CORE-MD

Coordinating Research and Evidence for Medical Devices

Recommendations on PROMs for conformity assessment and post-market surveillance

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Authors:	Ola Rolfson (UGOT), John Eric Chaplin (UGOT), Claudia Louati (EPF), Yasemin Zeisl (EPF), Ingrid Weindorfer (EPF), Bianca Pop (EPF)
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Acronyms and abbreviations*

EMA	European Medicines Agency
FDA	The United States Food and Drug Administration
HrQoL	Health related Quality of Life is a patient reported outcome (PRO). It is a subjective, multidimensional assessment of how disease and treatment affect a patient's sense of overall function and wellbeing and can Include emotional, social and physical aspects of the individual's life. HRQOL is among the accepted primary outcomes in clinical trials owing to its recognized importance to patients.
MCID	Minimal Clinically Important Difference is the smallest improvement considered worthwhile by a patient.
MDC	Minimal Detectable Change is a parameter of reliability that is defined as the 'smallest change in score that can be detected beyond measurement error'
MDDT	Medical Device Development Tool. The program is a way for the FDA to qualify tools that medical device sponsors can choose to use in the development and evaluation of medical devices.
MIC	Minimal Important Change is the smallest change in score in the construct to be measured which patients perceive as important.
PASS	The Patient Acceptable Symptom State (PASS) is a treatment-response criterion developed to determine the clinical relevance of a treatment effect.
PREM	Patient-Reported Experience Measures (PREMs) are questionnaires that measure patients' perceptions of their experiences about the process of care. They are not satisfaction surveys but can be used to evaluate quality of care.
PRO	A Patient-Reported Outcome is a health outcome directly reported by the patient who experienced it. It stands in contrast to an outcome reported by someone else, such as a physician-reported outcome, or a nurse-reported outcome.
PROM	Patient Reported Outcome Measure is a quantitative representation of outcome that is estimated by the patient to measure one or multiple PROs (i.e., uni- or multidimensional PROM). PROMs are often classified either as a generic PROM or as a specific PROM (i.e., for a certain disease or condition).
QoL	Quality of Life. Within health care research QoL is often used as a short-hand for HrQoL. However, QoL is a concept including multiple aspects of people's lives, which would include health, but might also include material comforts, personal safety, relationships, creative expression etc. The World Health Organization defines QoL as *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns."*

**See Appendix A1 for a full list of Acronyms, including the PROMS scales*

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Executive Summary

Europe has a clear opportunity to be a global leader in regulatory science by harnessing meaningful and timely patient involvement. Patient involvement in medical devices' development, conformity assessment, and post-market monitoring is in its infancy, contrary to pharmaceuticals where significant progress on integration of patient experience data for regulatory purposes has been made in recent years.

Several data sources can be considered to capture patient experiences, including patient-reported outcome measures (PROM), performance measures, wearable devices, and biosensors, as well as comprehensive collection and analysis of clinical events. In this report, we have focused on PROMs, specifically their use and utility in trials, studies, and post-market surveillance of high-risk medical devices. A core element of this research was to include the patient perspectives through consultation. This report is based on two approaches to data gathering, firstly via a systematic literature review, and secondly via a Delphi study, online surveys and focus groups with patients and caregivers.

The literature review identified a very large of number of studies which compared different aspects of implanted devices. It is noted that there were a large number of PROMs being used although certain generic PROMs were more frequent; the mode of delivery was predominantly via a paper questionnaire although there was one study that used telephone interviews. The PROMs outcomes were presented in several different ways and their stated or implied purpose was either to measure a global or condition-specific concept of 'quality of life' (QoL), or a specific symptom such as pain, satisfaction, or adverse effects. The review identified several important themes:

1) The need for consistency in PROM reporting procedures. The type of PROMs being used varied between conditions: there were more condition-specific PROMs used in diabetes research than in the other conditions, and more movement-related PROMs in orthopaedics. However, there were also many generic PROMs used, and data collection and reporting procedures varied not only between conditions but within conditions.
2) None of the studies defined what was meant by QoL or how the chosen PROM was selected, other than that it had been used previously. An important observation was the lack of discussion concerning the characteristics of the PROMs being used. The distinction between domains measured by different instruments illustrates the need to consider the construction of instruments carefully before applying them in a study.
3) Issues relevant to the regulation of medical devices may not be captured by existing PROMs. The Delphi study identified outcome priorities that did not match the elements of most of the PROMs being used. Patients in the Delphi expressed an emphasis on specific concepts and symptoms rather than overall QoL. None of the studies that were reviewed, indicated that patients had been involved in the development or selection of PROMs.
4) The reporting and interpretation of results were unclear. In comparison studies, PROM results were reported either as a mean score change using a statistical significance test, as a difference without statistical testing, as a pre-defined change (e.g. 30%), or in reference to a previously published minimal clinically important difference (MCID).
5) Study designs were not optimized for PROM research. It was noted that use of MCID to determine population size and statistical power was seldom used; additional statistical considerations for

equivalence testing were not discussed; and the choice of technique for imputing missing data, and the use of multiple measurements over time and their effect on precision, were not discussed.

6) Only a few device-specific PROMs were found in cardiovascular and diabetes research. There were also a few studies that used FDA MDDT program-qualified PROMs. Device specific questionnaires had the additional focus on acceptance of the device and how the device affected body image.

7) PROM data collection was often carried out in the clinic, at the time of a medical consultation, but also via postal surveys at regular intervals. There are resource advantages to PROM data collection coinciding with clinical visits, but changes in patient-perceived outcomes may not be coincident with clinical changes.

8) Given that patient outcomes are intrinsically subjective and that patient participation in research is increasingly encouraged, it was noted that there were no references in the analysed studies to consultation with the patient about the choice of which concepts to measure. Patients did not have the opportunity, as far as can be seen in the literature, to describe what were their important outcomes. This of course is a general observation concerning PROM research in all medical fields.

Overall, the literature review found that a great deal of PRO data was collected and used to provide evidence related to medical devices, not only in terms of contrasting aspects of their design or construction but also the acceptance of devices, their effects upon daily life, and differences in population characteristics that might affect acceptance.

The collection of PRO data poses several key challenges. From a scientific and logistical standpoint, PROMs require comprehensive planning and instruction in the protocol and during the conduct of the trial, to optimise subsequent analysis and reporting. Other key challenges are that patients generally lack familiarity with PROMs and may not realise that they are completing a PROM questionnaire. It was noted in the Delphi study that none of the participants had completed a PROM, which illustrates that PROMs are not used routinely during clinical treatment with devices. Unclear information about data usage, lack of feedback and irrelevant questionnaire content hinder engagement and reduce response rates that affect the value of the data collected at the group level.

The Delphi study showed that patients want to be involved in the co-design of devices and share feedback on their experiences, needs, and concerns, yet do not have methods or communication opportunities to do so. Solutions to increase the relevance and use of PROMs include educating patients about PROMs, providing clear feedback, ensuring transparency about data usage, and involving patients in questionnaire design to enhance relevance and engagement. A strong signal from regulators that PROMs are valued for the assessment of the benefit/risk ratio and post-marketing surveillance of devices is also needed to encourage the development of devices that meet patients' needs.

1 Introduction

The patient's voice is critical to advancing medical research and medical products, which can eventually improve health outcomes for the patient from his or her perspective. A recent EMA workshop report which looked at the importance of inclusion of the patient's voice in regulatory decision-making, defined Patient Experience Data (PED) as *"data collected via a variety of patient engagement activities and methodologies to collect patients' experience of their health status, symptoms, disease course, treatment preferences, quality of life and impact of health care. For EU regulators, PED not only involves quantitative sources of evidence (e.g., patient reported outcomes or patient reported experience measures) but also qualitative sources (i.e., any information obtained as part of patient engagement activities that reflect the wider perspective of patients' experience, for example, the outcome of focus groups, surveys or interviews)."* (EMA 2022)

A key challenge for research into new health products has been how to translate this patient perspective or "patient voice" into scientifically valid data that can inform their design. In this report we will look at how the patient voice is included in research into the evaluation of high-risk medical implants. PROMs are of particular importance for the monitoring and management of chronic conditions affecting QoL and therefore have an important role in the individual assessment of the patient and in support of decisions related to aspects of quality of care and QoL (Lauck et al 2021; Spertus 2018; Arbelo et al 2021; Moons et al 2023).

A patient-reported outcome is "*any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else*" (FDA 2009 page 6). Patients with medical devices rely for their health and safety on strong pre-market conformity assessments and on the ongoing monitoring and surveillance of their implanted medical device. One way to measure outcomes is through the use of PROMs. International regulatory authorities, health policymakers, and patients have all recognised the importance of PROMs. PRO trial results, if captured in a scientifically rigorous way, may inform clinical decision-making and patient decision-making, medical product labelling, and influence healthcare policy. PROs may also be the only way of assessing and demonstrating treatment benefit. Consequently, interest in and use of PROs has increased over the last few decades (Porter 2010; Black 2013).

The EMA (EMA 2005, 2022) and the FDA (FDA 2009) have been at the forefront of regulatory development in regard to PROMs. Guidance on the development, translation and use of PROMs has been published and supported by scientific societies such as the International Society of Quality of Life (ISOQOL) and the International Society for Outcomes Research (ISPOR). There has been a strong push to use PROMs, from regulators, and collaboration between regulators to align how they evaluate PRO data.

With regard to medical devices, according to a recent report by Wilson et al (2019) in EFORT Open Reviews, there are a number of different stakeholders and uses for PROMs that they list, as reproduced below in Table 1.

Table 1. Relation between stakeholders and uses of PROMs

Stakeholder	Uses of PROMs
Health system policymakers / system managers	• Compare outcomes at a local regional, provincial and international level as well as over time. • Compare different models of care and clinical pathways (e.g. referral patterns). • Support health service allocation decisions ('value-based' care). • Inform quality improvement initiatives.
Healthcare organizations	• Monitor organization and provider performance. • Conduct comparisons with peer organizations. • Inform quality improvement initiatives.
Healthcare providers	• Provide feedback to inform care plan. • Provide evidence on improved or maintained health of patients. • Improve clinician-patient communication. • Facilitate performance comparisons with expected standards. • Facilitate comparative effectiveness research.
Patients	• Provide opportunity to give feedback regarding treatment, care processes and preferences. • Increase awareness of expected outcomes of care. • Enhance communication with providers. • Increase involvement in care planning and decision-making.

As will be seen from this list, for our purposes, a critical stakeholder is missing and that is the regulator. It is unclear at this point what PROM data would be considered valid information for regulators to base their decisions upon, in regard to the assessment of new, high-risk, medical devices. Our question in this report is therefore not only how PROMs are being used but how we can add the regulators of medical products to the list of stakeholders. In Europe this group includes the organizations in charge of conformity assessments, namely the notified bodies, which adds another level of complexity. In addition to the regulators, another group of stakeholders are missing, namely the designers, developers, and innovators of medical devices who also need to know what data will be acceptable to regulators.

Capturing the patient's perspective on high-risk medical devices involves the collection of unique information on the patient's experience and on the device's functioning. It also provides an opportunity to better understand the impact of a device on the patient's quality of life, which may contribute to the development of more appropriate health care interventions to support living with a medical device.

PROMs are seen as a means of easily obtaining and quantifying patients' perspectives in a quantitative manner. These instruments provide a subjective measurement of outcome which is otherwise not captured consistently or in a standardized way in order to enable comparison and quality control assessments of treatments, procedures and devices. The importance of collecting PROM data has been increasingly recognized as an essential complement to clinical diagnosis and to patient safety. The use of PROMs is encouraged both by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) guidelines for medicinal products development. Data covering single and multi-dimension measures such as symptoms, feelings, functioning, well-being and treatment satisfaction can be collected. Inclusion of PROMs as an endpoint in a clinical trial is considered to be of added value for various stakeholders including regulators, health technology assessment bodies/payers and professional organizations, by contributing to a better understanding of the effects of medical products with similar functions. PROMs are included almost routinely in clinical trials to assess domains of patients' health status without the introduction of possible third-party bias (Black 2013; Cella et al 2015).

PROMs can be classified in various ways. There is usually a distinction made between generic instruments designed to measure broad health concepts, and disease-specific instruments which focus on specific symptoms. The benefits of condition-specific instruments tend to be that they have higher clinical relevance and have been shown to be more responsive to change. However, this is not always the case and is dependent upon the specific population for whom they were designed. Condition-specific PROMs might also fail to capture unexpected treatment-related events affecting the overall QoL of the patient. The specific nature of the questions also means that comparisons between conditions are not possible. The different types of PROM are described below.

The focus of the study presented in this report is to summarise the evidence on the utility of PROMs in medical device research from two perspectives. Firstly, from a systematic literature review of studies investigating the effects of high-risk medical implants in the fields of orthopaedics, cardiovascular and diabetes. Secondly, from a qualitative viewpoint, to understand a patient perspective on the issues that are of the greatest importance to them.

The University of Gothenburg (UGOT) has carried out a systematic literature review, and the European Patient Forum (EPF) has convened a Delphi Panel and focus groups, to reach consensus on a core outcome set for assessing which PROMs should be included for patients with orthopaedic, diabetes or cardiovascular medical devices.

Based on this accumulated experience, we will seek to contribute to understanding the requirements for the regulatory approval of evidence from PROMs concerning high-risk medical devices.

In order to do this, it is necessary firstly to see where PROMs fit within the clinical data gathering process. A PROM is a quantitative source of a clinical outcome assessment (COA) that reflects how a patient feels, functions, or survives. However, there are other sources of this evidence such as observer-reported outcomes (ObsROs), clinician-reported outcomes (ClinROs) and Performance outcomes (PerfOs).

Secondly, it is necessary to define what is meant by a PROM. A PRO refer to a health or treatment outcome reported directly by the patient without the interpretation of a clinician or another person (FDA 2009). The EMA defines a PRO as:

"Any outcome evaluated directly by the patient himself or herself. A PRO can be measured by self-report, generally in the form of a questionnaire, or by interview, provided that the interviewer records only the patient's response. PRO measures must have acceptable responsiveness, reliability and validity, and may include reference to symptoms, functional status, treatment adherence or satisfaction with care. In clinical research, the use of a PRO measure is advised when measuring a concept best known to the patient or best measured from the patient perspective." (EMA 2014)

PROMs can therefore include questionnaires, rating scales (e.g., numeric rating scale of pain intensity, or verbal rating scale of global improvement on a medical treatment) and counts of events (e.g., patient-completed diary of seizure episodes).

PROMs are increasingly being recommended for the evaluation of health conditions and responses to treatments. Over the last decades, there has been a gradual shift towards a value-based and patient-centred health care, resulting in a stronger focus on PROs such as health-related quality of life (HRQOL) and symptom burden (Porter 2010; Black 2013). PROMs have been used mostly at the aggregated level to evaluate health-care quality (OECD – PaRIS 2019), but their use is increasingly being advocated at the individual level. Their use at individual level as part of personalized care is considered to add value and

provide insight into patients' perceived health and needs, as well as enhancing patient-professional communication and shared decision-making.

Even though there is no consensus in the literature about which PROMs are appropriate to select as clinical trial endpoints, some PROMs are used more frequently than others as is shown in this review.

Despite recognition by major regulatory authorities of the importance of PROMs, there are issues related to sensitivity to change and interpretation of results from studies that pose significant challenges to the construction of evidence. These issues include:

i) lack of standards in the selection and methodology of PRO used;
ii) poor conduct of studies resulting in missing data and bias;
iii) confusing side effects with disease symptoms;
iv) measures that focus on negative symptoms and thus fail to measure or capture concerns at the more positive end of the scale or in asymptomatic patients, and;
v) the frequent use of open-label or single-arm designs.

Table 2 summarises the main features of the principal categories of PROMs.

Table 2. Different types of PROMs

Main Characteristics	
Health-related quality of life (HRQL)	Multidimensional –physical, mental, social specific to age groups. Can be generic or condition-specific
Symptoms and symptom burden	Are specific to type of symptom of interest. May identify symptoms not otherwise captured
Health behaviors	Specific to different types of behavior. Typically measure frequency of behavior
Patient experience /PREM	Perception of health care delivery, treatment recommendations, and medications (or other therapies); Reflects actual experiences with health care services; Fosters patient activation.
Device experience	Reflects experience (outcomes) and attitudes (acceptance & predictors) towards a medical device

Health Related Quality of Life (HrQoL) measures attempt to measure complex aspects of life which are modified by the disease and therapeutic interventions. HrQoL, is a subjective concept and will vary with gender, experience, age, education, disease stage, and cultural background. The EMA (2022) states that measurement of PED complements the range of traditional indicators by adding patient experiences of outcome (EMA/354012/2020).

- **Generic HrQoL instruments measure** health concepts that are relevant to a wide range of patient groups, enabling aggregation and comparisons across varied conditions and settings.
- **Condition-specific HrQoL PROMs** capture elements of health relevant to a particular patient group or condition.

Functional status PROMs can be used in addition to performance-based measures of function like step-tests or range of motion. These reflect the individual's actual performance of activities.

Symptom PROMs provide the primary perspective of treatment effectiveness and capture side-effects of therapy.

Health behaviour PROMs target specific health behaviours such as healthy eating or exercise, or adherence to medical regimen.

Device-related PROMs target the experience of living with a medical device and can focus on satisfaction or function. There are significant hurdles facing comparisons of patients' outcomes related to medical implants, including adjusting for patient differences, health system factors and approaches to survey administration. While comparisons of implant outcomes using patient-reported outcomes shows significant promise, much work on standardizing sampling design, variables and analytical methods is needed. It is recognized that device management can mean dealing with both substantial symptoms and functional limitations. Therefore, patients' overall 'holistic' perspective can add value to our understanding of the therapeutic effects of their device.

