Improving cardiovascular care and outcomes: data variables, definitions and capture across geographies

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Publications

Chapter 1 of this thesis comprises the following publication by the candidate:

1. **Bhatty A**, Wilkinson C, Sydes M, Gale CP. Defining the need for cardiovascular event definitions. *Eur Heart J Qual Care Clin Outcomes*. 2024;10(2):105-107. doi:10.1093/ehjqcco/qcae008

2. Wilkinson C, **Bhatty A**, Smith AB, Dwight J, Sanders J, Gale CP. Embracing the promise of patient reported outcome measures in cardiology. *Eur Heart J Qual Care Clin Outcomes*. 2024;10(8):651-652. doi:10.1093/ehjqcco/qcae073

Chapter 3, 4, 5 and 6 of this thesis comprises of the following publications by the candidate:

1. **Bhatty A**, Wilkinson C, Aktaa S, et al. Outcome measures for randomised clinical trials and multicentre observational studies of cardiovascular diseases published in major clinical journals: systematic review and evidence mapping. Heart. 2025 Jun 27:heartjnl-2025-326045. doi: 10.1136/heartjnl-2025-326045. Epub ahead of print. PMID: 40533147.

2. **Bhatty A**, Wilkinson C, Batra G, et al. Standardised and hierarchically classified heart failure and complementary disease monitoring outcome measures: european Unified Registries for heart Care evaluation and randomised trials (EuroHeart). *Eur Heart J Qual Care Clin Outcomes*. Published online October 9, 2024. doi:10.1093/ehjqcco/qcae086

3. Wilkinson C, **Bhatty A**, Batra G, et al. Definitions of clinical study outcome measures for cardiovascular diseases: the European Unified Registries for Heart Care Evaluation and Randomized Trials (EuroHeart). *Eur Heart J*. 2025;46(2):190-214. doi:10.1093/eurheartj/ehae724

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Abstract

Introduction

Cardiovascular (CVD) disease represents a significant health and economic burden. Adherence to guideline indicated medical therapy is associated with improved outcomes and quality of life. An avenue for further gains in mortality and morbidity is the adoption of standardised outcome definitions for both clinicians reported outcomes (CROs) and patient reported outcome measures (PROMs) in both research and routine care. Implementing such standardised outcomes may be possible within the wider framework of an international unified registry across Europe.

In this thesis my aim was to create an internationally derived catalogue of standardised cardiovascular outcome measures that includes PROMs for the common CVD.

Methods

Both a systematic and scoping review on CROs and PROMs (alongside contemporary qualitative assessment of PROMs) were performed. These were used to inform consensus work to develop a catalogue of defined, internationally derived cardiovascular outcome measures using the modified Delphi method.

Following feedback from delegates we conducted a separate modified Delphi exercise to collate a checklist evaluating the feasibility of implementing PROMs in a variety of settings.

Results

The systematic review demonstrated heterogeneity in CROs and variation in composite outcome component selection. Similarly, the scoping review showed that most HRQoL PROMs require further validation studies prior to routine use. The final defined candidate list includes 9 PROMs that were ranked highest and

25 mandatory and 50 optional CROs across the five domains. The feasibility checklist included eight unique candidate items.

Discussion

I present two catalogues of internationally derived definitions for CROs and PROMs for a range of common CVD, and a checklist that evaluates the feasibility of implementing PROMs prior to use. These structured catalogues may be used to facilitate high-quality observational and randomised research and enable care to be more patient centred.

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List of abbreviations

ACS	Acute Coronary Syndrome
ADAPTABLE	Aspirin Dosing: A Patient Centric Trial Assessing Benefits and Long Term Effectiveness
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillaton Effect on Quality of Life
AFHLQ	Atrial Fibrillation Health Literacy Questionnaire
AF-QOL	Quality of Life Questionnaire for patients with Atrial Fibrillation
AFSS	Toronto Atrial Fibrillation Severity Scale of Quality of Life
AHA	American Heart Association
ARC	Academic Research Consortium
AS	Aortic Stenois
ASCVD	Atherosclerotic cardivoascular disease
ASIAN-HF	Asian Sudden Cardiac Death in Heart Failure registry
ASTA	Arrhythmia Specific Questionnaire in Tachycardia and Arrhythmia
BARC	Bleeding Academic Research Consortium
BNP	Brain Natriuretic Peptide
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CANVAS	Canaglifllozin and Cardiovascular and Renal Events
CARDS	Cardiology Audit and Registration Data Standards
CaReQoL CHF	Care Related Quality of Life Survey For Chronic Heart Failure
CCS	Canadian Cardiovascular Score

