for these trial designs. Moreover, once these new standards and guidelines are developed, it is critical to validate them using existing data from academic and pharma-led clinical trials. Finally, PRO findings based on these recommended analyses must be communicated in a simple and accurate way to clinicians, patients and other stakeholders.

To be able to address this challenge, the concerted efforts of different experts from various organisations are needed. It is critical to have a broad based consortium to include a wide range of experts and organisations. For instance, patient groups and their representatives, healthcare decision makers, regulators and representatives from HTA authorities and other public health bodies are needed, as well as experts from the pharmaceutical industry. Small and medium-sized enterprises (SMEs) may also play a role in the development of data visualisation software which should demonstrate added value to the regulatory and HTA bodies.

Scope

The scope of this Call topic is to develop recommendations for the different analyses and interpretations of HRQOL and PRO endpoints in cancer clinical trials that will be tailored towards addressing specific research objectives within each clinical trial. This Call topic aims for a global scope and is of strong interest to individuals from various regulatory and HTA bodies, key cancer organisations, the pharmaceutical industry, specialised vendor organisations, academic societies and international patient organisations. The buy-in of these various key stakeholders is crucial, as this will help identify a set of similar expectations, facilitate the implementation of these recommendations, and harmonise the analysis and interpretation of HRQOL and PRO data on a global scale.

The main objectives are to:

- achieve international consensus, across stakeholders, on the optimal use of HRQOL and PRO data in cancer clinical trials;
- improve the quality of statistical analysis of HRQOL and PRO data in cancer clinical trials;
- improve the standards of reporting of HRQOL and PRO data, and as such the interpretability of the data. It is hoped that this will result in more reliable interpretation, and ultimately faster dissemination, of HRQOL and PRO findings, as well as cross-referencing within and between different cancer settings, whenever this is deemed feasible.

Expected key deliverables

The work should lead to several important key deliverables and consensus documents that are aligned with relevant stakeholders; alignment with regulatory and HTA bodies will be especially important as this will be critical to successful implementation. Continuous collaboration throughout the project with representatives from patient advocacy groups is vital to ensure the patient-centricity of the research recommendations, dissemination strategies and patients' understanding of educational programmes.

The deliverables below should be achieved during the 48 months duration of the project.

- Work towards the development of internationally agreed consensus-based guidelines and recommendations for HRQOL and PRO analysis for RCTs, supported by relevant publications:
  a) recommendations to support the development of industry guidelines for the design, analysis and interpretation of HRQOL and PRO findings from cancer clinical trials;
  b) recommendations to support the development of regulatory guidance, such as European Medicines Agency (EMA) Points to Consider, and HTA guidelines for the design, analysis and interpretation of HRQOL and PRO findings from cancer clinical trials;
  c) recommendations to support the European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines on assessing clinical benefit using HRQOL and PRO data from cancer trials;

d) recommendations for dissemination strategies and educational programmes designed specifically to improve patients' understanding of HRQOL/PRO and empower their abilities for shared decision making;
e) recommendations for clinically meaningful change for HRQOL/PRO instruments used in cancer clinical trials.

- Delivery of a case study database to retrospectively validate consensus recommendations;
- A freely accessible toolbox providing recommendations for the communication, presentation and visualisation of HRQOL and PRO findings from cancer RCTs, including templates that are freely available to all users and promoted in all literature;
- Evaluate the feasibility of developing recommendations for non-RCTs, using single-arm studies as a case study (this should be closely linked to the main recommendations for RCTs to ensure uniformity in terminology and synergy of complementary ideas);
- A sustainability and capacity building plan to ensure that recommendations for PRO analysis in cancer clinical trials remain constantly up to date and relevant, including establishing an ongoing governing advisory board (with defined roles and responsibilities) to give advice on future updates to the recommendations.

Recommendations will be widely disseminated, where appropriate, and made available through a publicly accessible website that also allows access to other deliverables; use of this website's resources, along with implementation of the recommendations by regulatory agencies and HTAs, will be instrumental in ensuring the success of this initiative.