2 Literature review

2.1 Methodology

Following a PROSPERO registration, we performed a literature search of MEDLINE, CINAHL, and the Cochrane trials database (January 2000–June 2022) of orthopaedic, cardiovascular and diabetes medical implants, where PROMs had been used. Search strings were developed using keywords, MeSH terms, and names of PROM instruments. For orthopaedic PROMs, we retrieved English-language articles reporting evaluation of hip and knee implant surgeries with at least three months follow-up.

A protocol was written before the start of the literature search. Inclusion criteria, research questions and data to be extracted were specified in advance. Due to the exploratory nature of this review, some objectives could not be specified until the full text screening was completed.

Text mining was undertaken to identify key words and MeSH terms.

2.1.1 Data extraction (selection and coding)

Records were identified through database searching and were then exported to Endnote reference manager (Endnote X9, 2019); duplicates were removed. The remaining references were then exported to Rayyan, a software program that allows the manageable screening of citations (Ouzzani, 2016). Further duplications were removed that are at least 85% duplicates. Titles and abstracts were screened by at least two researchers, and records excluded based on inclusion and exclusion criteria. The remaining articles were full text screened for eligibility. Reasons for exclusion were documented in the protocol. Any uncertainties regarding inclusion were referred to supervisors for consensus decision. Further exclusion criteria were applied during the full text screening process. Reference lists of the included studies were hand screened for potential studies.

In order to address the systematic review question, the following data were extracted:

1. PROM instrument used
2. Intended aim/purpose of the PROM
3. Constructs measured
4. Mode of delivery
5. Response rate
6. What contribution does the PROM make to understanding the medical product?

2.1.2 Selection of databases

Three databases were searched in order to provide wide coverage and to minimise the risk of missing any relevant articles. The databases searched were OVID Medline, Cochrane and CINAHL. Medline is a large database which would likely host most of the articles of interest, while CINAHL, aimed at nursing, might contain articles not found in Medline. Cochrane was added to the search to further decrease the risk of missing any articles.

In additional the reference lists of included studies were searched.

2.1.3 Inclusion criteria and filters

The inclusion criteria were that the studies must include an orthopaedic (knee or hip), cardiovascular or diabetes (closed-loop) device or surgery related to a device, that a PROM was used to capture the patient's perspective, and that there should be a follow-up of at least three months. Publications after year 2000 was an inclusion criteria for the orthopaedics and cardiovascular reviews, publication after 2013 was used for diabetes publications. See Table 4 below.

There were no limitations concerning participant age, severity of condition, or previous treatments.

2.1.4 Exclusion criteria

Articles were excluded according to the following criteria: 1. irrelevant focus, 2. unable to locate full text, 3. duplicate that was not previously identified.

Irrelevant focus included studies aimed at evaluating pharmaceutical products or rehabilitation therapies. Protocols and reviews were excluded, but were searched for issues related to the utility of PROMs and to help identify additional studies that had been missed by the search algorithm. In addition, psychometric studies investigating validity and reliability without looking at a patient's outcome were excluded. Filters available within the databases were applied where appropriate to focus the selection process e.g. English language texts. For Cochrane, a filter was used to limit the search to trials. Within CINAHL it was possible to use a filter to exclude Medline articles, which reduced the number of duplicates when searching multiple databases.

2.1.5 Condition-specific approaches

The data collection period varied according to the focus of the different medical conditions.

Orthopaedics and Cardiovascular

Requirements for inclusion were for studies to be randomised or non-randomised clinical trials, prospective or retrospective studies using standardised or non-standardised PROMs aimed at generic outcomes or condition-specific outcomes, with at least 12 weeks of follow-up.

Diabetes

Requirements for inclusion were for studies to be clinical trials, aimed at evaluating closed-loop insulin therapy in patients with diabetes including the names of the most commonly found models, such as the MiniMed 670G, MiniMed 780G, Control-IQ and Diabeloop DBLG1, and using PROMs, with at least 12 weeks of follow-up. Since closed-loop systems are a new technology, with the first systems being commercially released in 2016, only studies published between 2013 and 2023 were considered for the diabetes review.

2.1.6 Search strategy

The key issues were formulated according to the population, intervention, comparison, and outcomes (PICO) criteria (Aslam & Emmanuel 2010). See Table 3.

Table 3. PICO requirements

PICO requirements	
Population	Adults and children with orthopedic, cardiovascular or diabetes
Intervention	Surgically implanted device
Comparison	Time before and after treatment or comparison with other device, surgical operation or different materials used in the manufacture of the device.
Outcome	Patient-reported outcome with at least 12 weeks of follow-up.

The inclusion criteria and methods were specified in advance and documented in the protocol, which was published with PROSPERO

Table 4. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
English language	Studies about pharmaceuticals
Published 2000-2022 – Cardio & Orthopaedics Published 2013-2023 – Diabetes	Studies about rehabilitation
Randomized or observational trials	Case-reports
Patients with orthopedic, cardiovascular or diabetes conditions requiring implant surgery	Expert statements
Orthopedic: knee or hip implant or surgery Cardiovascular: all type of high-risk implants Diabetes: Closed-loop devices or artificial pancreas	Study does not use PROMs or PROM results not reported
Use of PROMs	Protocol with no published results
Minimum 12 weeks of follow-up with PROMs	Less than 12 weeks of follow-up with PROMs

2.1.7 Creation of search strings

Search strings were made of the following databases from year 2000: Ovid MEDLINE, CINAHL, The Cochrane Central Library and the Centre for Reviews and Dissemination (CRD).

Search strings were developed around the following key concepts:

i. Patient reported outcome measures, PROMs
ii. Device/implants in orthopaedics (knee & hip), cardiovascular disease, diabetes (closed loop).

Search strings were developed for Medline and adapted for the other databases using Polyglot Search Translator (https://sr-accelerator.com/#/polyglot) and validated for content. The search algorithm for each database and condition are provided in the appendix.

Medline

Several algorithms were tested on the basis of key words covering the name of PROMs and the names of devices. This tended to produce a large number of hits, many of which were irrelevant. The names for PROMs and devices are often not unique and can include words that are used for other purposes eg 'vanguard', 'Exeter', 'gamma'. Therefore, searches were performed to find relevant papers and MeSH-terms. However, in order not to miss valuable articles a comprehensive search was carried out with the intention of narrowing this down at the title review stage.

Multiple terms for the same type of device were used if there were variations in spelling or differences in the use of apostrophes etc. To remove review articles, the search was limited to review articles, and then the "NO" operator was used to remove those articles from the search. The search string was deemed to be of acceptable quality when all anchor references, as well as all relevant articles found during the search, could be found among the search hits.

Cochrane

The algorithm used for searching Cochrane used the same basic structure as the one used for Medline, with search blocks combined with an (AND) operator, limiting the search studies in orthopaedics to knee and hip and limiting the search to studies about diabetes and closed-loop insulin delivery systems. Overall, the Cochrane search algorithm mainly had small differences in the choice of MeSH-terms and subheadings, determined by which ones were available.

CINAHL

The CINAHL algorithm also used the same basic structure as the other systems, although a slightly different approach was adopted for the diabetes review. The initial plan was to use the same strategy as above, however, during assessment of the resulting hits, it became apparent that nearly all articles of interest contained the terms closed-loop or artificial pancreas in the title. It was therefore decided to adopt a simplified approach to reduce the number of irrelevant hits. The searches also resulted in a number of reviews on psychosocial outcomes during closed-loop therapy, which provided anchor references that could be used to assess the final search string for coverage. The search blocks were combined with an "AND" operator. All terms describing the devices had been found during the scoping review or provided by colleagues.

2.1.8 Screening process

2.1.8.1 Stage 1. Removal of duplicates

The results of the three searches were combined and the titles and abstracts copied into EndNote to search for duplication. Duplicate removal in EndNote is superior to other database software available but only looks for exact matches. Therefore, the resulting list of abstracts was copied into Rayyan where a partial match of titles could be carried out, allowing further duplications to be removed.

2.1.8.2 Stage 2. Screening of abstracts

Abstracts were screened in Rayyan by experts in the field. The screening was performed by the authors of the report and experts in the different medical fields, a psychologist and two healthcare masters students and three medical students in their final year. All abstracts were assessed by a minimum of three people and a maximum of five. This was done as a blinded protocol and then disagreements in assessment were discussed in the team to arrive at a consensus. Figure 1.

Titles and abstracts were read, and articles which fulfilled the PICO requirements or were deemed likely to fulfil them, were moved to a “maybe” folder for articles which would go through full-text review. Articles which did not meet PICO requirements were moved to an “exclude” folder. One of the inclusion criteria was the use of PROMs, which often could not be determined solely by reading the abstracts. These articles were also moved to the “maybe” folder, to go through full-text review. Employing Rayyan allowed for the use of text-mining to aid in screening. Keywords which were likely to appear in the abstracts of articles that would eventually be included were highlighted in green, while keywords that were likely to appear in excluded studies were highlighted in red. This mainly allowed the process of excluding articles based on short follow-up durations to be sped up.

The initial evaluation of the abstracts could also be carried out in Rayyan which searches for search term words and pairs of words (bi-grams). The machine learning algorithm was not used on the version of Rayyan that we had available. A second search of the introductory sections of the identified articles was carried out in Excel in order to further focus the selection of relevant articles.

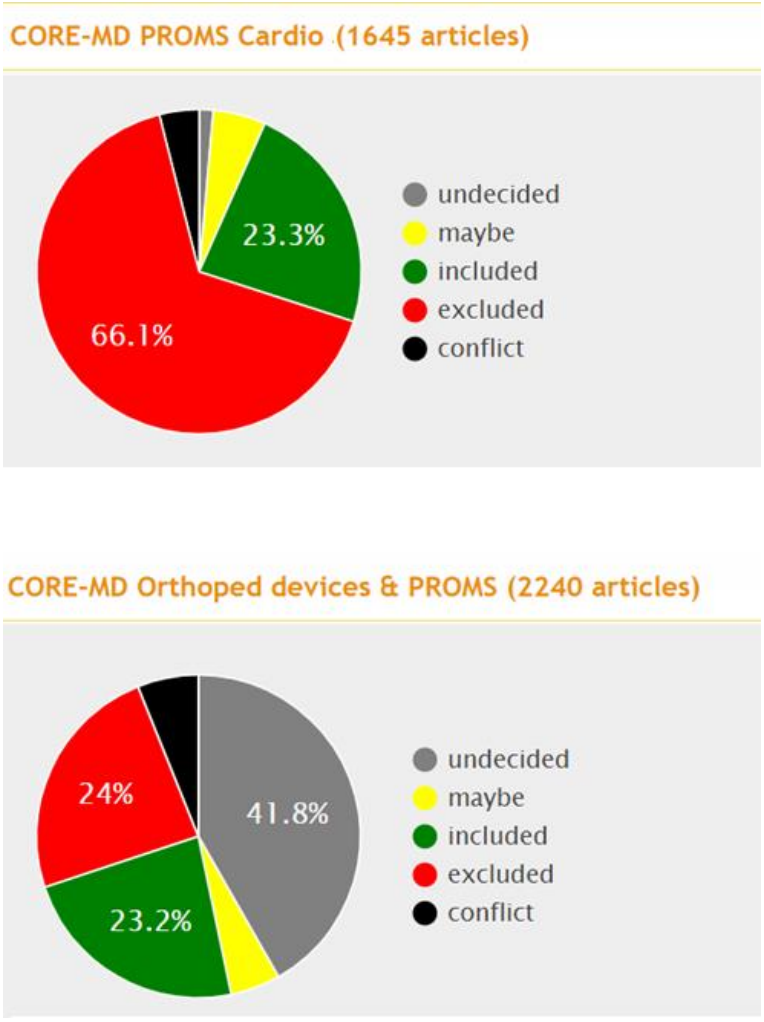

Figure 1. Screening of cardiovascular and orthopaedic abstracts in Rayyan

2.2 Data extraction

2.2.1 Acquiring full text

Endnote's automatic full text retrieval function was used to retrieve a portion of all articles that were to be screened for eligibility. The remaining papers were accessed manually through the Gothenburg University library. Articles which could not be accessed through Gothenburg University were not sought further through alternative routes, such as directly contacting authors, due to time constraints. Approximately 10% of articles could not be accessed.

2.2.2 Initial automatic review of the literature

This was conducted in Rayyan and in Excel and undertaken to identify the names and number of PROMs being used from the abstracts.

2.2.3 Full text screening

Articles were downloaded as PDFs and underwent a thorough full-text review. The most common reason for exclusion was the absence of PROMs among the study endpoints. Another common reason for exclusion was that papers were study protocols, with no published results available. Each protocol was manually assessed for published results before being excluded.

2.2.4 Extraction and tabulation of data

Data for all variables of interest were extracted and coded in a Microsoft Excel spreadsheet. In order to quickly detect the presence or absence of data for certain variables, such as power and MCID, word searches for words related to these variables were performed, and if no results were found the data were considered to be missing. Data for several variables related to study types, study methodology, population characteristics, devices, PROMs, outcomes and limitations were extracted and coded.

2.2.5 Risk of bias in the diabetes review

Risk of bias assessment was conducted with the diabetes review by using the Mixed Methods Appraisal Tool (MMAT) (Hong et al 2018). This tool was chosen as it allows for the assessment of both randomized and observational studies, which would cover all included trials. The assessment was focused on sample sizes, whether all data were reported, statistical analysis, consideration of the multiple comparison problem, adherence to the intervention therapy, and whether the study population was an accurate representation of the general diabetes population. For randomized trials, blinding of researchers and the comparability of intervention and control groups were also assessed. The papers were then graded as having a high, moderate or low risk of bias.

2.2.6 Synthesis of results

The included studies were a mix of randomized controlled trials and non-randomized trials, and study populations varied across studies, as did interventions, control treatments and choices of PROMs. Due to the resulting heterogeneity, it was deemed that any statistical analysis of the PROs would only present a

biased view. The PROMs were therefore narratively synthesised to be presented in plain text. The grouping of different PROMs into outcome domains was accomplished by assessing the names of PROMs and examining what reasons for choosing the PROMs were stated by authors. Outcomes related to sample size clinical significance.

A narrative analysis was chosen as the most appropriate form of analysis in an attempt to understand the significance of the findings beyond the boundaries of simply describing the results. Polkinghorne's theory of narrative analysis states that "data elements can be used to fill in the gaps bringing narrative meanings to the story that are not explicit in the data thereby allowing the configuration of the data into a coherent whole" (Flick, 2014, p. 197). In keeping with Polkinghorne's theory, and in order to contextualise the findings into the larger body of research, the data have been organised into themes, which will be interpreted within the context of PROM utility.

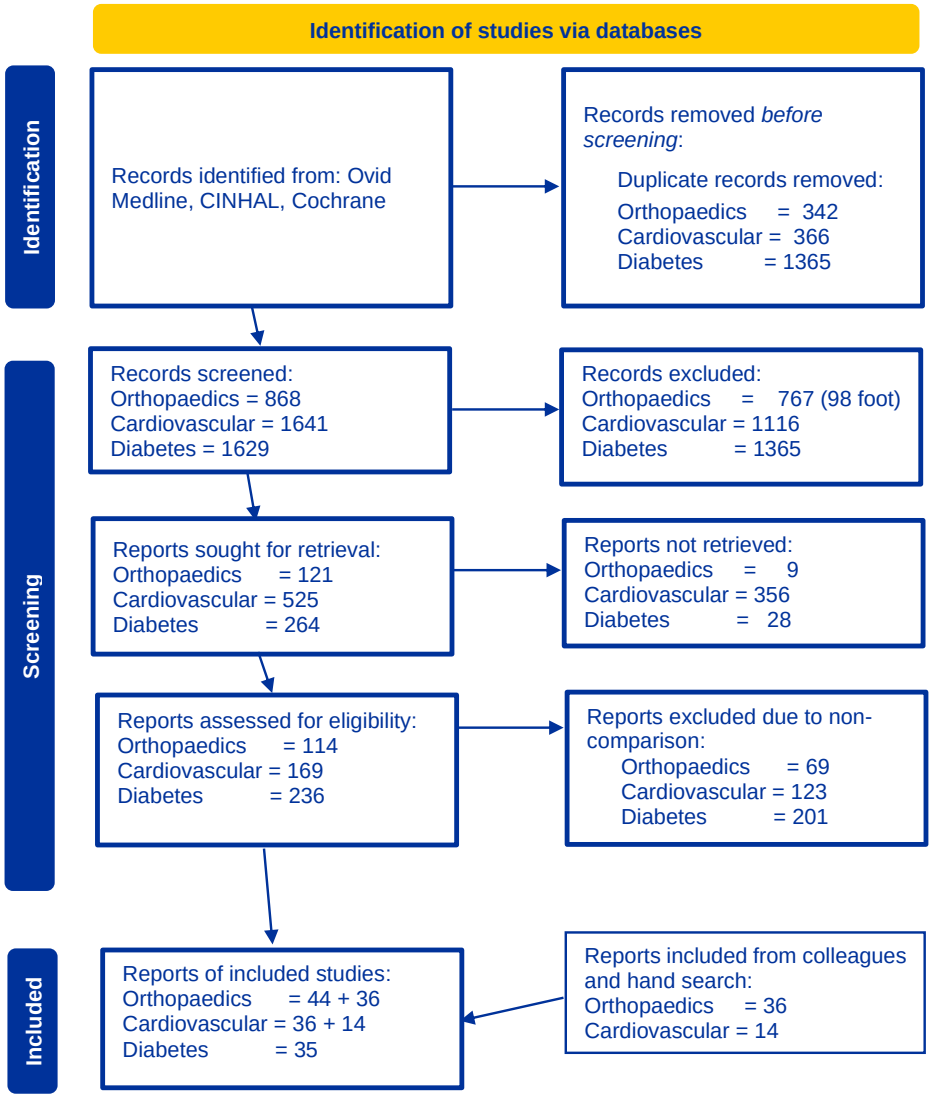

Figure 2. PRISMA flow diagram

2.3 Results of the exploratory full-test screening

This screening was carried out on 200 randomly selected orthopaedic and cardiovascular articles to obtain keywords and issues for the Delphi study.