CFA	Confirmatory Factor Analysis
CHAT	Chronic Heart Failure Assessment Tool
CHFQOLQ-20	Chronic Heart Failure Related Quality of Life Questionnaire
CI	Confidence Interval
CKD	Chronic Kidney Disease
COA	Clinical Outcome Assessment
COMET	Core Outcome Measures for Effectiveness Trials
COMPare	The Centre for Evidence Based Medicine Outcome Monitoring Project
CONSORT	Consolidated Standards of Reporting Trials
COS	Core Outcome Set
COSMIN	Consensus based Standards for the selection of health Measurement Instruments
CROs	Clinician Reported Outcomes
CRT	Cardiac Resynchronisation Therapy
CTT	Classical Test Theory
CVD	Cardiovascular disease
DELIVER	Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction
DSG	Data Science Group
EF	Ejection Fraction
EFA	Exploratory Factor Analysis
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EMPRO	Evaluating the Measurement of Patient Reported Outcomes
EORP	EURObservational Research Program

EORTC	European Organisation for Research and Treatment for Cancer
EQ5D	EuroQol-5 Dimension
ESC	European Society of Cardiology
ESCAPE	Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness
EuroHeart	the European Unified Registries for Heart Care Evaluation
EXCEL	Evaluation of XIENCE verse Coronary Artery Bypass Surgery for Effectiveness of Left Main Revasularization
FACTOR3	Feasibility-items Checklist for assessing implementation characteristics of patient reported outcome measures in research, regulation and routine clinical care
FDA	Food and Drug Authority
GDP	Gross Domestic Product
GRADE	Grading of Recommendations Assessment Development and Evaluation
GRASP	Global Registries and Surveys Program
HF	Heart Failure
HFA	Heart Failure Association
HFiEF	Heart Failure with Improved Ejection Fraction
HRQoL	Health Related Quality of Life
ICC	Inter class correlation
ICD	Implantable Cardioverter defibrillator
ICHOM	International Consortium for Health Outcomes Measurement
IQR	Interquartile Range
IRT	Item Response Theory

ISPOR	International Society for Pharmacoeconomics and Outcomes Research
JAMA	Journal of American Medical Association
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVAD	Left Ventricular Assist Device
LVD-36	Left Ventricular Dysfunction Questionnaire
MACE	Major Adverse Cardiac Events
MacNew	MacNew Heart Disease Health Related Quality of Lfe
MDASI-HF	MD Anderson Symptom Inventory Heart Failure
MI	Myocardial Infarction
MID	Minimal Important Difference
MIDAS	Myocardial Infarction Dimensional Assessment Scale
MILQ	Multidimensional Index of Life Quality
MLHF	Minnesota Living with Heart Failure
NEI	National Eye Institute
NEJM	New England Journal of Medicine
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NOBLE	Nordic Baltic British Left Main Revascularisation Study
NYHA	New York Heart Association
ObsRO	Observer Reported Outcomes
ORBITA COSMIC	The Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia and Microvascular Resistance

PCI	Percutaneous Coronary Intervention
PCORI	Patient Centered Outcomes Research Institute
PerfO	Performance Outcome
PPAQ	Patient Perception Arrhythmia Questionnaire
PREMs	Patient Reported Experience Measures
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient Reported Outcomes
PROMIS Plus HF Profile	Patient Reported Outcome Measurement Information Systems Plus Heart Failure Profile
PROMs	Patient Reported Outcome Measures
PROTEUS	Patient Reported Outcomes Tools: Engaging Users and Stakeholders
QALY	Quality Adjusted Life Years
QI	Quality Indicator
QLAF	Atrial Fibrillation specific measure of Patient Reported Health Related Quality of Life
QLMI	Quality of Life After Myocardial Infarction
QLQ-C30	Core Questionnaire Quality of Life Questionnaire
QLQ-SHF	Quality of Life in Severe Heart Failure
RELAX-AHF	Relaxin for the Treatment of Acute Heart Failure
Re-QOL-10	Recovering Quality of Life
SAQ	Seattle Angina Questionnaire
SCL	Toronto AF symptoms checklist