Expected impact

A consensus and clear set of agreed methodological recommendations for the statistical analysis of HRQOL and PRO data in cancer studies will improve their interpretability. This is an important prerequisite for better adoption and increased use of these outcomes in various decision-making contexts (regulatory approval, HTA/reimbursement decisions, shared decision making between physicians and patients). Importantly, the expected outcomes of this initiative will be of mutual benefit to all stakeholders involved, including the most important beneficiary of healthcare, the patient. Reaching a broad international consensus is a prerequisite for a broader adoption of HRQOL and PRO data and is likely to result in:

- more reliable findings and faster dissemination of HRQOL and PRO data in cancer studies;
- advances in statistical science and improved statistical practice in cancer studies;
- improved interpretability of the data because of greater familiarity with standardised reporting;
- broader use and adoption of PRO data to inform benefit-risk evaluation in regulatory appraisals, added benefit evaluation in HTAs and reimbursement decision processes as well as shared treatment decision making contexts;
- better and improved shared decision making between patients and their treating physicians which may lead to improved patient satisfaction, an increased likelihood of adherence to treatment, higher likelihood of treatment success and a reduction in health-care cost;
- better and more efficient use of increasingly finite research and healthcare funding;
- improved and more efficient clinical trial designs that also investigate the cancer patient perspective on treatment outcomes.

Applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example engaging suitable small and medium-sized enterprises (SMEs).

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding. Proposals should document how collaboration will be achieved.

Possible synergies and collaborations will exist with the following initiatives and it is vital for the success of this project that close collaboration and alignment with these institutions should be sought by the applicants:

- The Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium, managed by the European Organisation for Research and Treatment of Cancer (EORTC), currently working on guidelines for the analysis of PRO data;

- The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)-PRO/ Consolidated Standards of Reporting Trials (CONSORT)-PRO (https://www.equator-network.org/reporting-guidelines/spirit-pro/) who recently published standards and are collaborating on standards for designing clinical trials, including non-RCT cancer trials;
- The Critical Path Institute (C-PATH - https://c-path.org/): a group working on PRO in the United States and working on the important area of developing electronic PRO measurements;
- EMA who have developed guidelines on PRO assessment; [9]
- The Food and Drug Administration (FDA) who have recommendations on PRO assessment in label claims, although limited guidance in terms of statistical analysis or interpretation; [10]
- The International Society for Quality of Life Research (ISOQOL; http://www.isoqol.org/) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR: https://www.ispor.org/) working groups;
- Health Canada (https://www.canada.ca/en/health-canada.html) and the Japanese Clinical Oncology Group (http://www.jcog.jp/en/) who are developing new efforts towards making PRO an important national endpoint;
- Oncology societies that have made major steps in oncology: ASCO (https://www.asco.org/) and ESMO (https://www.esmo.org/).
- Study data from existing EU-funded (from the FP6/FP7/H2020 research portfolio) RCTs and observational studies addressing palliative, end-of-life and survivorship care could be potentially used to validate the recommendations for statistical analyses developed in this initiative, if feasible.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Boehringer Ingelheim (lead)
- AbbVie
- Bayer
- Bristol-Myers Squibb
- Merck KGaA
- Pfizer

The industry consortium will contribute the following expertise and assets:

- in-depth knowledge of the advantages and disadvantages of various statistical methods and how they can be matched to identified research objectives;
- contributing to the review of clinically important responders and clinically important differences for various instruments and developing best practice recommendations for future instruments including outcome item banks;
- participation at all consensus meetings; making proposals, discussing options and contributing to guideline drafting and review;
- validating guideline recommendations by re-analysing existing data-sets and implementing them in prospective case studies;
- discussing and assessing the operational feasibility of implementing guideline recommendations in future cancer studies;
- contributing to developing educational tools and dissemination materials.

Indicative duration of the action

The indicative duration of the action is 48 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA is EUR 2 900 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 2 000 000 and EUR 900 000 as financial contribution to the beneficiaries receiving JU funding in the selected action.

At stage 1, applicants should provide a suggested allocation of the total financial contribution (EUR 3 180 000) in the budget of their short proposal in order to achieve the proposed objectives.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 2 282 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium, which will join the selected applicant consortium in preparation of the full proposal for stage 2.

To be successful, the applicant consortium will need to effectively combine the expertise of the various stakeholders in order to harmonise and standardise HRQOL and PRO analysis for cancer RCTs. Therefore, the successful consortium should have representatives from these key stakeholders or demonstrate plans to bring in necessary stakeholders and in-depth knowledge, as appropriate:

- regulatory affairs expertise with a proven track record of interacting with key regulatory agencies;
- representatives from HTA agencies;
- biostatisticians, epidemiologists, psychologists, and HRQOL and PRO researchers with experience in cancer RCTs (mandatory as participants);
- clinicians and other health-care professionals with experience in the design and conduct of cancer randomised clinical trials;
- representatives from academic medical and methodological societies;
- experts in the visualisation and presentation of HRQOL and PRO data;
- cancer patient advocacy groups, with knowledge and experience in cancer clinical trials (for activities in work package 7).