The purpose of this exploratory full-text screening was to identify which issues of relevance to patients were examined in the literature, in order to provide data for a Delphi study where these issues could be confirmed or complemented by representative input from patients. Screening of 100 randomly selected full-text articles in each of the orthopaedic and cardiovascular areas was undertaken, focusing on domains that documented PROMs used. The most frequently used PROMs are reported below; two 'word clouds' were produced as aids to discussion with patients about the important outcome issues from their perspective, including their perceptions of quality of life.

Figure 3. Orthopaedics word cloud of primary concepts measured by PROMs

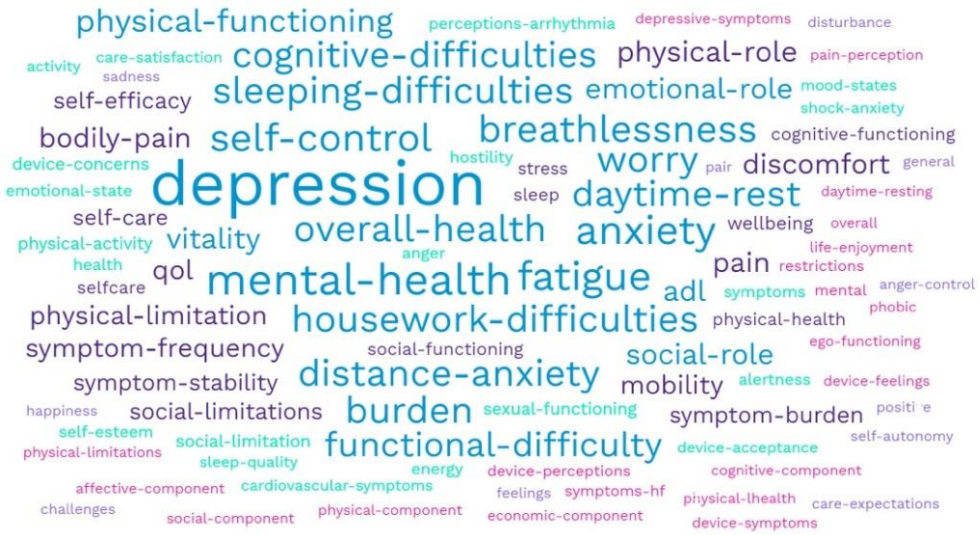

Figure 4. Cardiovascular word cloud of primary concepts measured by PROMs

2.4 Results of the literature review

In the table below the characteristics of the three reviews are described. It can be seen that in 20-26% of the reports, PROMs were being used as a primary outcome. In the orthopaedic RCT studies the mean sample size of studies where PROMs were the primary outcome measurement was smaller than where PROMs were used as secondary outcome measurement. This relationship was reversed in cardiovascular, however this was due to the inclusion of two very large trials, one with 628 patients (Reynolds et al 2012) and the other with 935 patients (Bundgaard et al 2019). Both of these studies used the MLHFQ.

Table 5. Characteristics of the selected populations for detailed study

	Cardiovascular	Orthopaedics	Diabetes
Number of studies (adult/child)	48/2	80	15/20
RCTs with PROM as prime	11 (22%)	17 (21%)	10 (28%)
RCTs with PROM as secondary	8 (16%)	24 (30%)	4 (11%)
Observation studies	21 (42%)	7 (9%)	12 (34%)
Registry studies	1 (2%)	5 (6%)	0
Retrospective studies	7 (14%)	20 (25%)	9 (26%)
Mean (sd) sample size			
RCT PROM primary	214(259)	86(24)	90
RCT PROM secondary	133(162)	159(123)	84
Mean age (sd) RCT/PROM primary	68(7)	67(9)	2 and 68 years
Mean age (sd) age RCT/PROM secondary	64(8)	69(9)	2 and 68 years
Year of study			
2000-2014	31	26	
2015-2023	19	54	35
Region of primary contact			
Europe	21	59	19
America/Canada	20	9	11
Asia/Middle East	5	2	1
Australia/NZ	1	7	4
Africa	0	0	

PROMs can be categorized either as generic or condition-specific. In the table below we have identified separately those PROMs which have been specifically designed for use during the evaluation of high-risk medical devices.

Table 6. Frequency of types of PROM used

Medical specialty	Number of types of PROMs used	Types of PROM instruments		
		Generic	Condition-specific	Device specific PROM
Cardiovascular n=50	79	51	23	5
Orthopaedics n=80	130	56	80	
Diabetes n=35	125	25	99	1

The cardiovascular review revealed a much larger number of generic PROM instruments being used than condition-specific PROMs. In this review there were also a number of non-standardised instruments or modified instruments used.

In Table 7 below the frequency of PROM use is indicated alongside a column indicating where the PROM is known to have been used in association with pre-market evaluation of a device. A third column indicates which PROMs have been indicated as part of a 'core set' of PROMs that could be used in all studies in order to be able to compare results more accurately across studies. These core sets will include shorter, non-licensed questionnaires that have been translated into multiple languages so that they can be more easily applied globally. There are two additional things to note in Table 7, firstly three questionnaires were found that had been designed especially for use with evaluation of high-risk medical devices. These were more recently developed questionnaires than others that were being used. The other thing to note is the presence of two questionnaires that have been 'qualified' as medical device development tools (MDDTs) by the FDA. These are the Kansas City Cardiomyopathy (KCCQ) (MDDT020) and the Minnesota Living with Health Failure Questionnaire (MLHFQ) (MDDT026). Both have substantial validation data that have been assessed by the MDDT program. In this review they were being used in the larger RCT trials where PROMs were used as the primary outcome measure. These two questionnaires were the first FDA MDDT qualified PROM instruments in 2018.

Table 7. PROMs in cardiovascular device trials

ADULT GENERIC	Frequency	Pre-market	Core set	ADULT CONDITION SPECIFIC	Frequency	Pre-market	Core set
SF-36	17	#		**Kansas City Cardiomyopathy** KCCQ*	4	#	#

SF-12	3		#	**Minnesota Living with Heart Failure** MLHFQ*	1	#	
EQ-5D	6	#		KCCQ-12	1		
HADS	5			Seattle Angina Questionnaire	1	#	
EQ-VAS	2			EuroQoL-HF	1		
State-Trait Anxiety Inventory (STAI)	2			Cardiac Anxiety Questionnaire (CAQ)	1		
PHQ-9	1		#	**MODIFIED for children**			
Profile of Mood States (POMS)	1			Patient scar assessment questionnaire (PSAQ)	1		
Quality of Well Being Schedule	1	#					
WHOQoL-Bref	1						
Satisfaction	1						
MODIFIED				**DEVICE SPECIFIC**			
”A short QoL questionnaire”	1			Florida Patient Acceptance Survey (FPAS)	3		
Karolinska questionnaire	1			Florida Shock Anxiety Scale (*FSAS*)	1		
NHQ /SF-36	1			Implanted Device Adjustment Scale (IDAS)	2		

**MDDT qualified by FDA; # = documented use during ”pre-market” evaluation of a medical device; or indicated for a ”core set” of standard PROMs.*

The orthopaedic studies also demonstrated a large number of PROMs used, but in this case there were more condition-specific PROMs. This is somewhat inflated in our review due to its focus being on both knee and hip implants, since two of the PROMs exist in separate versions for these joints. As in Table 7, in Table 8 the pre-market and core-set PROMs are also indicated. Here it is clear that the pre-market questionnaires are those that are longer and therefore more detailed and thus more sensitive to change, i.e. the SF36 is used rather than the SF-12. The core-sets, however, favour the shorter versions of the questionnaires. In the orthopaedic review no device-specific questionnaires were found and none of the questionnaires were ‘qualified’ by the MDDT program of the FDA.

Table 8. PROMs used in orthopaedic device trials

ADULT GENERIC	Frequency	Pre-market	Core set	ADULT CONDITION SPECIFIC	Frequency	Pre-market	Core set
EQ-5D	25		#	Western Ontario and McMaster Universities Arthritis Index (WOMAC)	16	#	
SF-12 (VR-12)	9		#	Oxford Knee Score (OKS)	12		
SF-36	6	#		Oxford Hip Score (OHS)	11		
				Harris Hip Score (HHS)	9		
Non-validated / single item				Knee Injury and Osteoarthritis Outcome (KOOS)	9	#	#
Satisfaction VAS	18		#	Hip Disability and Osteoarthritis Outcome (HOOS)	7	#	#
Numeric rating scale (NRS) pain	37	#	#	UCLA activity /function score	5		
VAS rating of disability	1			KSS expectation / satisfaction	2		
Disability index: self-admin	1			Forgotten Joint Score	1		
Questions about noise	1			Paffenbarger physical activity	1		
Unnamed questionnaire	1			Intermittent Constant Osteoarth-Pain (*ICOAP*	1		

In the Table above the NRS and VAS are listed as non-validated. Attempts have been made to validate these scales (eg. Chiarotto et al 2018 for a systematic review in low-back pain) have concluded that there NRS and VAS measurement properties were underpinned by no, low, or very low quality evidence.

The detailed study of the PROMs used in diabetes trials revealed a total of 40 different PROMs being used. A list of all identified PROMs, with the numbers of times they were used, as well as the frequency at which they found statistically significant differences in PROs, is shown in Table 9. Some PROMs appeared in several different versions, such as adult, child and parent proxy versions, but were all grouped together under one name for simplicity.

Table 9. PROMs used in diabetes device trials

Outcome domains & PROMs	Times used	Statistical differences/ measured (%)	Outcome domains & PROMs	Times used	Statistical differences/ measured (%)
General QoL			**Satisfaction**		
WHO-5	3	2/3 (66.7)	DTSQ	15	9/15 (60)
SWLS	1	0/1 (0)	APAQ	2	1/2 (50)
DISABKIDS	1	0/1 (0)	GMSS	3	2/3 (66.7)
Diabetes-specific QoL			GME-Q	1	1/1 (100)
PedsQL Diabetes Module	4	2/4 (50)	DTQ	1	0/1 (0)
DQoL	3	3/3 (100)	TAS	1	0/1 (0)
QoL-Q Diabetes	1	1/1 (100)	TES	1	0/1 (0)
W-BQ28 4-question module	1	1/1 (100)	SUS	2	1/2 (50)
DIDP	2	1/2 (50)	VAS	1	0/1 (0)
Emotional distress			TA:DS	2	0/2 (0)
STAI	2	1/2 (50)	INSPIRE*	3	1/3 (33.3)
PSS-10	1	0/1 (0)	IDDS	1	1/1 (100)
Diabetes- distress			SQASAID	1	0/1 (0)
PAID	9	1/9 (11.1)	**Sleep quality**		
DDS	6	3/6 (50)	PSQI	9	2/9 (22.2)
CISS	1	1/1 (100)	ESS	1	0/1 (0)
CES-D	1	1/1 (100)	PROMIS	1	1/1 (100)
Fear of hypoglycaemia			**Depression**		
HFS	20	10/20 (50)	GDS	1	0/1 (0)
HCS	5	2/5 (40)	**Cognitive function**		
Hypoglycaemia aware			PRMQ	1	0/1 (0)
Clarke	7	3/7 (42.8)	**Coping**		
Gold	5	1/5 (20)	Brief-COPE	1	1/1 (100)
Hyperglycaemia Fear			GSES	1	0/1 (0)
HAS	1	0/1 (0)	MHLC	1	0/1 (0)
			AIS	1	0/1 (0)

*The right column shows how often each PROM was used to discover statistically significant differences in PROs. Studies which did not calculate statistical significance were included. * MDDT 'qualified'.*

The Hypoglycaemia Fear Survey (HFS) was the most frequently used PROM, being employed in 20 trials. The HFS consists of two subscales, the HFS-Worry and HFS-Behaviour, which measure fear of hypoglycaemia and the patient's behaviour to avoid hypoglycaemia, respectively. The two subscales were usually used together in order to measure a total HFS score. Five studies only used the HFSWorry subscale, omitting the behaviour subscale.

One questionnaire – INSPIRE – had been 'qualified' as a medical device development tool (MDDT) by the FDA (MDDT Q191073).

2.5 Thematic analysis

There are a number of themes that emerge from the literature review, relating to the potential utility of PROMs for the regulatory evaluation of high-risk medical devices.

2.5.1 Choice of instrument - Intended aim/purpose of the PROM

2.5.1.1 Choice of PROM dependent upon primary or secondary PROM usage

There was no indication of a substantial difference between the PROM outcomes obtained from the different PROMs. The choice of instrument and how it will be evaluated, together with what constitutes an improvement or equivalence was stated in advance of data collection and could be seen in a pre-specified analysis plan. However, outcome domains were rather vague (e.g. QoL), and what constituted a change differed between studies. In orthopaedics, for example, the EQ5D was used in 50% of studies where PROMs were used as the primary outcome measurement and in 70% of studies where PROMs were the secondary outcome measurement. Non-standardised instruments were used rarely, more frequently as a primary generic outcome (n=5) than as a secondary outcome (n=1). Where PROMs were the primary measurement there was a tendency to use multiple instruments (generic prime 6, secondary 4; condition-specific prime 9, secondary 4).

The reasons why a PROM instrument was chosen were rarely given in the literature. One reason which was mostly implied was that the instrument had been used in previous similar studies. Some limitations of availability of instruments have to be acknowledged. Instruments are not available in all languages, and many instruments require license agreements and may require purchase. Additionally, researchers may be familiar with one instrument and therefore tend to use it rather than considering alternatives. Comparison between instruments is complex, and although there are many reviews and the literature on PROMs is extensive, this is difficult and time-demanding. None of the studies referred to the domain structure as the reason for choosing an instrument.

The instruments that are most commonly used, as we see in the literature, are those that are the most generic. They can be applied in many more situations than the condition-specific and have been translated and validated in many different populations making them more available and better understood.

2.5.1.2 Digitalization affecting PROM choice

The digital transformation of PROM data collection and its analysis also affects the choice of instrument. As we move closer to full digital collection, or towards more digital questionnaires being available, choice

of which instrument to use may be influenced by their availability as a digital platform. None of the studies in the literature review used digital data collection. The enormous opportunities for the inclusion of the patient's voice in clinical science through digitisation and the possible resource savings will mean that these platforms will be increasingly used. Mobile health tools could allow real-time monitoring and remote participation of patients in observational studies or clinical trials, which would free data-collection from the constraints of available resources or clinical timetables.

However, digitalization also brings challenges for data collection, since not all patients may be familiar with such systems, they may not trust them, and the systems need to have data control, security, and ethical governance that complies with EU legislation.

From a measurement perspective, there are issues related to the equivalence of data. Questions asked on paper will probably need to be presented in a different way digitally, depending on the software [e.g., one question per screen, possibility of including additional information or having revealable information, use of pictures, emojis, etc.]. Adaptations might be considered to contribute to an increase in response rates, but they may alter the way that people answer questions, with the result that it is not possible to compare results with data collected previously in a different format or on different digital platforms. Novel endpoints will need to be validated.

If we look at how the results are reported we also understand why measures were chosen. In the majority of cases results were given in terms of overall change in total quality of life.

2.5.2 Constructs measured

2.5.2.1 Identified outcome domains

The identified PROMs were grouped into three common outcome domains – pain, satisfaction and QoL. QoL could be further divided into emotional, physical and social sub-domains. A list of these broad domains, with the percentages of how often they were explored in all studies, is given in Table 10. Quality-of-life, as an overall concept, was the most commonly assessed domain, while pain was also frequently assessed in studies of orthopaedic devices.

Table 10. Constructs measured

Medical specialty	Pain	Satisfaction	QoL			
			Overall QoL	Emotional	Physical	Social
Cardiovascular	6%	14%	74%	88%	80%	62%
Orthopaedics	61%	27%	71%	40%	100%	40%
Diabetes		47%	100%	33%		

2.5.3 Data collection time-points

A large variety of these were found. In orthopaedics the range was from 3 to 120 months with a mean of 42 months overall. In RCTs where PROMs were the measure of primary outcome the mean follow-up time was 34 months, and if secondary 43 months. For cardiovascular studies, the mean number of months of

follow-up was 16, with the PROM primary outcomes having a mean of 10 months and PROMs as secondary outcomes a mean of 25 months. This data was not collected for diabetes. None of the studies gave reasons for the PROM time-points. Data collection usually coincided with a scheduled medical examination, and was not based theoretically on the likelihood of change in psychological, social or emotional factors.

Table 11. Mean months in follow-up

Medical specialty	All studies	PROMs as primary outcome	PROMs as secondary outcome
Cardiovascular	16	10	25
Orthopaedics	42	34	43

2.5.3.1 Factors affecting efficacy of time-points

As subjective changes are being measured, it is necessary to consider what might influence them. One issue which again is not mentioned in the literature is the time of year when measurements are taken. An initial measurement in the winter followed by a six month follow-up in the summer might indicate an improvement of QoL that has nothing to do with a medical treatment or condition.

2.5.4 Mode of delivery

In all of the studies included in this review the mode of delivery of the PROM was via a paper form questionnaire. In only one study was a different mode of presentation reported. In a study concerning submammary pacemakers and ICDs in women, patients' satisfaction was assessed via a telephone interview (Giudici et al 2010); questions related to the initial decision, the pre-procedure education, implant experience, recovery, complications, and long-term satisfaction.