SCTI	Standardized data Collection for cardiovascular Trials Initiative
SD	Standard Deviation
STEMI	ST elevation Myocardial Infarction
TAVI	Transcatheter Aortic Valve Implantation
UK	United Kingdom
US	United States
Val-HeFT	Valsartan Heart Failure Trial
VARC	Valve Academic Research Consortium
WG	Working Group

Chapter 1
Introduction

The prevalence and incidence of cardiovascular disease (CVD) across Europe is rising (1) (2) and despite the success of guideline indicated care in improving morbidity and mortality,(1, 3, 4) these figures are forecasted to increase.(5, 6) An avenue for further gains in improving morbidity, mortality and quality of life for patients with CVD may be predicated on the development of novel therapies that are translated appropriately to real world practice by leveraging an existing international unified registry such as the European Unified Registries for Heart Care Evaluation and Randomized Trials (EuroHeart).(7, 8)

Central to developing safe and effective novel therapies is the adoption of clearly defined standardised outcomes by contemporary trials that are important to both patients and healthcare providers.(9) This includes clinician reported outcomes (CROs) and patient reported outcome measures (PROMs).(7, 10) Inappropriately selected CROs that have heterogenous definitions may skew the results of a trial, lead to inconsistent findings in comparison with similar trials and therefore obscure the accurate interpretation of an intervention's safety and efficacy.(9) Standardising patient outcomes involves adopting questionnaires that have robust psychometric properties as PROMs are more accurate, reliable and reproducible in portraying a patient's symptoms and quality of life over a clinician's interpretation and are an independent predictor of poor outcomes.(11-13)

In this thesis, I will look to standardise the use of CROs and PROMs for commonly occurring CVD conditions, within the EuroHeart framework, using a modified Delphi method that informs the multi-disciplinary expert consensus with a contemporary literature review. In **Chapter 1**, I will provide a broad overview of the health and economic burden of CVD, what CROs and PROMs are and the case for standardisation, limitations of existing CVD outcome catalogues and limitations of existing European registries. I will report the findings of my literature review into CROs and PROMs in **Chapter 3** and **Chapter 6**, respectively. The expert consensus methodology in standardising outcomes and their results is provided in **Chapter 4, Chapter 5 and Chapter 7.**

The results of an additional project that developed a checklist to evaluate the feasibility of implementing a PROM is provided in **Chapter 8** with my critical discussion of the MD provided in **Chapter 9.**

1.1 Burden of cardiovascular disease

In this section I will provide an overview of the health and economic burden of CVD in Europe and why improving CVD outcomes are important.

1.1.1 Health burden of cardiovascular disease

Cardiovascular disease remains a leading cause of morbidity and mortality worldwide despite advances in medical care.(1) In Europe, CVD accounted for over four million deaths, which is just under half of all recorded deaths in one year.(1) Although CVD burden is projected to increase across Europe due to an ageing population, middle income countries have around 30% greater incidence of CVD compared to higher income countries, illustrating an unequal distribution of CVD burden across Europe.(2) Furthermore, an estimated 85 million disability adjusted life years are lost due to ill health, disability and early death each year within the European Union.(5, 14)

1.1.2 Economic burden of CVD

Similarly, CVD represents a significant financial burden within Europe. In 2021 alone, it was estimated that €282 billion was lost within European Union nations due to CVD with healthcare costs accounting for 46% of the total, and productivity losses 17%.(15) There is variation in CVD health expenditure across countries, which ranges from 2.9% of gross domestic product (GDP) to 11.9% in middle and high income countries, respectively. Despite the CVD burden disproportionally affecting middle income countries the variation in healthcare expenditure has the potential to deepen health disparities across Europe and worldwide.(15, 16) Moreover, healthcare expenditure is forecasted to increase further due to an ageing population and advances in cardiovascular

care that leads to patients living longer with chronic CVD.(5, 6) Therefore CVD presents a challenge for healthcare policy makers at present and in the near future.

1.1.3 Variations of cardiology care and outcomes across Europe

Implementing evidence based therapies that inform guideline indicated care have significantly improved mortality and morbidity for patients with CVD over recent years.(1, 3, 4) However, translating guideline indicated therapy into real world practice has been inconsistent across Europe. Registry data demonstrates that adherence to contemporary clinical guidelines is variable within and between countries.(17, 18) Bridging this gap between guideline indicated care and real-world practice has been shown to decrease cardiovascular events and improve care.(19, 20) There is an opportunity to improve cardiovascular outcomes by improving adherence to guideline directed care.