Optional:

- representatives from key cancer/medical journals;
- experts (including SMEs) in communication and knowledge dissemination;
- experts in interaction and communication with an international, multi-disciplinary stakeholder group.

The applicant consortium is also expected to have access to closed, completed cancer randomised controlled trial datasets with HRQOL/PRO assessments. Ideally, such data sets will be international and collected in the academic based clinical trial setting. The applicant consortium is expected to possess the necessary project management skills suitable for the consortium activities including organising and conducting consensus meetings.

The resources allocated should be adequate for the complexity and size of the consortium.

Suggested architecture of the full proposal

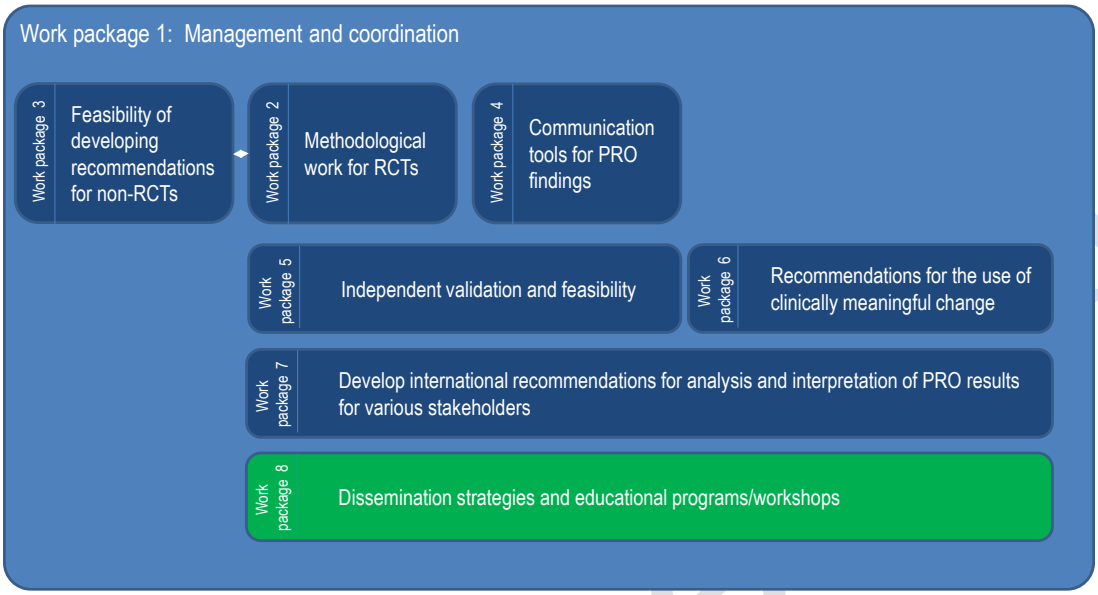
The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise provided below.

In the spirit of the partnership, and to reflect how IMI2 JU Call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, regulatory, clinical and healthcare practice. A plan for interactions with Regulatory Agencies/health

technology assessment bodies with relevant milestones, resources allocated should be proposed to ensure this e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion.

The below architecture for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this call topic.



Work package 1 – Management and coordination

The goals of this work package are to:

- establish a working governance structure, ensuring that various key stakeholder groups are well-represented;
- establish an internal communication structure to ensure the harmonisation of work across project teams;
- organise project-wide meetings;
- budget administration;
- communicate with the project team and relevant external stakeholders to ensure alignment and uptake of recommendations;
- establish an independent ethics advisory task force to help ensure all ethical aspects of the research and their recommendations conform to H2020 standards and norms.

Industry contribution:

- project leader;
- coordination across different work packages (including overall scientific and strategic oversight).

Expected applicant consortium contribution:

- project coordinator;
- professional project management expertise (daily operational support with project meetings, reporting and internal communication), see also section on applicant consortium.

Work package 2 – Methodological work for cancer RCTs

The goals of this work package are to:

- identify and update valid PRO objectives for RCTs and translate them into estimands;
- set criteria to help design the timing and frequency of PRO assessments (including baseline), balancing the need for assessments at clinically relevant time points and reducing patient burden;

- set criteria to assess quality of collected PRO data, ensuring that there is enough good quality data available to respond to the PRO objectives;
- set criteria to identify appropriate statistical methods to analyse PRO data;
- match appropriate statistical methods to valid PRO objectives;
- provide recommendations on the interpretation of PRO findings based on the trial objectives, data quality and statistical methods used;
- ensure close communication with work package 3, ensuring that the key criteria needed for drawing conclusions of PRO findings are correctly represented in the communication tools for various stakeholders;
- provide guidelines on when an update of the methodological work would be needed.