A second dimension is the location of completion. Often this was not stated, but it can be assumed that the questionnaires were completed at the time of the clinical follow-up and therefore at a medical facility. An alternative is to use postal delivery of the questionnaires. This reduces the burden on the patient to come to the facility and reduces the staff time for administration, but it can lead to a loss of follow-up. A common procedure was to complete the PROM at baseline and then mail-out the PROM at the 3 or 12 month follow-up. Even with longer follow-up times PROMs were mailed to the subjects. One study that utilised a combination of clinic and postal delivery was reported by Beard (2020) and had the following design (Table 12):

Table 9. Outcome measure by time point

Outcome measure	Time point						
	Pre-operative	Post-op. (months)	Post randomisation (years)				
	Baseline	2	1	2	3	4	5
OKS (self-report function)	▲	o	o	o	o	o	o
OKS-APQ (self-report function)						o	o
UCLA (self-report activity)	▲	o	o	o	o	o	o

HAAS (self-report activity)	▲	○	○	○	○	○	○
EQ-5D (global heath)	▲	○	○	○	○	○	○
Lund (patient satisfaction)		○	○	○	○	○	○

▲ *clinical outpatient visit;* ○*, postal questionnaires.*

2.5.5 Response rate

2.5.5.1 Questionnaire response frequency

Questionnaire response frequency was defined as the number of subjects who had complete questionnaire data at both baseline and study end for each PROM, divided by the number of subjects at the start of the trial. Response rates were not extracted as exact values, as those could not be determined in the majority of studies. For some studies it was not possible to determine the exact response rates, but it was possible to estimate average response rate ranges for most RCT studies.

Orthopaedic RCTs had a response rate of 89%, although in several studies it is not clear if all subjects contributed PROM data at all follow-up procedures. If we count only where actual numbers are given then the response rate dops to 75%. The lowest recorded response rate was 58% in a study of internal fixation versus hemiarthroplasty for displaced fractures of the femoral neck with a population age ≥ 70 years, diagnosed dementia and/ or severe cognitive dysfunction, according to the SPMSQ (Blomfeldt 2005). Data were collected via proxy report using the Euroqol (EQ-5D).

In the cardiovascular studies, the mean response rate was 82%. The lowest response rate was in a randomized trial comparing on-pump versus off-pump coronary artery bypass graft surgery (Motallebzadeh et al 2006) SF-36 scores were collected from 72% of participants at 6-months and from 46% at 18-months. The study by Passman et al 2007 also illustrated the fall-off of respondents over extended follow-up times. In their study of 458 patients with implantable cardioverter defibrillators QoL was evaluated using the SF-12 and the MLHFQ at 1 month after randomization, every 3 months. There was a average of 9.4±5.1 (mean±SD) visits per patient. QoL data was collected at all time-points from only 145 patients (36%). Thirty nine percent (n=178) of patients had missing QoL data from more than 2 visits.

Questionnaire response frequencies were adequately reported in 23 of 35 diabetes articles. Average response rates are therefore not presented in exact percentages, but rather percentage ranges with increments of 10%. Out of 23 studies that reported response rates, 13 studies had an average response rate above 90%. Six studies reported response frequencies between 80 and 89%. Three studies achieved response rates between 60 and 69%. One 24-week crossover RCT achieved a response rate between 50 and 59%, which was the lowest response rate across all the diabetes studies (Barnard, et al., 2015). The study measured treatment satisfaction, using the DTQ survey, in adults and children. The authors did not report the dropout rates. One study achieved response rates of 90% in the DTSQ and HFS surveys, while the DQoL response rate was 59.7% due to the lack of a validated version of the DQoL in German (Choudhary, et al., 2022).

2.5.6 Dealing with missing PRO data

Multiple follow-ups over an extended period of time resulted in loss of PRO data. It has been noted elsewhere that obtaining complete follow-up PROMs data for all randomised participants is very difficult

(Altman 2009). Where response rates or follow-up rates were low, resulting in substantial missing data, there may not have been sufficient data to meet pre-specified requirements for analysis of effectiveness. If this were the case regulators may ask to extend the trial in order to collect more data. In order to avoid this, methods of dealing with missing data should be specified in the study protocol and those actions taken reported in the articles. These methods were not outlined in any of the literature we examined.

Using statistical methods to deal with missing data is, however, a common approach to dealing with the problem. This may not be an optimal method as missing data can then lower the power of the study to identify a result and be interpreted as failure to find a result. Studies should look at how to maximise PRO compliance rates through PRO-specific strategies for research design, implementation and reporting. Methods of dealing with missing data should be considered before the outset of the study. They can include (Mercieca-Bebber et al 2016):

- carefully designing PRO assessment schedules (e.g. to ensure that PRO assessments are taken at clinically informative times) and defining termination rules (e.g. to continue PRO assessments after treatment failure);
- reducing the burden to patients e.g. by minimising PRO assessment time-points and not having them too close together;
- appointing a PRO coordinator to manage resources and standardise procedures;
- providing PRO-specific training for staff with specified staff roles in PRO data collection;
- ensuring PRO studies are adequately resourced; and
- conducting continuous quality assurance.

Strategies for transparent interpretation and reporting of missing PRO data include utilising auxiliary data to inform analysis; transparently reporting baseline PRO scores, rates and reasons for missing data; and methods for handling missing PRO data.

2.5.7 Minimal Clinical Important Difference (MCID)

The most frequent approach to compare groups or within populations was to test for statistically significant differences at the 0.05 level eg. Kristensen et al (2016) compared pain and satisfaction VAS scores using students t-test of posterior vs direct lateral approach hemiarthroplasty for femoral neck fracture. In the applications to the FDA for device approval, absolute values for PROMs were given such as a >30% improvement in VAS pain scores, which appears to be used commonly as a threshold in pre-market studies. Although MCID is often thought to be a superior method, it poses some challenges. MCIDs are based on the idea that a statistically significant change may not correspond to a clinically important change, and therefore that another measure must be applied in order to identify what is a noticeable change. The most frequently used instruments, as identified in our review, have been used to publish MCIDs that are referenced in this literature. MCIDs found in the review were calculated based on one of two approaches, either distribution-based or anchor-based. The distribution-based approaches were built upon the statistical properties of the study's results. Two anchor methods were used: receiver operating characteristic (ROC) curves and the change difference. The anchor items varied, as did the number of items used (1 – 3) and the number of points on the response scale (3 – 10).

2.5.8 How to measure satisfaction

There was no standard method used to measure satisfaction. It was measured as a single item or as multiple items (e.g., physical limitation, disease perception, and treatment satisfaction), using a VAS scale or using a Likert type scale with four or five categories (e.g. very satisfied, satisfied, neutral, somewhat dissatisfied, very dissatisfied). These scales were within other PROMs or standalone, validated or constructed for the study where they were applied.

Patient satisfaction is an important outcome measure however there have been consistent reports of discrepancy between clinicians' and patients' ratings of health status (eg Suarez-Almazor et al 2001). Alignment of the goals of the surgeon and the patient before a procedure makes it more likely the patient will be satisfied (Noble. et al 2013). There are various scales that have been used, which are detailed below. Apart from the measurement properties it is also important to understand the target of the judgement being made and the composition of the concept being measured.

Recording a patient's 'satisfaction' can focus either on their current clinical condition, or on the outcome of their treatment. This latter topic is a popular patient-centered variable in orthopaedics, that is most often reported as an overall stand-alone variable. Satisfaction measured using a VAS scale, however, has only modest correlation with the physical condition of the patient, both divergent and convergent validity shows a poor relationship to physical factors (Brokelman et al 2012). Satisfaction is likely to be highly related to those aspects of the condition that prompt the surgical intervention eg in orthopaedics this might be pain (Brokelman et al 2012). Thus, without defining 'satisfaction' it can represent any aspect of the patient's perspective. As a subjective measure it could include personal and process variables and be influenced by patients' personalities and expectations as well as their perceptions of the quality of medical care that they have received.

2.5.8.1 Methods identified to measure patient satisfaction in the literature search

Visual Analogue Scale (VAS)

In some studies the scale was given as 1-10 or as 0-100 where 0 represented very unsatisfied. The Patient-Administered Questionnaire (PAQ) (Nishikawa-Pacher, 2022) measures satisfaction by a visual analog scale from 0 to 10 where 0 is unsatisfied and 10 fully satisfied. Based on this scale, patients with scores of 6 or greater are considered satisfied or very satisfied and patients with 4 or less are considered dissatisfied. The satisfaction addressed in the PAQ scales, closely reflects patients' willingness to accept their current condition, which probably integrates both physical and psychological considerations. Including this type of satisfaction makes the PAQ scales better able to capture how patients view the overall effects of their hip or knee condition on their current life. Lee et al (2009) collapsed the visual analog scale 0-10 responses into four categories to determine patient satisfaction: 2 or less, fully dissatisfied; 3 to 5, somewhat dissatisfied; 6 to 8, satisfied; and 8 to 10, fully satisfied. They acknowledged that this categorization was 'somewhat arbitrary and has not been scientifically validated', but they nevertheless believed it would provide a useful impression of the degree of patient satisfaction.

Single item Likert scale (dichotomised)

A study by Beard (2020) used the 'Lund scale' which is a single question regarding the operated knee with four possible answers: 1) very satisfied, 2) satisfied, 3) uncertain or 4) dissatisfied. Robertsson et al (2000)

asked "How satisfied are you with your knee?" (Dissatisfied, uncertain, satisfied, very satisfied). This was analysed as a binary outcome of satisfied/very satisfied versus dissatisfied/uncertain.

8.1 Multidimensional models

Giuseppe et al (2021) interprets the outcome of the HOOS as an indication of satisfaction. The HOOS is a 40-item self-reported questionnaire comprising 5 subsets: pain, symptoms, activities of daily living, sport, and hip-related quality of life. "*The score is expressed as a percentage with a higher value corresponding to a higher patient satisfaction*". HOOS was developed as an instrument to assess the patient's opinion about their hip and associated problems. In no other studies that we found were the results of the HOOS referred to as 'patient satisfaction'. However, "*patients' opinion about their hip*" could be interpreted as satisfaction. In this case therefore '*satisfaction*' is a multi-dimensional concept that includes pain, other symptoms, function in activities of daily living (ADL), and function in sport and recreation (Sport/Rec), and hip-related quality of life (QOL).

The second most commonly found PROM in the diabetes literature was the Diabetes Treatment Satisfaction Questionnaire (DTSQ) this was used in 15 studies. This questionnaire comprises two subscales: the status (DTSQs) and change (DTSQc). The DTSQs assesses treatment satisfaction at a specific time, while the DTSQc measures satisfaction relative to a previous point in time. Some studies used only the DTSQs, while others exclusively used the DTSQc.

Example from orthopaedics

The patient's subjective assessment of their knee or hip function can be expressed as a percentage of an entirely normal function. This subjective value (SV) can be determined entirely by each patient by answering the question: "*What is the overall percent value of your hip / knee if a completely normal hip / knee represents 100%?*" Correlation between the SV and the patient's subjective assessment expressed as a percentage of an entirely normal function, which would score of 100% can be used as a measure of satisfaction (Gilbart & Gerber 2007). The SV is an easily administered, responsive, and valid measure of function. Thus the SV may offer an improvement over normal function. The goal of such measurement systems is to provide a reproducible, responsive, and valid assessment of a patient's function.

The important attributes of an outcome measure are that it accurately reflects the perspective of the patient and that it is independent of the diagnosis. The assessment should ideally be simple and easy to administer for both the patient and the examiner. Current scoring systems may be suboptimal in their simplicity and in their ability to truly reflect the clinical state of the joint for the individual patient. The SV was developed with the purpose of providing a simple score reflecting the view of the patient in a precise manner. A Subjective Hip Value (SHV) and the Subjective Knee Value (SKV) offer a useful adjunct to established hip and knee outcome measurements, and they are easy and quick to perform and interpret. The SV reflects the view of the patient and is independent of the diagnosis (Krueger et al 2020; Plachel et al 2022).

2.5.9 Combinations of questionnaires / equivalents

It is often useful to compare the results of PROM measures conducted in different patient groups. In many cases this is a complex process of conducting cross-walk studies to find equivalents. Some large studies have been done to achieve this, for example the *PROsetta* Stone project provides tables that convert scores between two different measures. An increasing number of 'cross-walks' between PROMIS measures and other PROM instruments have been established (prosettastone.org/). [The Patient

Reported Outcome Measurement Information System (PROMIS) is a widely used multi-domain, generic PROM measurement system originating from a NIH grant, with the aim of being an international standard using modern psychometric methods.]

In some cases, there is a direct link that has been created at the time of the construction of the questionnaires. For example, the HOOS, a measure to evaluate symptoms and functional limitations related to the hip, is an adaptation of the KOOS, an earlier measure of symptoms and functional limitations related to the knee. The HOOS contains all WOMAC LK 3.0 questions in unchanged form [Nilsdotter 2003]. WOMAC scores can thus be calculated from the HOOS questionnaire. The HOOS dimension Activity of Daily Living is equivalent to that of Function in the WOMAC.

2.5.10 Power and sample size

Patient outcomes and subjective assessments can challenge medical practices and statistical analyses. To support research, the Consensus-based Standards for the Selection of Health Status Measurement Instruments (COSMIN) checklist has become an essential tool in science and practice. It can be used to evaluate the measurement properties of advanced health-related patient-reported outcomes (HR-PROs) and the methodological quality of medical studies that employ such subjective instruments.

Assessing the measurement properties of an instrument can approve its applications across domains, provide reliable conclusions, and support the further development of diagnostic techniques. By having a clear set of standards in the form of an checklist, experts can get a better understanding of design requirements for research to improve medical practice. Good criteria are particularly important in studies that utilize patient-reported outcomes and Item Response Theory (IRT) tools – simply because the subjective nature of the constructs may challenge statistical analyses and conclusions (Mokkink et al., 2010).

Looking at the diabetes studies we found that power calculations for PROMs were reported in only one study, which calculated that a sample size of 40 would provide a power of 0.94 to detect medium-sized treatment effects in sleep quality (PSQI) after using a closed-loop insulin delivery system (Cobry, 2020). Another study with 168 participants did not provide power calculations, but the authors estimated that power for PROMs was well below 90%, and determined that the study was underpowered to detect differences in PROs (Kudva, et al., 2021). Other studies did not provide power calculations.

It was also noted in the review that in many cases the objective of the study was not to identify a difference in PROM scores but to identify equivalence. Adequate statistical methods for equivalence trials need to be established and the biggest difference that would be 'clinically meaningless' established in order to confirm that there are no differences. This also affects sample size calculations and statistical power.

2.5.11 Device-related PROM instruments

In this section we look at those PROM instruments that have been designed to inform researchers or clinicians on the patient's acceptance of their medical device or its use.

We found only a few studies that had used these instruments. None was found in the orthopaedic literature search, but two instruments were reported in the cardiovascular literature: the ICDC Patient

Concerns Questionnaire, and the Florida Patient Acceptance Survey (FPAS) (Burns et al 2005; Badair et al 2015; Ng et al 2020; Singh et al 2021) - both described below in more detail below. A Florida Shock Acceptance Survey (FSAS) has also been developed with items derived from the clinical experiences of an electrophysiologist, psychologist, and graduate student in clinical and health psychology (Kuhl et 2006). Within the diabetes literature there were instruments related to the Technology Acceptance Model (TAM) (Venkatesh & Davis 2000) and to the INSPIRE (Weissberg-Benchell et al 2019).

Below is the eight-item ICD Patient Concerns (ICDC) questionnaire developed by Frizelle et al (2006) and later adapted and abbreviated by Pedersen et al (2005). It has six questions that concern worry about the operation of the ICD and 2 questions about worry that activities of daily living will cause the ICD to fire.

Table 13. ICD Patient Concerns (ICDC) questionnaire

I am worried about
1. My ICD firing
2. Getting too stressed in case my ICD fires
3. Symptoms/pain associated with my ICD firing
4. Having no warning my ICD will fire
5. Time spent thinking about my ICD firing
6. Not being able to prevent my ICD from firing
7. Working too hard/overdoing things causing my ICD to fire
8. Doing activities/hobbies that may cause my ICD to fire

A second questionnaire that was found in the literature was the Florida Patient Acceptance Survey Versteeg et al (2012; 2019). This is another instrument that has been developed specifically for subjective concerns about a medical device. It was used in four of the studies that we identified.

The final FPAS comprised 15 items, which represent four factors, plus three filler items (items numbered: 9, 11, 16); thus, yielding 18 items in the final FPAS, which is presented in Table 14.

This questionnaire was originally developed to measure patients' acceptance of implantable cardiac devices (i.e., pacemakers, implantable cardioverter defibrillators). It was used in review studies to identify accepters and non-accepters of devices and to compare population parameters. There is no validated cut-off for categorising device acceptance into poor and good, with previous studies using individual study cohorts to determine cut-offs based on the lower tertile of patients.

Table 14. Florida Patient Acceptance Survey (FPAS)

Factor 1: Return to Function (RTF)
1. I am not able to do things for my family the way I used to.
2. I am confident about my ability to return to work if I want to.
3. I am concerned about resuming my daily physical activities.
4. I have returned to a full life.
Factor 2: Device-Related Distress (DRD)
5. When I think about the device I avoid doing things I enjoy.
6. I avoid my usual activities because I feel disfigured by my device.
7. It is hard for me to function without thinking about my device.
8. Thinking about the device makes me depressed.
9. I am careful when hugging or kissing my loved ones.
Factor 3: Positive Appraisal (PA)
12. The positive benefits of this device outweigh the negatives
13. I would receive this device again.
14. I am safer from harm because of my device.
15. My device was my best treatment option.
Factor 4: Body Image Concerns (BIC)
17. I feel less attractive because of my device.
18. I feel that others see me as disfigured by my device.
Filler items (Not used for calculation of the factor scores)
9. I have continued my normal sex life.
11. I know enough about my device.
16. I am knowledgeable about how the device works and what it does for me.

In these studies, the FPAS collects more information than the ICDC, not only distress but also positive appraisal, concerns about body image and aspects of returning to function. They found that the "Non-Acceptors" showed very high levels of anxiety, depression and worse mental health. Age emerged as a risk factor, with younger adult patients showing worse acceptance. None of these instruments tell us very much about the device itself, except that the more trustworthy the device then the more likely it will be that distress will be reduced. The FPAS also has a domain on body image which was not looked at in any of the other studies. No other PROM used in this review had included the aspect of body image.