1.1.4 Summary

Cardiovascular disease represents a major healthcare and economic problem that is important for patients, healthcare professionals and policymakers across Europe and worldwide. Consequently, there is a need for safe and effective evidence-based CVD interventions evaluated by robust outcome measure definitions that are implemented into real world practice. Utilising both CROs and PROMs represents the totality of health outcome research and may contribute to generating novel interventions to improve both CVD mortality and morbidity.(7)

1.2 Outcomes

It is important to define what CROs and PROMs are, and how they may be used within evidence generation as this is core to the MD thesis.

1.2.1 Clinician reported outcomes

The United States (US) Food and Drug Authority (FDA) classifies CROs and PROMs as specific types of clinical outcomes assessment that is defined as evaluating clinical outcomes made by a broad range of assessors **(Table 1.1**).(21) For the purposes of this thesis, only CROs and PROMs will be discussed.

Table 1.1. The four types of clinical outcomes assessment (COA) as per the US FDA guidance

Type of COA	Definition
CROs	A measurement based on a report that comes from a trained health-care professional after observation of a patient's health condition
PROMs	A measurement that is reported directly from the patient about their health status and condition without interpretation from anyone else
ObsRO	A measurement of a patient's health condition based on observable signs, events or behaviours reported by someone other than the patient or a health professional
PerfO	A measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions

Abbreviations: CROs: clinician reported outcomes; PROMs: patient reported outcome measures; ObsRO: observer reported outcomes; PerfO: performance outcome.

Importantly, CROs includes long standing outcomes used within CVD research such as all-cause mortality, myocardial infarction (MI) and stroke. CROs, otherwise known as endpoints, form an integral part of studies by informing the number of patients needed to conduct randomised clinical trials (RCTs), for example, but also used to ascertain if a trial was successful in achieving its main aims and objectives (as primary endpoints, or outcome measures). (22) Guidance for conducting trials, stipulate the *a priori* selection of CROs alongside

their full definitions to ensure the results are easily interpretable and accurately reported. (23)

1.2.2 Patient reported outcome measures

PROMs are defined as a patient's report on their own health condition status without any interpretation from a clinician or anyone else, through a carefully curated questionnaire or survey.(24) The items assessed are usually symptoms, health related quality of life (HRQoL), resumption of work and functional status(25) and so incorporates the patient voice directly into their care.(26)

This contrasts with the CROs, or 'traditional' outcomes, used within cardiology research which requires interpretation / evaluation by a clinician. However not all patient data qualifies as a patient reported outcome. As an example, questionnaires that evaluate the patient's perception of their healthcare experience (also known as patient reported experience measures; PREMs) are not considered during this MD.(27) Data garnered through smart devices such as heart rate variability or feedback in free text form from patients are not considered patient reported outcomes,(25) and is outside the scope of this MD. Further discussion on PROMs and their relative strengths and weaknesses are discussed in **section 1.4.5.**

1.2.3 Randomised controlled trials

This type of clinical study is designed to evaluate the potential benefits and harms of a proposed intervention (whether drug or medical device) on the target population.(28) A key aspect of RCTs is randomising prospective patients into typically two branches; the control arm (normal treatment or placebo) and the treatment arm (proposed intervention).(29) By blinding (or masking) both the patients and clinical researchers conducting the trial, RCTs reduce the likelihood of conscious or unconscious patient selection bias. Further treatment bias is also reduced by allowing patients with similar baseline characteristics to be enrolled in both the treatment and control arm.(22, 29) This means that any differences between the similar patient groups may be attributed to the

proposed treatment and thus results from RCTs are integral to informing clinical guideline recommendations.(30)

Importantly there are weaknesses associated with this study design. For example, RCTs are sometimes costly to run - especially when attempting to identify small differences between treatments arms. This may involve recruiting large number of patients over multiple countries to do so, thus highlighting its unsustainability. Additionally RCTs have limited generalisability of trial results to real world practice as certain patient groups (such as women) are usually underrepresented in trials with stringent eligibility criteria.(31)

1.2.4 Observational studies

Observational data, from cohort studies, mainly falls into two categories; descriptive and hypothesis generating for further testing in an RCT for example.(31) Describing the life cycle of a disease involves assessing its burden and evaluating current quality of care falls into the first category whereas hypothesis generation is mainly evaluating the associations between described exposures such as blood pressure on important CROs such as stroke.(28) Important sources of observational data comes from registries and electronic health records.(31) In contrast to RCTs, causality can rarely be inferred and even when controlling for important confounders (unmeasured variables that influence the cause and result of a trial,(22)) such as co-morbidity and treatment, conclusions from observational trials may be misleading.(32)