Work package 3 – Feasibility of developing recommendations for non-RCTs, with single-arm studies as a case study

The goals of this work package are to:

- identify case studies in which PROs were used in single-arm cancer clinical trial studies;
- identify the needs of various stakeholders to assess PROs in single-arm studies;
- identify valid PRO objectives that can be addressed by single-arm studies and set criteria needed to evaluate PROs in single-arm studies as well as criteria to evaluate the potential bias for single arm, open-label studies;
- evaluate aspects of RCT recommendations that can be adapted to single-arm studies.

It is recommended that this work package be closely linked to the main work for RCTs to ensure uniformity in terminology and synergy of complementary ideas.

Work package 4 – Communication tools for PRO findings from cancer clinical trials

The goals of this work package are to:

- set criteria and general guidelines for presentation and visualisation of PRO findings from cancer RCTs – this should be done in close collaboration with work package 2;
- identify the needs of various stakeholders (regulatory, HTA, patients, clinicians, journals, academics) on how they want the PRO results from clinical trials to be reported;
- produce templates for the visualisation and presentation of PRO findings that would fit the needs of different stakeholders;
- provide guidelines on when an update of the communication tools would be needed.

Work package 5 – Independent validation and feasibility of methodological work and communication tools

The goals of this work package are to:

- manage and coordinate the use of research data including legal and ethical considerations;
- identify case studies for this project:
  - retrospective cancer clinical trials data with HRQOL/PRO assessment;
  - prospective cancer clinical trials that will include a HRQOL/PRO assessment.
- using the case studies, implement and assess the feasibility of the approaches from work packages 2–3, including identifying gaps and recommending solutions for each of these gaps;
- provide guidelines on when additional validation and feasibility checks would be needed.

Work package 6 – Develop international recommendations for the terminology and definitions of clinical meaningful change in cancer clinical trials

The goals of this work package are to:

- identify best practices to develop clinical meaningful change research objectives for the most commonly used HRQOL/PRO instruments in cancer trials that clearly differentiate group level differences and individual level differences. Recommendations need to recognise the wide-range of

terminologies currently used in the literature which include, but are not limited to minimum clinically important differences (MCIDs) / minimum important differences (MIDs) and responder thresholds;
- investigate whether these approaches can be generalised to emerging new instruments and item banks;
- Develop final recommendations for the use of terminology and definitions in HRQOL/PRO assessments in cancer trials that are agreed by the main stakeholders including regulatory agencies, HTA agencies as well as ESMO and ASCO;
- Provide guidelines on when updates of recommendations would be needed.

Work package 7 – Develop international recommendations for analysis and interpretation of PRO results for various stakeholders

The goals of this work package are to:

- identify a procedure to ensure recommendations are based on a consensus and that key experts and stakeholder groups are well-represented;
- ensure that the needs of the various stakeholders are considered in the final recommendations including feedback from representatives of leading patient advocacy organisations;
- provide final recommendations based on the combined results from work packages 2, 4, 5 and 6 for the various stakeholders to:
    - support the development of industry guidelines for the design, analysis and interpretation of PRO findings from cancer clinical trials;
    - support development of regulatory and HTA guidelines for the design, analysis and interpretation of PRO findings from cancer clinical trials;
    - support ESMO and ASCO guidelines on assessing clinical benefit.
- provide guidelines on when an update of the recommendations would be needed.

Work package 8 – Dissemination strategies and educational programmes/workshops

The goals of this work package are to:

- provide a continuous dissemination and communication plan (including social media) to ensure that project results are communicated to both internal and external stakeholders;
- provide an educational tool based on the work from the different work packages for different stakeholders;
- ensure close collaboration with all Work package leaders to ensure proper and efficient dissemination of results from the various work packages are disseminated;
- a feasibility plan and guidelines for updating relevant PRO objectives, statistical methods and handling of missing PRO data based on future developments in methodology and changes in the cancer clinical trial environment. The goal is to have a live document that will be available for all stakeholders in the long-term;
- provide educational tools and develop required knowledge to assess, analyse and interpret PRO data in cancer clinical trials for all relevant stakeholders including patients.

References

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