2.6 Comparing diabetes devices before and after CE mark approval

Due to the focus on a single type of implant (closed-loop) it was possible to compare studies that had been performed before or after CE-mark approval in the diabetes area. The table below shows the differences in study design that were found. Average sample size was higher before CE approval. After CE approval there were fewer RCTs and fewer studies where PROMs were the primary outcome, but a larger number of PROMs had been used.

Table 10. Characteristics of studies before and after CE mark approval

Diabetes	Before CE mark	After CE mark
Number of studies	17	12
Average sample size	99.6	67.1
Median sample size	98	44
Adult studies (%)	5 (29.4)	5 (41.7)
Paediatric studies (%)	5 (29.4)	3 (25)
Mixed age studies (%)	7 (41.2)	4 (33.3)
Studies with upper limits on HbA1c (%)	5 (29.4)	5 (41.7)
Mean follow-up in months	5.9	4.4
Median follow-up in months	6	3.7
Randomized trials (%)	12 (70.6)	6 (50)
Observational studies (%)	5 (29.4)	6 (50)
Average number of PROMs per study	3.8	4.5
PROMs as primary outcome (%)	8 (47)	2 (16.7)

Table 11. Number of times domains were measured before and after CE mark approval

DIABETES	Before CE mark (n = 17)	After CE mark (n = 12)
Treatment satisfaction (%)	12 (70.6)	9 (75)
Fear of hypoglycaemia (%)	11 (64.7)	9 (75)
Diabetes-specific distress (%)	8 (47)	6 (50)
Sleep quality/Sleepiness (%)	4 (23.5)	5 (41.7)
Diabetes-specific QoL (%)	5 (29.4)	5 (41.7)
Hypoglycaemia awareness (%)	4 (23.5)	4 (33.3)
General QoL (%)	3 (17.6)	2 (16.7)

The dates when CE marking was obtained were not available for all closed-loop systems, therefore six studies could not be identified as pre- or post-conformity assessment and were excluded from this particular analysis. 17 studies were conducted prior to CE marking, and 12 were conducted after CE marking. Studies conducted prior to CE marking used, on average, a sample size of 99.6 patients, compared with an average sample size of 67.1 for post-CE studies. Sample size, study length, study characteristics and population characteristics for pre- and post-CE studies are available (Table 15). The seven most commonly assessed outcome domains were compared for frequency of appearance between studies prior to and after CE marking (Table 16).

Randomized trials versus observational studies

Randomized trials and observational studies were compared to assess the rates at which they find statistically significant differences in the most commonly measured PRO domains. Observational studies had higher rates of significant discoveries in all included outcome domains.

Table 12. Diabetes - Statistical differences in PROs: randomized vs observational studies

Outcome domain	Significant differences found in RCTs (%)	Significant differences found in observational studies (%)
Fear of hypoglycaemia	4/11 (36.4)	7/9 (77.8)
Treatment satisfaction	5/13 (38.5)	6/6 (100)
Diabetes-distress	3/8 (37.5)	3/6 (50)
Diabetes-specific QoL	5/8 (62.5)	2/2 (100)
Sleep quality/sleepiness	0/5 (0)	3/6 (50)
Hypoglycaemia awareness	1/4 (25)	3/4 (75)

3 Delphi study with patients and carers of patients

3.1 Background and objective of the study

The role of the European Patients' Forum (EPF) in Task 1.3 on 'Regulatory utility of patient-reported outcome measures' focused on contributing a patient-centric approach to understand and incorporate Patient-Reported Outcome Measures (PROMs) into the evaluation of medical devices. EPF's involvement underscores the importance of patient engagement in shaping methodologies for generating clinical evidence.

To achieve this aim, EPF led, as part of Task 1.3, a consultation with patients and caregivers of patients, consisting of two surveys and two focus groups (Delphi study) to identify and establish a core set of outcome measures that reflect the priorities and experiences of cardiovascular, diabetes, and orthopaedic patients and their caregivers in the context of medical devices. This study responds to a series of research questions about the use, utility, efficacy, and regulatory implications of PROMs, thereby contributing to the project's overarching goal of refining methodologies for the clinical investigation of medical devices.

The research targeted patients with high-risk medical devices (e.g. cardiac stent, pacemaker, infusion pump, circulatory support pump) but also covered other medical devices (e.g. automated insulin delivery systems, including closed-loop delivery systems; insulin pumps) based on the availability of volunteers in the study.

The key objectives of the Delphi study were:

Patient-Centric Research

The focus on collecting information and feedback from patients and their caregivers in the Delphi study underscores the commitment to patient-centric research. Understanding their experiences, preferences, and outcomes is essential for developing products that not only fulfil economic and biological markers but also take into account patients' personal experiences, needs, and lifestyles.

Complementing the Literature Review

The study sought to complement the literature review and analysis presented in this report by introducing patient perspectives. By doing so, it aimed to bridge the gap between traditional clinical assessments and the real-world impact of these devices on patients' lives.

Consensus on PROMs' Utility

Through the Delphi study, the consultation aimed to reach a common consensus among participating patients and caregivers on the use and utility of PROMs. This consensus informed recommendations for the regulatory approval and post-market surveillance of medical devices, contributing to a more standardised and patient-centred approach.

In summary, the Delphi study stands at the intersection of regulatory science, patient engagement, and clinical research, with the overarching objective of advancing methodologies for the evaluation of medical devices while placing patients at the core of decision-making.

3.2 Methodological approach and activities

The methodological approach to the consultation was a Delphi study, which allows a group of different participants to arrive at a common consensus through an iterative process. To identify the most useful PROMs for patients, the consultation generally consisted of multiple rounds of questioning in which participants first provide answers to a set of questions and, in subsequent steps, reviewed and provided feedback on the collected responses. This way, results were refined and validated to arrive at a consensus on main topics of interest. The applied approach, notably, was a somewhat modified Delphi since additional key questions were introduced in later consultation rounds to complement and further build on generated findings. This decreased the risk of response fatigue among participants as it avoided a large volume of questions from the very start of the consultation. Instead, key topics were further built on or newly introduced, based on previous findings. This also allowed participants to gradually increase their familiarity and understanding of explored topics throughout the process, keeping them engaged. The key findings are presented in chapter 3.3 Main results.

To implement the study, EPF first recruited cardiovascular, diabetes, and orthopaedic patients and caregivers of such patients in mid-July 2023. Following recruitment and preparatory activities, the consultation was carried out between October 2023 and January 2024 through four consecutive rounds: two surveys, followed by two focus groups (see

Table below). Before the launch of the first round, all participants were provided with an information pack explaining the CORE-MD project and objectives of the consultation. Throughout the consultation, participants received additional background information as needed.

The total number of participants was 22, including 5 cardiovascular, 1 orthopaedic, and 16 diabetes patients and caregivers. Initially, 20 participants were recruited; however, one of the participants dropped out before the launch of the consultation due to time constraints. At a later stage, three additional cardiovascular and orthopaedic patients were recruited to achieve a better coverage of the targeted disease areas, as most volunteers were diabetes patients or caregivers. 17 patients were using a non-implantable medical device (e.g. insulin pump) for the management of their condition and 5 patients had an implanted device. The female-to-male participant ratio was approximately 3:2. The age ranges roughly covered 18-64-year-olds.[1]

The online surveys were conducted with all participants to gather initial reactions and thoughts on the topics and start forming a consensus. To avoid the risk of group dynamics weakening the validity of focus group results, participants were randomly divided into two cohorts of approximately equal size. Each of the two focus groups was conducted with a different cohort.

[1] The age indication is a rough approximation since participants could select between different wider age ranges.

Table 18. Overview of research activities performed

Round	Research tool	Timeframe	Objective
1	Online survey	24 Oct – 8 Nov 2023 (extended to 12 Jan 2024 to accommodate additionally recruited participants)	Collecting data on participants' experiences with, and expectations of, their device and their reactions to a list of outcomes currently collected by manufacturers and researchers investigating the user acceptability of medical devices.
2	Online survey	15 Dec 2023 – 7 Jan 2024 (extended to 15 Jan 2024 to accommodate additionally recruited participants)	Presenting aggregated statements and findings from the first survey to participants and gathering their views. Further exploring PROM domains important to patients.
3	Online focus group	15 Jan 2024	Further exploring findings from surveys, specifically regarding patient information about medical devices, PROs selection after a device implant, and most important PROM domains. Research on frequency, detail, and format of PROMs.
4	Online focus group	22 Jan 2024	Final validation of findings on patient information about medical devices, PROs selection after a device implant, and most important PROM domains. Validation of research on frequency, detail, and format of PROMs.

3.3 Main results of the Delphi

The research gathered feedback on the use of PROMs, and possible ways to enhance them, as well as priorities and experiences of individuals in the context of medical devices.

3.3.1 Patient experiences with medical devices

Patients' experiences with their medical devices were explored in both surveys and focus groups to achieve a common consensus. The first survey collected responses from 25 individuals about important domains/criteria when thinking about a medical device. Based on the findings from the first survey, participants ranked the different domains by importance. These findings were validated in the focus groups to form a common consensus and are presented in Table .

Table 19. Ranking of important domains relating to medical devices

Rank (1=most important, 10=least important)	Criteria
1	• Safety and performance of the device
2	• Concerns about misfunctioning

Rank (1=most important, 10=least important)	Criteria
3	• Security
4	• Control of the device
5	• Comfort
6	• Replacement of the device
7	• Noise • Size • Feeling under the skin
8	• Shape
9	• Appearance of the device
10	• Colour

Survey questions further asked about participants' feelings and views about these important domains. Key outcomes are elaborated below.

Safety and device performance

Safety, device performance, and risks of misfunctioning emerged as paramount concerns for patients. While some participants felt their device was completely safe (56%), others felt that their device was not completely safe (32%). The reasons for these personal perceptions could not be explored due to the limitations of the study, but the feeling of safety – or lack thereof – is an important aspect to take into account in view of the importance of safety generally for patients. 32% of them responded that they took safety into consideration at first when getting their device, while many of them (56%) still regularly think about it. 72% of patients noted that possible risks associated with the device bother or scare them.

Comparing device function with other aspects, 56 % of surveyed participants reported the function of the device as more important than anything else to them. The large majority of participants also strongly agreed on the importance of the functionality of the medical device over the design (e.g. size, shape, noise, materials). No participant disagreed on the ranking of domains.

Regarding performance, all participants agreed that the effectiveness of the device was very important to them in improving or adequately managing their medical condition. Further examining the topic, participants were asked how important the durability, longevity, and robustness (e.g. waterproofness, battery life, maintenance of good condition over time, frequency of replacement) was to them and all responded very important or important.

These results confirm the importance of prioritising safety, functionality, and performance in the evaluation and regulation of medical devices from a patient perspective. Concerns regarding patient safety should be further explored.

Impact on quality of life

Devices' influence on personal activities and fitness varied among participants, emphasising the multifaceted impacts on quality of life and the variety of personal situations depending on the conditions and available technologies. Overall, 60% of surveyed participants indicated that their medical device does

not restrict their personal activities (e.g. dressing, eating, washing yourself, using the toilet, communicating), and 72% of participants agreed that the medical device does not restrict their work activities (e.g. tasks for their job/employment). Regarding social activities, a significant number of respondents indicated that the device does not restrict their meetings with friends/family or their hobbies (72%). By comparison, only 56% found themselves physically fit with their device.

Sleep and noise also elicited mixed responses. Many (48%) reported that they sleep better with the device, whereas 28% have disturbed sleep due to the device. Sleep and noise are related concerns especially for diabetic patients, as devices have alarm modes that can be fatiguing for the patient especially if they disturb sleep. Device noise can also interrupt other daily activities, such as cinema visits or working at an office. About half of respondents (48%) indicated they are irritated by the noise/buzz/vibration of their medical device. 24% of respondents indicated the contrary and the 28% did not find noise an important aspect. Overall, 36% of respondents stated that they would change the device if they could, whereas 44% of respondents would not change their device. This data shows that devices are not fully adapted to a significant number of participants and more can be done to match the right device with the right patient.

Design of devices

Overall, respondents found the design of the device (e.g. appearance, shape, colour, size) not as important as other factors, as shown in the ranking above. Most respondents also did not mind if the device or parts of the device are visible to other people (76%). A few participants indicated that younger patients may care more about the look of a device especially when it is visible. Usability issues, like noise and alarm fatigue, also deserve consideration from the patient perspective.

Worries about the material of the device were raised by some participants, underlining the need for hypoallergenic materials and transparent information about the composition of medical devices. Findings from the second survey show that 48% of participants usually worry about what the device is made of, while 44% did not worry at all. This demonstrates that design aspects were important to participants when they are related to safety.

3.3.2 The use of PROMs

The main results regarding the utilisation of PROMs are presented below.

3.3.2.1 Limited familiarity with PROMs

Most participants expressed unfamiliarity with PROMs, underscoring the need for increased awareness and education regarding the purpose and application of these measures. Some respondents also reported that they might have filled in a questionnaire but may not have realised that they were PROMs. During the focus groups, several participants noted that the PROM questionnaires they received were not up to date, included repetitive questions, or did not focus on the aspects that mattered to them (e.g. material, size, shape, etc. of the device). An important aspect that is overlooked in PROM questionnaires is attitude towards the software, if the device contains one. Some also felt that the questions appeared to focus on very subjective aspects, which did not seem relevant right away.

3.3.2.2 Co-creation and feedback pathways

Participants in the focus groups expressed a keen interest in co-designing medical devices and information materials about them, highlighting the importance of involving patients in the development process to make devices and information more patient-friendly, accessible, and meaningful. Focus group discussions showed that the majority of participants is interested in providing feedback about their experiences with devices and finds it important, in particular in the context of post-market surveillance and sharing of experiences with fellow patients. When sharing feedback, however, patients want clear information and communication about how their data are used by researchers and industry, how data privacy is ensured, and what are the results of the data analysis. Routine use of PROM results not only for research purposes but also to help patients maintain or improve their own health is more likely to keep them engaged, as focus group findings indicate. Participants also saw the value of registries to collect long-term data.

Another important common difficulty highlighted by the focus groups is that patients often do not know how to effectively share their feedback with manufacturers (e.g. if and how to contact manufacturers, or if feedback shared with their physicians will in fact reach manufacturers). Some participants felt that manufacturers did not receive the information when they had issues with their devices. Clear, available feedback pathways for patients to share their experiences, concerns, and needs are necessary to address this challenge.

3.3.2.3 Frequency of PROM use

In the focus group discussions, patients found PROMs valuable tools that support HCPs in offering personalised and appropriate care. Most participants expressed interest in completing a questionnaire on a regular basis, approximately every 3-6 months or 2-4 times a year. It was noted that this frequency would adequately capture changing opinions, emotions, and outcomes over time.

3.3.2.4 Detail and format of PROM questionnaires

Questions about the detail and format of PROM questionnaires triggered different responses in the focus groups. Some respondents shared that they would not like to spend more than 10-15 minutes completing a PROM questionnaire. Some respondents further stated that they spend about 30 minutes with their HCP in regular checkups at a hospital or clinic. Other focus group participants shared that they would prefer completing questionnaires online at home, as it is more convenient and would give them time to reflect on questions and answers.

Considering the short amount of time available during checkups, a shorter, less detailed PROM questionnaire would be sensible if completed at the hospital or clinic. This could be done online or on paper. Additionally, online formats could be made available for patients who want to take more time to reflect and complete them in their own time, at home for example.

3.3.3 Patient information about medical devices

Understanding patient preferences and needs for information about medical devices was a focal point of the consultation. Key findings are presented below.

3.3.3.1 Importance of device choice

When selecting a medical device, almost all participants (92%) agreed that having a choice between different devices is extremely important for them. This was validated in the focus groups. Survey results further show that most respondents have thought about this issue before. 72% of respondents are still thinking about this issue, while 20% of respondents thought about it at first when getting a device. Some participants reported, however, that choice was not always possible as many hospitals only work with one provider, which means other models are not available, and healthcare systems do not always reimburse all options. One participant mentioned choosing to pay out-of-pocket for a device that was not offered by the hospital, while noting that not all patients have the financial means to do so.

Those who responded that they do not necessarily need to have a choice, emphasised nonetheless that their doctor should be able to explain why they chose a particular device over another and present their experience with the device (how many times they used it, what were the outcomes, etc.).

To inform their choice, participants also emphasised the importance of having easy access to information about all the features of the different medical devices on the market. That information must be up-to-date, comprehensive, and available to the public. Especially diabetes patients reported this as important because it allows them to choose a device that fits their personal lifestyle, as diabetes requires very individualised treatment. These patients are generally highly aware of innovations that come onto the market, and they compare new products with what they are using.

3.3.3.2 Desired information and learning materials

According to survey and focus group findings, participants considered a mix of different information and learning materials, both on paper and online, optimal to fully understand the use and functions of different medical devices. These include for instance user manuals, videos, leaflets, courses, and websites. A preference for a balance in the volume of information was also noted – not too much and not too little.

Many diabetes participants had received in-person training sessions (generally as a group of 4-5 families) with representatives from manufacturing companies accompanied by HCPs. While some were highly satisfied with the structure and content of the training, others stated that the training mostly focused on technical support and did not provide the in-depth information they needed to match the use of the device to their individual needs and lifestyles.

Focus group participants agreed that it is important to them to access and receive information materials and training before starting to use their device, but the information becomes clearer as they start using the device. Practical training with apps as is done with some user-made systems, where the patient unlocks additional information once they master a given functionality, was mentioned by one participant as a didactic and useful option.

3.3.3.3 Importance of visual information

Participants highlighted the need for more visual information formats (e.g. videos) to complement written materials. Patients mentioned explanatory videos, which demonstrate how to use a device in detail, as useful. Crucially, easy-to-follow, visual information would also support patients with lower levels of health-literacy.

3.3.3.4 Role of online communities

In one of the focus groups, online communities (e.g., WhatsApp, Telegram, Facebook groups) were emphasised as valuable resources for information about devices and first-hand accounts of other patients' experiences. To avoid a barrage of misinformation, participants supported moderation of online communities by patients' organisations and by clinicians. Some respondents reported that compared to information received from an HCP, online communities would help them better assess the advantages and disadvantages of different medical devices on the market and their appropriateness for their personal lifestyle and situation. Several patients mentioned that the "lived experience" of other patients was very important to complement the "institutional" information provided by healthcare professionals.

3.3.4 Strengths and limitations of the Delphi study

A key strength of the Delphi study was that participants showed much enthusiasm in engaging with the addressed topics and actively gave feedback, resulting in lively, purposeful discussions and meaningful findings.

At the same time, a limitation in the Delphi study was the restricted availability of relevant volunteers. Many of the participants were diabetic patients or carer of patients who use medical devices, including insulin pumps, continuous glucose monitors, and closed-loop insulin delivery systems, but not implantable devices. To address this limitation, additional participants were recruited later during the consultation to increase the number of patients with high-risk implantable devices.

3.3.5 Conclusions from the Delphi study

The CORE-MD Delphi study provides valuable insights into the perspectives of patients and caregivers regarding high-risk and other medical devices. Unsurprisingly, safety, effectiveness, and functionality remain the most important factors for patients when considering their devices. Among the participants in the study, there was generally a strong assumption of safety and performance of available devices, which reflects the fact that many devices in the disease areas concerned are well-established and used widely. The emergence of new technologies slightly challenges these assumptions, with patients requiring more information and evidence about software, software updates, and control of the algorithms. For example, a diabetes participant reported in the survey being worried about others/third parties being able to access their insulin pump as it has a Bluetooth system. Another diabetes patient in a focus group also expressed concern about algorithms in insulin pumps which decide on the dosage to administer, as they can learn from experience and make independent decisions without patient control. Further, a lack of care in upgrading device software was raised as another major concern. Providing the level of information that answers patients' questions, complemented by adequate post-market oversight, will be important to ensure patients gain trust in these new technologies.

In this context, other aspects that are closely linked to the use of the device and its impact on their day-to-day life, drive patients' perceptions of their device and their choice of one device over another. Patients' preferences may change over time as new technologies become available, and they are closely linked to their lifestyle, which may vary based on the disease area. The study has showed that patients

are looking for information on "real-life" use and impacts of a device, which at the moment is overwhelmingly provided directly by other patients, in particular through online communities.

As a result, it is essential that the information about devices' impacts on quality of life and of aspects that matter to patients is collected, available, and used to inform decision-making. It would enhance healthcare professionals' ability to provide personalised advice to their patients and to match patients with the devices that best suit their needs. The dimension of shared decision-making between patients and healthcare professionals must be further embedded into patients' care and into healthcare systems at large. Patients are often not perceived as partners in the health decision-making process. A cultural shift is still very much needed to ensure patients are effectively involved in their own care. Of note, integrating the patient perspective would also inform hospital procurement and reimbursement decisions. In view of limited healthcare budget, taking into account patients' experiences with devices would help identify those devices that provide a true added value to patients from those that are less useful. Patient-centred approaches contribute to the sustainability of healthcare systems in the long run (Coulter 2016; Epstein and Street 2011).

Most importantly, patient feedback enriches research and device innovation. It helps identify areas for further improvements for the development of devices that truly meet patients' needs. The importance of patient involvement in the design and development of new devices is demonstrated by the growing importance of user-driven open-source initiatives, namely devices made by patients for other patients, especially in the diabetes field (O'Donnell et al. 2019; Vallis and Holt 2022). These devices are expected to address patients' concerns based on lived experiences, showing the importance of integrating the patient perspective throughout the device's lifecycle.

The use of PROM provides a standardised way of collecting this information about patients' lived experience with a device. However, their use must be made more systematic, and their usability and usefulness must be significantly enhanced in order to fulfil their potential.

Results show that patients appear willing to share feedback on their experience with devices. In particular, patients generally feel a moral obligation to share information about potential adverse effects or post-market issues, but they do not always know how and where to share this feedback. Clear information about easily accessible, user-friendly reporting mechanisms should be provided to patients as part of the information material they receive when they obtain their device. In addition, manufacturers should be required to reply to complaints to show that they considered patients' feedback. Competent authorities also have an important role to play in ensuring transparency and providing comprehensive and timely information about the safety and effectiveness of devices under investigation. In general, patients' access to information on adverse events related to devices remains difficult in the European Union, especially given the lack of implementation at the time of writing, of the medical devices database EUDAMED.

There are also several challenges related to regular, continuous participation in PROMs by patients. In particular, there is still a general lack of awareness of PROMs among patients, who often do not realise they are asked to fill in a PROM and do not receive the results/findings afterwards. This makes their participation less meaningful to them, increasing the risk of them dropping out after a certain amount of time. In addition, patients often do not receive clear, comprehensive information about how their feedback will be used by researchers and industry, which may impede their motivation to participate. Finally, PROM questionnaires are often not adapted to patients' expectations and do not always address the aspects that are most important to them, making the questionnaire look irrelevant and not worth the time needed to complete it.

4 Summary and conclusions

The present deliverable illustrates the findings of the study conducted in Task 1.4 to ascertain how PROMs are being used to contribute to differentiating between well-performing and under-performing devices.

In this literature review we have found a large volume of studies that have utilised PROM data in clinical trial assessment of medical devices. There is some apparent consensus in the literature about which instruments to use. The generic PROMs that have been developed decades ago emerge as the most frequently used PROM questionnaires.

Although it is often quoted that condition-specific instruments are more sensitive to change, this is not always demonstrated in the literature. Perhaps because of this, several studies have used both generic and condition-specific instruments. This might at first seem like an ideal solution but there are negative consequences of increased patient burden. Repetition of similar questions in multiple PROMs may irritate patients and require caution in statistical analysis. While most of the studies reviewed presented results related to statistically significant differences between design elements or surgical techniques, there were a few studies that attempted to look beyond the statistics to perceivable or minimal clinical differences for the patient. In other studies, a standard improvement in scores was accepted as evidence of change (e.g. >30% increase in VAS pain scores). Using MCID as a clinically relevant metric also has challenges, since it relies on the reference population being similar to the group investigated.

The studies show that PROM data provide an alternative understanding of results that can represent the patient's view-point. PROM data also inform a study on background information about the patients and situation that can help to explain other findings and predict which factors such as age, sex, preoperative disease severity, and comorbidities broadly affect outcomes at the population level. It may be possible to use appropriately designed PROMs to inform designers and regulators of important issues or the extent of the effect of issues that could affect the acceptance and tolerance of a medical device. Different types of PROMs were found that go beyond the simplified distinction of generic or condition-specific. The domains within a PROM or a QoL measure need to be considered when choosing an instrument and these choices were mostly not explicit in the literature, and rarely given especially if the stated outcome was 'quality-of-life'.

What emerged from this review of instruments was that the domains assessed by PROMs in studies are largely those that were mentioned as most important by the patients in the Delphi study, namely function and safety. That is also to say that acceptability is based on trust, i.e. the patient needs to trust the device. The instruments that were designed especially for use in populations with implants also focus mostly on function and anxiety. The diabetes PROMs are more concerned with the acceptance of using technology and having to manage the complexity of the closed-loop device themselves.

The FPAS introduces the aspect of body image which is not found elsewhere. Despite there being many hundreds of body image questionnaires, none were found in this review. This is interesting because this is one aspect that the Delphi panel also took up. Concerns were raised about the appearance and size of the implant. This is probably more of an issue in diabetes with closed-loop devices being visible, but the scarring following orthopaedics or cardiovascular implant surgery could also lead to body image concerns for the patient.

In order for PROMs to be useful in the regulation of medical devices it is necessary to adequately determine which variables are important to measure, which instruments can provide these variables in a

valid and reliable manner, and what constitutes either a non-trivial change or an adequate measure of equivalence. There are a number of studies that provide general recommendations for optimal practice and future directions for the use of PROMs in clinical treatment, research and for shared decision-making (Kendir et al 2022 page 34; Moons et al 2023 page 3415). Study designs for medical device development need to be developed with consideration of the nature of the patient outcome measured and what is an appropriate outcome.

Some of the limitations of PROMs seen in the literature have already been tackled but they remain not yet in common use. Digital questionnaire formats can take advantage of modern psychometric techniques that improve the measurement quality of the instruments and allow greater flexibility in the selection of relevant domains, providing more accurate information about relative weightings, with fewer questions and therefore reduced demands on patients. This in turn increases the chance of maintaining adequate response rates over longer periods of time. For example, the PROMIS Health Organisation system uses item response theory to calibrate individual questions allowing different combinations of questions to arrive at a standard measurement. These profile approaches avoid the 'black-box' of quality-of-measures and open the way to a more tailored approach without losing the possibility of comparison between studies, populations, conditions or countries. PROMIS and other IRT or Rasch based item-banking systems are relatively recently available and have still not found widespread usage, perhaps due to a reliance upon digital presentation for the full implementation of such systems. This is gradually changing, however, and more and more of these measures are being accepted as evidence for labelling purposes.

There are PROM measurement and implementation issues that challenge the validity and reliability of the instruments that need to be investigated in future research. More work is of course needed on the validation of PROMs for the purpose of implant design and management. In the recommendations below we present recommendations relating to specific issues that are important for device medical regulation.

5 Recommendations

The study has demonstrated that more work is needed to make PROMs more relevant, in order to develop their utility to inform the clinical evaluation and post-market surveillance of medical devices. These initial recommendations from the CORE–MD project could be addressed in future research and guidance:

1. The choice of PROM needs to be guided by trustworthy resources that outline the adequacy of the measurement i.e., what is being measured and how to interpret the results. Therefore, a set of PROMs should be identified or developed that address patients' device-specific concerns. The qualification process of these instruments should clearly state the requirements for evidence of validity and sensitivity.
2. The objectives of PROM collection need to be clearly communicated to all stakeholders and provide feedback to patients about the use of their data, and share results/updates. Channels for feedback that benefit patients, healthcare providers, and device manufacturers need to be established.
3. Provide study protocol developers with guidance on how to incorporate PROMs and identify the specific evidence that is sought from device-specific PROMs.
4. Where PROMs are used for primary or secondary outcome measurement, the sample size should be determined on the basis of the distribution of PROM scores in the target population. If an MCID threshold is to be used for determining sample size, the assumptions on differences between groups should be based on proportions reaching MCID threshold.
5. PROM data collection follow-up times should be based on expected change in patient reported variables. Frequencies of not more often than every 3 to 6 months are considered optimal with long-term follow-up at intervals determined by expectations of change in condition.
6. Facilitate PROM collection to ensure patients' engagement and willingness to contribute. Various PROM formats can be used for data collection, such as paper or electronic options, data collected at the hospital or at home. Additionally, integrating with registries would improve patient follow-up and streamline the collection of long-term data.
7. Develop ways to integrate PROMs, and patient experience data more generally, in the regulatory process for medical devices and assessment of the benefit-risk. Exclusive focus on questionnaires may not be optimal in all cases.
8. Involve patients throughout the lifecycle of medical devices, including in the development of information/communication materials. A plan for a systematic involvement of patients in the early stages of device development would ultimately support and guide the planning and generation of PROM data.
9. Alignment among decision-makers is needed. A clear message needs to be conveyed that EU regulators welcome the use of PROMs and how PROM data will be used. An early dialogue with all stakeholders needs to be carried out to address requirements and expectations in a timely manner.
10. Training on the use of PROMs in RCTs should also be provided to trialists.
11. The digital transformation of PROM data collection and analysis offers enormous opportunities for the inclusion of the patient voice in clinical science. Integration is recommended with ongoing activities in the European Health Data Space and the Big Data work plan 2022-2025.

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Appendices

A.1 Acronyms and abbreviations of the most commonly used generic PROMs

Acronyms and abbreviations of the most commonly used generic PROMs	
AIS	Acceptance of Illness Scale
CES-D	Center For Epidemiologic Studies Depression Scale
CES-D 12	Center for Epidemiological Studies—Depression Scale (CES-D)12
CISS	Coping Inventory for Stressful Situations
COPE - Brief-	Brief Coping Orientation to Problems Experienced
DS14	Type D Scale (DS14) The 14-item Type D Scale (DS14) distressed (Type D) personality
EQ-5D	The EuroQoL (EQ) general health questionnaire evaluates five domains (5D), mobility, self-care, usual activities, pain/discomfort and anxiety/depression
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ-5D-VAS	European Quality of Life visual analog scale of overall state of health
ESS	Epworth Sleepiness Scale
GDS	Geriatric Depression Scale
GSES	General Self Efficacy Scale
IIRS	The Illness Intrusiveness Rating Scale (IIRS) 13 life domains
MHLC	The Multidimensional Health Locus of Control
MMSE	Mini-Mental State Examination
MMSE	Mini-Mental State Examination (MMSE) Cognition impairment as determined with a 30-point questionnaire
MSPSS	Multidimensional Scale of Perceived Social Support Social support. Three subscale scores: family, friends, and significant others
PedsQL	Pediatric Quality of Life Inventory
PRMQ	Prospective and Retrospective Memory Questionnaire

PROMIS	Patient-Reported Outcome Measurement Information System
PSQI	Pittsburgh Sleep Quality Index
PSS-10	Perceived Stress Scale-10
QoL-Q	Quality of Life Questionnaire
SF-12	Short-Form –12 questions Mental health, Physical health
SF-36	Short-Form-36 questions: Physical functioning, Bodily pain, Emotional/Physical role limitations, Mental health, Social functioning, Vitality, General health
SPPC & SPPA	Self-Perception Profile for Children and for adolescents
STAI	State Trait Anxiety Inventory
SWLS	Satisfaction With Life Scale
VAS	Visual Analog Scale
W-BQ28	Well-Being Questionnaire
WHO-5	World Health Organisation- Five Well-Being Index: Cheerful, relaxed, active, fresh, life filled with things that interest me

A.2 Acronyms and abbreviations of diabetes PROMs

Acronyms and abbreviations of most commonly used diabetes PROMs	
AHCL	Advanced hybrid closed loop
APAQ	Artificial Pancreas Acceptance Questionnaire
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DAWN2	Impact of Diabetes Profile
DDS	Diabetes Distress Scale
DQoL	Diabetes Quality of Life

DTQ	Diabetes Treatment Questionnaire
DTSQ	Diabetes Treatment Satisfaction Questionnaire
FCL	Fully closed-loop MDI Multiple daily injections
GME-Q	Glucose Monitoring Experiences Questionnaire
GMSS	Glucose Monitoring Satisfaction Survey
HAS	Hyperglycaemia Avoidance Scale
HCL	Hybrid closed loop
HCS	Hypoglycaemia Confidence Scale
HFS	Hypoglycaemia Fear Survey
IDDS	Insulin Delivery Device Satisfaction
INSPIRE	INsulin Dosing Systems: Perception, Ideas, Reflections and Expectations
LGS	Low-glucose suspend PLGS Predictive low-glucose suspend
PAID	Problem Areas in Diabetes
SAP	Sensor-augmented pump
SQASAID	Standardized questionnaire for acceptance and satisfaction with an AID system
SUS	System Usability Survey
TA:DS	Technology Attitudes: Diabetes Specific
TAS	Technology Acceptance Survey
TES	Technology Expectations Survey

A.3 Acronyms and abbreviations of orthopaedic PROMs

Orthopaedics acronyms and abbreviations	
AKSS	American Knee Society Score – T (1) clinical assessment (Clinical AKSS – 'Knee Score') (2) assessment of functionality (Functional AKSS – 'Function Score').
HAAS	High Activity Arthroplasty score - • walking, • running, • stair climbing and • general activities
HSS	The Hospital for Special Surgery (HSS) score, six parts: pain, function, range of motion, muscle strength, knee flexion deformity, and stability (10 points).
HOOS	The hip disability and osteoarthritis outcome score • Stiffness • Symptoms • Pain • ADL • Sports and recreation • QoL
ICOAP	The intermittent and constant osteoarthritis pain score
KOOS	The Knee Injury and Osteoarthrosis Outcome Score • Stiffness • Symptoms • Pain • ADL • Sports and recreation • QoL
KOS-ADLS	Knee Outcome Survey-Activities of Daily Living Scale the Knee Outcome Survey Activities of Daily Living Scale (ADLS) Sports Activity Scale (SAS).
KSS	The Knee Society Score • Pain • Physical Function • Motion

OKS	Oxford Knee Score • Pain • Physical Function • Complications
OKS-APQ	Oxford Knee Score – Activity and Participation Questionnaire (OKS-APQ) • higher levels of activity • social participation
OHS	The Oxford Hip Score • Pain • Physical Function • Complications
SPMSQ	Short Portable Mental Status Questionnaire, assessment of organic brain deficit in elderly patients.
UCLA	UCLA Activity Score: the University of California Los Angeles Activity Score
UCLA AS	UCLA Activity Score – 10 descriptive activity levels ranging from • wholly inactive and dependent on others (level 1), • moderate activities such as unlimited housework and shopping (level 6) • regular participation in impact sports such as jogging or tennis (level 10).
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index • Activities of daily living, • functional mobility, gait, • general health, quality of life. • Pain • Physical function • Stiffness • Symptoms

A.4 Cardiovascular specific PROMs used

Cardiovascular specific PROMs used	
EuroQoL-HF	
LHFQ	Minnesota Living with Heart Failure Questionnaire (LHFQ),
HHS	Harris Hip Score • Pain • Physical Function • Deformity • Range of motion
KQ	The modified Karolinska questionnaire
M-LHFQ	Minnesota Living with Heart Failure Questionnaire • HRQoL • physical • emotional
QWB	The Quality of Well-Being Scale • physical activities, • social activities, • mobility, and • symptom/problem complexes

A.5 CORE-MD PROM systematic review search strategy

A.5.1. Orthopaedics. Search of Medline, Cochrane and CINAHL

A.5.1.1. Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations

MESH	1	patient reported outcome/ or quality of life/ or Health Adjusted Life Years/ or patient satisfaction/ or anxiety/ or Distress, Psychological/
.mp.	2	(EuroQol or European QoL or EQ-5D or SF36 or SF12 or SF6 or SF-36 or SF-12 or SF-6 or RAND-36 OR IPAQ or PROMIS or Health Utilities Index Mark 2 or HUI2 or Health Utilities Index Mark 3 or hui3 or 16D or 17D or Quality of Wellbeing Scale or QWB or HADS* or Short Form-36 or Specific Activity Scale or time trade-off or PEDsQL or WHOQOL-BREF or SEIQoL or Sickness Impact Profile or RAND-36).mp.
.mp.	3	(oxford hip score or oxford knee score or KOOS or KOOS-child or HOOS or KOOS-PF or KOOS-PS or HOOS or HOOS-PF or WOMAC or Knee Osteoarthritis Outcome Junior Score or KoosJR or Kujala Anterior Knee Pain Score or ACL QOL or Knee Society Score or Harris hip or UCLA score* or UCH score* or Lower Extremity Functional Scale or Patient Specific Functioning Scale or Forgotten Joint Score OR American Knee Society score* OR Knee Society Score OR KSS OR OKS OR Numerical Rating Pain Scale).mp.
.tw.	4	(patient reported outcome or quality of life or Health Adjusted Life Years or patient satisfaction or anxiety or Distress or PROM).tw.
MESH	5	Arthroplasty, Replacement, Hip/ or Hip Prosthesis/ or Arthroplasty, Replacement, Knee/ or Knee Prosthesis/
.mp.	6	(knee replacement or hip replacement or knee arthroplasty or hip arthroplasty or hip prosthesis or knee prosthesis OR patella resurfacing OR knee osteoarthritis OR THR OR TKR).mp.
	7	2 or 3 or 4
	8	5 or 6
	9	7 AND 8
	10	limit 9 to (English language and full text and humans and yr="2000 -Current")

A.5.1.2. Cochrane Orthopaedics

ID	Search
#1	MeSH descriptor: [Arthroplasty, Replacement, Knee] explode all trees
#4	MeSH descriptor: [Arthroplasty, Replacement, Hip] explode all trees
~~#5~~	MeSH descriptor: [Hip [surgery]] 1 tree(s) exploded
#6	MeSH descriptor: [Hip Prosthesis] 1 tree(s) exploded
#7	MeSH descriptor: [Knee Prosthesis] 1 tree(s) exploded
#8	Hip surgery or knee surgery OR knee replacement or hip replacement or knee arthroplasty or hip arthroplasty or hip prosthesis or knee prosthesis
#9	MeSH descriptor: [Patient Reported Outcome Measures] explode all trees
#10	MeSH descriptor: [Quality of Life] explode all trees
#11	MeSH descriptor: [Patient Satisfaction] explode all trees
#12	MeSH descriptor: [anxiety] explode all trees
#13	MeSH descriptor: [Distress, Psychological] explode all trees
#14	Patient Reported Outcome Measures OR Quality of Life OR Patient Satisfaction OR anxiety OR Distress OR EuroQol or European QoL or EQ-5D or SF36 or SF12 or SF6 or SF-36 or SF-12 or SF-6 or RAND-36 OR IPAQ or PROMIS or Health Utilities Index Mark 2 or HUI2 or Health Utilities Index Mark 3 or hui3 or 16D or 17D or Quality of Wellbeing Scale or QWB or HADS* or Short Form-36 or Specific Activity Scale or time trade-off or PEDsQL or WHOQOL-BREF or SEIQoL or Sickness Impact Profile
#15	oxford hip score or oxford knee score or KOOS or KOOS-child or HOOS or KOOS-PF or KOOS-PS or HOOS or HOOS-PF or WOMAC or Knee Osteoarthritis Outcome Junior Score or KoosJR or Kujala Anterior Knee Pain Score or ACL QOL or Knee Society Score or Harris hip or UCLA score* or UCH score* or Lower Extremity Functional Scale or Patient Specific Functioning Scale or Forgotten Joint Score OR American Knee Society score* OR Knee Society Score OR KSS OR OKS OR Numerical Rating Pain Scale OR Quality of Recovery-15 score OR Knee Osteoarthritis Outcome Junior Score OR KoosJR
#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#17	#9 OR #10 OR #11 OR #12 OR #13 OR #15
#18	#16 AND #17 with Cochrane Library publication date Between Jan 2000 and Jul 2022, in Cochrane Reviews, Cochrane Protocols, Trials

A.5.1.3. CINAHL Orthopaedics

No.	Specification
1	knee replacement or hip replacement or knee arthroplasty or hip arthroplasty or hip prosthesis or knee prosthesis
	AND
2	((MH "patient reported outcome") OR (MH "quality of life") OR (MH "anxiety") OR (MH"Patient satisfaction") OR (MH" Distress, Psychological"))
	OR
3	(oxford hip score or oxford knee score or KOOS or KOOS-child or HOOS or KOOS-PF or KOOS-PS or HOOS or HOOS-PF or WOMAC or Knee Osteoarthritis Outcome Junior Score or KoosJR or Kujala Anterior Knee Pain Score or ACL QOL or Knee Society Score or Harris hip or UCLA score* or UCH score* or Lower Extremity Functional Scale or Patient Specific Functioning Scale or Forgotten Joint Score OR American Knee Society score* OR Knee Society Score OR KSS OR OKS OR Numerical Rating Pain Scale OR Quality of Recovery-15 score OR Knee Osteoarthritis Outcome Junior Score OR KoosJR)
	Limiters - Research Article; Published Date: 20000101-202207**; Language: English Exclude MEDLINE records

A.5.2. Cardiovascular search term strategy

No.	Specification
1.	cardiovascular abnormalities/ or heart/ or cardiology/
2.	Heart Valve Prosthesis Implantation/ or Heart, Artificial/ or Heart Bypass, Left/ or Heart Valve Prosthesis/ or Heart Bypass, Right/ or Heart-Assist Devices/ or Coronary Artery Bypass, Off-Pump/ or Absorbable Implants/ or Defibrillators, Implantable/ or Transcatheter Aortic Valve Replacement/
3.	(Bioresorbable scaffolds or Left atrial appendage occlusion or Transcatheter mitral valve repair or Transcatheter mitral valve replacement or Leadless pacemaker or Subcutaneous implantable cardioverter-defibrillator or Surgical mitral valve* or Surgical aortic valve or Left Ventricular Assist Device).mp.
4.	patient reported outcome/ or quality of life/ or Health Adjusted Life Years/ or patient satisfaction/ or anxiety/ or Distress, Psychological/ or anger/ or fear/ or Locus of Control/ or Surveys/ or Questionnaires/ or Focus Groups/ or Qualitative Research/ or Health Care Evaluation/
5.	(PROM or EuroQol or European QoL or EQ-5D or SF36 or SF12 or SF6 or SF-36 or SF-12 or SF-6 or IPAQ or PROMIS or AQoL-6D or Child Health Utility or CHU9D or EQ-5D-Y-3L or Health Utilities Index Mark 2 or HUI2 or Health Utilities Index Mark 3 or hui3 or 16D or 17D or Quality of Wellbeing Scale or QWB or Hospital Anxiety or HADS* or Short Form-36 or Specific Activity Scale or time trade-off or Pediatric Quality of Life Inventory or PEDsQL or WHOQOL-BREF or Schedule for the Evaluation of Individualised Quality of Life or SEIQoL or Sickness Impact Profile).tiab.
6.	(Duke Activity Status Index or HeartQoL Questionnaire or Multidimensional Index of Life Quality or Quality of Life Index Cardiac version or Quality of Life Instruments for Chronic Diseases coronary heart disease or AF-QoL Questionnaire or Arrhythmia-specific Questionnaire in Tachycardia or Atrial Fibrillation Effect on Quality-of-Life Questionnaire or Patient Perception of Arrhythmia Questionnaire or Cardiac Health Profile of Congestive Heart Failure or Care-Related Quality of Life survey for Chronic Heart Failure

	or Chronic Heart Failure Questionnaire or Congenital Heart Disease-TNO or Fragebogen zur Erfassung or Heart Valve Disease Impact on daily life or Heart Failure Somatic Awareness Scale or Kansas City Cardiomyopathy Questionnaire or Kansas City Cardiomyopathy Questionnaire or KCCQ-12 or Left Ventricular Dysfunction Questionnaire or Memorial Symptom Assessment Scale-Heart Failure or Minnesota Living with Heart Failure Questionnaire or Quality of Life Questionnaire in Severe Heart Failure or Symptom Status Questionnaire Heart Failure or Angina-related Limitations at Work Questionnaire or Angina Pectoris Quality of Life Questionnaire or Cardiovascular Limitations Symptoms Profile or Myocardial Infarction Dimensional Assessment Scale or Quality of Life Index or Quality of Life Questionnaire or Seattle Angina Questionnaire or Summary Index for the Assessment of Quality of Life in Angina Pectoris or Rose Angina Questionnaire or heart-focused anxiety or Cardiac Anxiety Questionnaire or Minnesota Living with Heart Failure Questionnaire).tiab.
7.	(Patient Perception of Arrhythmia Questionnaire or PPAQ or AFImpact or AF-QoL or Atrial Fibrillation Effect on Quality-of-Life or AFEQT or Atrial Fibrillation Quality of Life Questionnaire or AFQLQ or Quality of life in AF patients or QLAF or University of Toronto Atrial Fibrillation Severity Scale or AFSS or Modified Postoperative Recovery Profile questionnaire or PRP-CABG or Coronary Revascularisation Outcome Questionnaire or CROQ or Cardiac Event Threat Questionnaire or CTQ or Cardiac Health Profile or CHP or Multidimensional Index of Life Quality or MILQ or Quality of Life Index-Cardiac Version or QLI-CV or ACHD PRO or CHD-TAAQOL or PedsQl cardiac module or Pediatric Cardiac QOL Inventory or CHAT or ConQol or Cardiac Health Profile or CHPchf or CaReQol CHD or CHAT or CHF-PROM or Chronic Heart Failure Questionnaire or CHFQ or Heart Failure Functional Status Inventory or HFFSI or Heart Failure Symptom Checklist or Kansas City Cardiomyopathy Questionnaire or KCCQ or Left Ventricular Dysfunction Questionnaire or LVD-36 or Minnesota Living with Heart Failure or MLHF or Quality of Life Questionnaire in Severe Heart Failure or QLQ-SHF or Traditional Chinese Medicine inquiry or TCM inquiry or Heart Transplant Stressor Scale or Rotterdam Quality of Life Questionnaire or Heart Valve Disease Impact on daily life or QLICH-HY or Angina Pectoris Quality of Life Questionnaire or APQLQ or Cardiovascular Limitations Symptoms Profile or CLASP or HeartQol or Quality of Life Index or QLI or QLICH-CHD or Seattle Angina Questionnaire or SAQ19 or Short version of the Seattle Angina Questionnaire or SAQ7 or Summary Index for the Assessment of Quality of Life in Angina Pectoris or LVAD Stressor Scale or MacNew Heart Disease Questionnaire or QLMI-2 or Myocardial Infarction Dimensional Assessment Scale or MIDAS or Quality of my Life Questionnaire or Cardiff Cardiac Ablation or Toronto Aortic Stenosis Quality of Life Questionnaire or TASQ or Arrhythmia-Specific questionnaire in Tachycardia or ASTA or Mayo Atrial Fibrillation Specific Symptom Inventory or MAFSI or Cardiac Surgery Symptom Inventory or CSSI or Cardiac Symptom Survey or Heart Surgery Symptom Inventory or HSSI or Symptoms of Illness Score or SOIS or Cardiac Symptoms Scale or Heart Failure Somatic Awareness Scale or HFSAS or Memorial Symptom Assessment Scale Heart Failure or MSAS-HF or San Diego Heart Failure Questionnaire or SDHFQ or WHO Rose Angina Questionnaire or Atrial Fibrillation Knowledge Assessment Tool or AFKAT or Atrial Fibrillation Knowledge Scale or Jessa Atrial fibrillation Knowledge Questionnaire or JAKQ or Knowledge about Atrial Fibrillation or KAFSP or Knowledge of Atrial Fibrillation test or KAF or Survey of Patient Knowledge or SATELLITE or Leuven Knowledge Questionnaire for Congenital Heart Disease or Barnason Efficacy Expectation Scale or Cardiac self-efficacy scale or Cardiovascular Management Self-efficacy or SE-ICD or European Heart Failure Self-care Behaviour Scale or Hypertension Self-Care Profile or HBP SCP or Duke Activity Status Index or DASI or Cardiac anxiety questionnaire or Cardiac Depression Scale or GYPES-CHD or VALIOSA or Control Attitudes Index or Cardiac distress inventory or Angina-related Limitations at Work Questionnaire or ALWQ).tiab.
8.	(Coronary Revascularisation Outcome Questionnaire or CROQ or Cardiac Event Threat Questionnaire or CTQ or Cardiac Health Profile or CHP or Multidimensional Index of Life Quality or MILQ or ACHD PRO or CHD-TAAQOL).tiab.

9.	(PedsQl cardiac module or Pediatric Cardiac QOL Inventory or CHAT or ConQol or Cardiac Health Profile of Congestive Heart Failure or CHPchf or CaReQol CHD or CHAT or CHF-PROM or Chronic Heart Failure Questionnaire or CHFQ or Heart Failure Functional Status Inventory or HFFSI).tiab.
10.	(Heart Failure Symptom Checklist or Kansas City Cardiomyopathy Questionnaire or KCCQ or Left Ventricular Dysfunction Questionnaire or LVD-36 or Minnesota Living with Heart Failure or MLHF or Quality of Life Questionnaire in Severe Heart Failure or QLQ-SHF or Traditional Chinese Medicine inquiry or TCM inquiry or Heart Transplant Stressor Scale).tiab.
11.	(Rotterdam Quality of Life Questionnaire or Heart Valve Disease Impact on daily life or QLICH-HY or Angina Pectoris Quality of Life Questionnaire or APQLQ or CLASP or HeartQol or Quality of Life Index or QLI or QLICH-CHD or Seattle Angina Questionnaire or SAQ19 or Short version of the Seattle Angina Questionnaire or SAQ7 or Summary Index for the Assessment of Quality of Life in Angina Pectoris or LVAD Stressor Scale or MacNew Heart Disease Questionnaire or QLMI-2 or Myocardial Infarction Dimensional Assessment Scale or MIDAS or Quality of my Life Questionnaire or Cardiff Cardiac Ablation PROM).tiab.
12.	(Toronto Aortic Stenosis Quality of Life Questionnaire or TASQ or Arrhythmia-Specific questionnaire in Tachycardia or ASTA or Mayo Atrial Fibrillation-Specific Symptom Inventory or MAFSI or Cardiac Surgery Symptom Inventory or CSSI or Cardiac Symptom Survey or Heart Surgery Symptom Inventory or HSSI or Symptoms of Illness Score or SOIS or Cardiac Symptoms Scale or Heart Failure Somatic Awareness Scale or HFSAS or Memorial Symptom Assessment Scale-Heart Failure or MSAS-HF or San Diego Heart Failure Questionnaire or SDHFQ or SSQ-HF or WHO Rose Angina Questionnaire or Atrial Fibrillation Knowledge Assessment Tool or AFKAT or Atrial Fibrillation Knowledge Scale or Jessa Atrial fibrillation Knowledge Questionnaire or JAKQ).tiab.
13.	(Knowledge about Atrial Fibrillation or KAFSP or Knowledge of Atrial Fibrillation test or KAF or Survey of Patient Knowledge or SATELLITE or Leuven Knowledge Questionnaire for Congenital Heart Disease or Barnason Efficacy Expectation Scale or Cardiac self-efficacy scale or Cardiovascular Management Self-efficacy or SE-ICD or European Heart Failure Self-care Behaviour Scale or Hypertension Self-Care Profile or HBP SCP or Duke Activity Status Index or DASI or Cardiac anxiety questionnaire or Cardiac Depression Scale or GYPES-CHDOR VALIOSA or Control Attitudes Index or Cardiac distress inventory or Angina-related Limitations at Work Questionnaire or ALWQ).tiab.
14.	1 or 2 or 3
15.	2 or 3
16.	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
17.	14 and 16
18.	15 and 16
19.	cardiovascular abnormalities/ or heart/ or cardiology/
20.	Heart Valve Prosthesis Implantation/ or Heart, Artificial/ or Heart Bypass, Left/ or Heart Valve Prosthesis/ or Heart Bypass, Right/ or Heart-Assist Devices/ or Coronary Artery Bypass, Off-Pump/ or Absorbable Implants/ or Defibrillators, Implantable/ or Transcatheter Aortic Valve Replacement/
21.	(Bioresorbable scaffolds or Left atrial appendage occlusion or Transcatheter mitral valve repair or Transcatheter mitral valve replacement or Leadless pacemaker or Subcutaneous implantable cardioverter-defibrillator or Surgical mitral valve* or Surgical aortic valve or Left Ventricular Assist Device).mp.
22.	patient reported outcome/ or quality of life/ or Health Adjusted Life Years/ or patient satisfaction/ or anxiety/ or Distress, Psychological/ or anger/ or fear/ or Locus of Control/ or Surveys/ or Questionnaires/
23.	(PROM or EuroQol or European QoL or EQ-5D or SF36 or SF12 or SF6 or SF-36 or SF-12 or SF-6 or IPAQ or PROMIS or AQoL-6D or Child Health Utility or CHU9D or EQ-5D-Y-3L or Health Utilities Index Mark 2 or HUI2 or Health Utilities Index Mark 3 or hui3 or 16D or 17D or Quality of Wellbeing Scale or QWB or

	Hospital Anxiety or HADS* or Short Form-36 or Specific Activity Scale or time trade-off or Pediatric Quality of Life Inventory or PEDsQL or WHOQOL-BREF or Schedule for the Evaluation of Individualised Quality of Life or Sickness Impact Profile).mp.
24.	(Duke Activity Status Index or HeartQoL Questionnaire or Multidimensional Index of Life Quality or Quality of Life Index Cardiac version or Quality of Life Instruments for Chronic Diseases coronary heart disease or AF-QoL Questionnaire or Arrhythmia-specific Questionnaire in Tachycardia or Atrial Fibrillation Effect on Quality-of-Life Questionnaire or Patient Perception of Arrhythmia Questionnaire or Cardiac Health Profile of Congestive Heart Failure or Care-Related Quality of Life survey for Chronic Heart Failure or Chronic Heart Failure Questionnaire or Congenital Heart Disease-TNO or Fragebogen zur Erfassung or Heart Valve Disease Impact on daily life or Heart Failure Somatic Awareness Scale or Kansas City Cardiomyopathy Questionnaire or Kansas City Cardiomyopathy Questionnaire or KCCQ-12 or Left Ventricular Dysfunction Questionnaire or Memorial Symptom Assessment Scale-Heart Failure or Minnesota Living with Heart Failure Questionnaire or Quality of Life Questionnaire in Severe Heart Failure or Symptom Status Questionnaire Heart Failure or Angina-related Limitations at Work Questionnaire or Angina Pectoris Quality of Life Questionnaire or Cardiovascular Limitations Symptoms Profile or Myocardial Infarction Dimensional Assessment Scale or Quality of Life Index or Quality of Life Questionnaire or Seattle Angina Questionnaire or Summary Index for the Assessment of Quality of Life in Angina Pectoris or Rose Angina Questionnaire or heart-focused anxiety or Cardiac Anxiety Questionnaire or Minnesota Living with Heart Failure Questionnaire).mp.
25.	(Patient Perception of Arrhythmia Questionnaire or PPAQ or AFImpact or AF-QoL or Atrial Fibrillation Effect on Quality-of-Life or AFEQT or Atrial Fibrillation Quality of Life Questionnaire or AFQLQ or Quality of life in AF patients or QLAF or University of Toronto Atrial Fibrillation Severity Scale or AFSS or Modified Postoperative Recovery Profile questionnaire or PRP-CABG or Coronary Revascularisation Outcome Questionnaire or CROQ or Cardiac Event Threat Questionnaire or CTQ or Cardiac Health Profile or CHP or Multidimensional Index of Life Quality or MILQ or Quality of Life Index-Cardiac Version or QLI-CV or ACHD PRO or CHD-TAAQOL or PedsQl cardiac module or Pediatric Cardiac QOL Inventory or CHAT or ConQol or Cardiac Health Profile or CHPchf or CaReQol CHD or CHAT or CHF-PROM or Chronic Heart Failure Questionnaire or CHFQ or Heart Failure Functional Status Inventory or HFFSI or Heart Failure Symptom Checklist or Kansas City Cardiomyopathy Questionnaire or KCCQ or Left Ventricular Dysfunction Questionnaire or LVD-36 or Minnesota Living with Heart Failure or MLHF or Quality of Life Questionnaire in Severe Heart Failure or QLQ-SHF or Traditional Chinese Medicine inquiry or TCM inquiry or Heart Transplant Stressor Scale or Rotterdam Quality of Life Questionnaire or Heart Valve Disease Impact on daily life or QLICH-HY or Angina Pectoris Quality of Life Questionnaire or APQLQ or Cardiovascular Limitations Symptoms Profile or CLASP or HeartQol or Quality of Life Index or QLI or QLICH-CHD or Seattle Angina Questionnaire or SAQ19 or Short version of the Seattle Angina Questionnaire or SAQ7 or Summary Index for the Assessment of Quality of Life in Angina Pectoris or LVAD Stressor Scale or MacNew Heart Disease Questionnaire or QLMI-2 or Myocardial Infarction Dimensional Assessment Scale or MIDAS or Quality of my Life Questionnaire or Cardiff Cardiac Ablation or Toronto Aortic Stenosis Quality of Life Questionnaire or TASQ or Arrhythmia-Specific questionnaire in Tachycardia or ASTA or Mayo Atrial Fibrillation Specific Symptom Inventory or MAFSI or Cardiac Surgery Symptom Inventory or CSSI or Cardiac Symptom Survey or Heart Surgery Symptom Inventory or HSSI or Symptoms of Illness Score or SOIS or Cardiac Symptoms Scale or Heart Failure Somatic Awareness Scale or HFSAS or Memorial Symptom Assessment Scale Heart Failure or MSAS-HF or San Diego Heart Failure Questionnaire or SDHFQ or WHO Rose Angina Questionnaire or Atrial Fibrillation Knowledge Assessment Tool or AFKAT or Atrial Fibrillation Knowledge Scale or Jessa Atrial fibrillation Knowledge Questionnaire or JAKQ or Knowledge about Atrial Fibrillation or KAFSP or Knowledge of Atrial Fibrillation test or KAF or Survey of Patient Knowledge or SATELLITE or Leuven Knowledge Questionnaire for Congenital Heart Disease or Barnason Efficacy Expectation Scale or Cardiac self-efficacy scale or Cardiovascular Management Self-efficacy or SE-

	ICD or European Heart Failure Self-care Behaviour Scale or Hypertension Self-Care Profile or HBP SCP or Duke Activity Status Index or DASI or Cardiac anxiety questionnaire or Cardiac Depression Scale or GYPES-CHD or VALIOSA or Control Attitudes Index or Cardiac distress inventory or Angina-related Limitations at Work Questionnaire or ALWQ).mp.
26.	(Coronary Revascularisation Outcome Questionnaire or CROQ or Cardiac Event Threat Questionnaire or CTQ or Cardiac Health Profile or CHP or Multidimensional Index of Life Quality or MILQ or ACHD PRO or CHD-TAAQOL).mp.
27.	(PedsQl cardiac module or Pediatric Cardiac QOL Inventory or CHAT or ConQol or Cardiac Health Profile of Congestive Heart Failure or CHPchf or CaReQol CHD or CHAT or CHF-PROM or Chronic Heart Failure Questionnaire or CHFQ or Heart Failure Functional Status Inventory or HFFSI).mp.
28.	(Heart Failure Symptom Checklist or Kansas City Cardiomyopathy Questionnaire or KCCQ or Left Ventricular Dysfunction Questionnaire or LVD-36 or Minnesota Living with Heart Failure or MLHF or Quality of Life Questionnaire in Severe Heart Failure or QLQ-SHF or Traditional Chinese Medicine inquiry or TCM inquiry or Heart Transplant Stressor Scale).mp.
29.	(Rotterdam Quality of Life Questionnaire or Heart Valve Disease Impact on daily life or QLICH-HY or Angina Pectoris Quality of Life Questionnaire or APQLQ or CLASP or HeartQol or Quality of Life Index or QLI or QLICH-CHD or Seattle Angina Questionnaire or SAQ19 or Short version of the Seattle Angina Questionnaire or SAQ7 or Summary Index for the Assessment of Quality of Life in Angina Pectoris or LVAD Stressor Scale or MacNew Heart Disease Questionnaire or QLMI-2 or Myocardial Infarction Dimensional Assessment Scale or MIDAS or Quality of my Life Questionnaire or Cardiff Cardiac Ablation PROM).mp.
30.	(Toronto Aortic Stenosis Quality of Life Questionnaire or TASQ or Arrhythmia-Specific questionnaire in Tachycardia or ASTA or Mayo Atrial Fibrillation-Specific Symptom Inventory or MAFSI or Cardiac Surgery Symptom Inventory or CSSI or Cardiac Symptom Survey or Heart Surgery Symptom Inventory or HSSI or Symptoms of Illness Score or SOIS or Cardiac Symptoms Scale or Heart Failure Somatic Awareness Scale or HFSAS or Memorial Symptom Assessment Scale-Heart Failure or MSAS-HF or San Diego Heart Failure Questionnaire or SDHFQ or SSQ-HF or WHO Rose Angina Questionnaire or Atrial Fibrillation Knowledge Assessment Tool or AFKAT or Atrial Fibrillation Knowledge Scale or Jessa Atrial fibrillation Knowledge Questionnaire or JAKQ).mp.
31.	(Knowledge about Atrial Fibrillation or KAFSP or Knowledge of Atrial Fibrillation test or KAF or Survey of Patient Knowledge or SATELLITE or Leuven Knowledge Questionnaire for Congenital Heart Disease or Barnason Efficacy Expectation Scale or Cardiac self-efficacy scale or Cardiovascular Management Self-efficacy or SE-ICD or European Heart Failure Self-care Behaviour Scale or Hypertension Self-Care Profile or HBP SCP or Duke Activity Status Index or DASI or Cardiac anxiety questionnaire or Cardiac Depression Scale or GYPES-CHDOR VALIOSA or Control Attitudes Index or Cardiac distress inventory or Angina-related Limitations at Work Questionnaire or ALWQ).mp.
32.	19 or 20 or 21
33.	20 or 21
34.	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
35.	32 and 34
36.	33 and 34
37.	limit 36 to english language
38.	limit 37 to yr="2000 -Current"

A.5.3. Diabetes search strategy

A.5.3.1. CINAHL 02-03-2023

	CINAHL
S1	AB "closed loop" or "closed-loop" or "artificial pancreas" or "bionic pancreas" or "automated insulin delivery" or "automated insulin delivery system*" or "closed loop insulin delivery" or "closed-loop insulin delivery" or "control-iq" or "minimed 670G" or "minimed 780G" or "CamAPS FX" or "Diabeloop DBLG1"
S2	AB (diabetes or "type 1 diabetes" or "type 2 diabetes" or "diabetes mellitus")
S3	MH "Diabetes Mellitus+") OR (MH "Diabetes Mellitus, Type 2") OR (MH "Diabetes Mellitus, Type 1+")
S4	(MH "Insulin Infusion Systems")
S5	S2 OR S3 OR S4
S6	S1 AND S5

A.5.3.2. Medline OVID 02-03-2023

	Medline OVID
1	("closed loop" or "closed-loop" or "artificial pancreas" or "bionic pancreas" or "automated insulin delivery" or "control-iq" or "minimed 670G" or "minimed 780G" or "CamAPS FX" or "Diabeloop DBLG1").tw.
2	(diabetes or "type 1 diabetes" or "type 2 diabetes" or "diabetes mellitus").tw.
3	exp Diabetes Mellitus, Type 2/ or exp Diabetes Mellitus/ or exp Diabetes Mellitus, Type 1/ or exp Insulin Infusion Systems/
4	2 or 3
5	1 and 4
6	limit 5 to "review articles"
7	5 not 6
8	limit 7 to yr="2013 - 2023"

A.5.3.3. Cochrane 02-03-2023

	Cochrane
#1	(("closed loop" or "closed-loop" or "artificial pancreas" or "bionic pancreas" or "automated insulin delivery" or "automated insulin delivery system*" or "closed loop insulin delivery" or "closed-loop insulin delivery" or "control-iq" or "minimed 670G" or "minimed780G" or "CamAPS FX" or "Diabeloop DBLG1")):ab
#2	((diabetes or "type 1 diabetes" or "type 2 diabetes" or "diabetes mellitus")):ti
#3	MeSH descriptor: [Diabetes Mellitus] explode all trees
#4	MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees
#5	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#6	MeSH descriptor: [Insulin Infusion Systems] explode all trees
#7	#2 OR #3 OR #4 OR #5 OR #6
#8	#1 AND #7

A.6 Poster presentations

PATIENT-REPORTED OUTCOME MEASURES IN CLOSED-LOOP TRIALS – A SYSTEMATIC REVIEW

UNIVERSITY OF GOTHENBURG

Degree project, program in medicine at The Sahlgrenska Academy. Part of the CORE-MD project.
Student: Ivan Gibanica, Supervisor: Assoc. Prof. John Chaplin, Institute for Clinical Sciences

For additional information, please contact: Ivan Gibanica, gusgibiv@student.gu.se

Background

Patient-reported outcome measures (PROMs) are standardized questionnaires used to measure health outcomes from the patient's perspective. PROMs have seen a recent increase in use, however, there is a lack of knowledge concerning the use of PROMs in clinical trials of medical devices. This review is part of a larger project aimed at improving the regulatory science concerning medical devices in the European Union.

Aims

To describe how PROMs have been used to evaluate closed-loop insulin delivery systems in clinical trials on patients with diabetes.

- Which PROMs are being used?
- What domains are being measured?
- What population sizes are being used to make assessments between devices?
- What measures of clinically important difference are being used?
- What differences are there in studies after EU approval (CE mark) different to those before approval?

Methods

A systematic review was conducted according to the PRISMA guidelines. Studies to be included were clinical trials of closed-loop insulin delivery systems in patients with diabetes, using patient-reported outcome measures with at least 12 weeks of follow-up. OVID Medline, Cochrane and CINAHL were searched. 1630 abstracts were screened for eligibility, and 265 articles were selected for full-text screening. Results were narratively synthesized using Microsoft Excel.

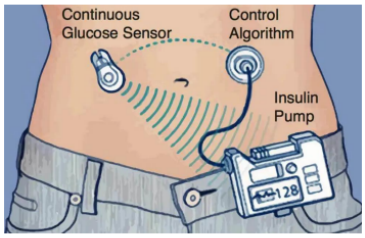


Table 1 – Outcome domains identified in included studies

Outcome	N
Diabetes-specific quality of life	10
General quality of life	5
Diabetes specific distress	15
General emotional distress	2
Treatment satisfaction	25
Fear of hypoglycaemia	22
Hypoglycaemia awareness	8
Sleep quality/sleepiness	11
Depression	1
Cognitive functioning	1
Coping	1

N = number of times an outcome was measured in the included studies.

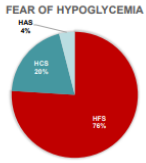
Results

35 studies included in final review
5.2 months Average follow-up
58 patients Median sample size Range: 5 - 302
40 PROMs divided into 11 domains

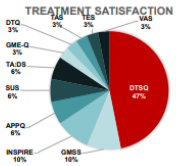
Treatment satisfaction and fear of hypoglycaemia were the most commonly measured outcomes. Treatment satisfaction was measured in various ways, with both standardised PROM instruments and with non-standardised single questions.

Questionnaire response rates were generally high. Thresholds for clinically significant differences in outcomes were available in five studies - one study provided MCIDs and four calculated effect sizes. 24 studies reported statistically significant differences in PROs after closed-loop therapy.

Patient groups were not included in the choice of outcome measures used. Follow-up durations were longer prior to EU approval, with observational studies more common after release than before.



PROMs measuring fear of hypoglycaemia



PROMs measuring treatment satisfaction

Conclusion

PROMs are more frequently used as secondary outcomes (25/35). The most commonly investigated domains are fear of hypoglycaemia and treatment satisfaction, which seem to be the two most useful concepts when evaluating patient-reported outcomes related to closed-loop devices. Further research should be conducted, using expert and patient representatives to reach consensus on whether these outcomes are the most important, and whether other important outcomes are lacking.

The generally high response rates suggest that PROMs are an acceptable burden to study participants. The lack of clearly defined methods to measure the clinically significant differences, and the reliance on statistically significant differences, makes it difficult for Notified bodies to use PROM data.

Take home message

- PROMs are usually secondary outcomes
- Clinical significance has rarely been determined
- Fear of hypoglycaemia is often included
- Treatment satisfaction is often measured but not in a standardised method.
- Many PROMS could be used but are not used

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ABSTRACTS

30th Annual Conference of the International Society for Quality of Life Research

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(2050) A Review of MCID in relation to Patient-Reported Outcome Measures used to evaluate orthopedic, high-risk implantable medical devices and surgeries

John Chaplin, PhD, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; Ola Rolfson, MD PhD, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Aims: The aim of this systematic review is to evaluate the utility of Patient-Reported Outcome Measures (PROMS) in the assessment of orthopedic surgery and medical implants. This study is part of a wider European CORE-MD (Coordinating Research and Evidence for Medical Devices) study which addresses regulatory improvement. **Methods:** Following a PROSPERO registration, we performed a literature search of MEDLINE, CINAHL, the Cochrane trials database and European registries for clinical and post-market studies (January 2000–June 2022) of orthopedic medical implants, where PROMS had been used. Search strings were developed using keywords, MeSH terms, and names of PROM instruments. We retrieved English-language articles reporting evaluation of hip and knee implant surgeries with at least 3 months follow-up. For this report we focus on those studies that identified measures of minimal clinically important difference (MCID). **Results:** We identified 868 studies describing knee or hip surgeries (knee 528; hip 340; knee and hip 109) with at least a three-month follow-up. The CONSORT Statement recommends that studies report results beyond p values and include treatment effect(s) and precision measures. Of the 868 studies, 85 reported MCID, and these were full-text reviewed for the current report. The most frequently used PROMs were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) used in 51 studies, the Harris Hip Score in 49 studies, and the EQ-5D in 35 studies. MCID was calculated based on different approaches, both distribution-based and anchor-based. The distribution-based approaches were built upon the statistical properties of the study's results. Two anchor methods were used: receiver operating characteristic (ROC) curves and the change difference. The anchor items varied, as did the number of items used and the number of points on the response scale. Differences in the MCID levels used were noted in several PROM instruments. **Conclusion:** Although it was expected that the majority of implementation studies using PROMs would not report or define a MCID, this study also shows that, where MCID is reported, there are differences in the thresholds used and methods of calculation. These differences will be discussed in terms of differences in the patient population, baseline levels, patient expectations, and the anchors used.

CORE-MD

CORE-MD, Coordinating Research and Evidence for Medical Devices, aims to translate expert scientific and clinical evidence on study designs for evaluating high-risk medical devices into advice for EU regulators.

For more information, visit: www.core-md.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 965246.