1.2.5 Registry based trials

Registry based trials or pragmatic trials leverage existing clinical registries to randomise and follow up prospectively recruited patients to a novel treatment.(33) Conducting registry based trials are usually significantly cheaper than traditional RCTs whilst also allowing for the results to be more generalisable as the inclusion criteria for prospective patients reflects what clinicians may encounter in real world practice.(33) Moreover, the addition of randomisation overcomes some of the potential biases and confounders that are present with traditional observational data.(31) An important consideration

to registry based trials, however, is enrolling sufficiently large numbers of patients to ascertain a treatment effect and ensuring the reliability and accuracy of the selected registry data as poor quality or high missingness of data may compromise its results.(31)

1.2.6 Clinical registries

Clinical registries are defined as the systematic collection of a minimum number of health-specific variables for patients with a certain condition, undergoing a particular procedure or those patients utilising a healthcare resource and the captured data is generally directly recorded by healthcare professionals into databases.(34) Thus clinical registries will capture outcomes of interest to healthcare professionals and serve a pre-defined purpose. Furthermore, the inclusion criteria for registries are generally broad with few exclusion criteria.(34)

Clinical registries serve multiple functions, namely they are an important source of observational data by highlighting the effectiveness of interventions in real world settings, offer further insight into the nature of the disease and how it impacts patients and generates important hypotheses for further study by highlighting associations between exposures and poor outcomes.(34-36) Another important function of clinical registries is its role in improving quality and safety of care, and these registries are termed clinical quality registries. I will discuss existing clinical registries that are operational across Europe in **section 1.6**.

1.2.7 Meta analysis

A meta-analysis is defined as a process of statistically synthesising the findings of multiple studies to calculate the absolute or overall effect of an intervention.(37) The statistical methods used account for differences in sample sizes, treatment effects and outcomes across included studies and involves a systematic review of the research question, outcome and data extraction from included studies, weighting and calculating effect sizes to give a final estimate

of the overall effect of an intervention.(38) They are also useful for identifying gaps in the literature.

1.3 Why standardising outcomes is important

In this section, I will present the case for standardising CROs for CVD.

1.3.1 Standardising clinician derived outcomes: Definitions determine results

The choice of primary outcome measure to evaluate the efficacy and effectiveness of an intervention and its definition can determine the results of RCTs. Outcome measures are typically cardiovascular events in cardiovascular trials, and their results can influence guideline recommendations and clinical practice.(22) For example, in the “Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL)” trial, peri-procedural MI was an important component of a primary composite outcome measure and differed in its definition to other studies.(39) As a consequence, PCI was found to be non-inferior to coronary artery bypass graft (CABG) surgery (hazard ratio for major adverse cardiac events [MACE] 0.93, 95% confidence interval (CI) [95% CI] 0.67 to 1.28, p=0.64). These results contributed to the European Society of Cardiology (ESC) guidelines for revascularisation in patients with left main stem disease that were considered at low to intermediate risk of peri-operative mortality according to their SYNTAX score.(30) However, subsequent *post hoc* analyses found that the rate of peri-procedural MI varied significantly according to the definition used and was significantly higher in the group that underwent percutaneous coronary intervention (PCI) compared to the CABG group according to more stringent definitions.(9, 40) Utilising a standardised definition of peri-procedural MI and other outcomes that is internationally derived can reduce uncertainty over the efficacy and safety of an intervention and reduce the need for large scale costly RCTs.

1.3.2 Limitations of composite outcomes

Composite outcome measures are a combination of two or more individual components that if either are present leads to a positive composite outcome.(22) They are useful when the expected incidence of each component is low, and provides logistical efficiency to detect a minimally clinically important

and statistically significant difference between randomised arms (as well as reducing the probability of a type two error). A type one error occurs when a study falsely posits that there is a statistical difference between groups of interventions where there is none and therefore rejecting the null hypothesis.(41) This error is sometimes referred to as a false positive and may occur in large sample sizes. A type two error occurs where a study falsely posits there is no statistical difference between groups of intervention where in reality there is, which is sometimes referred to as a false negative and may occur in small sample sizes where the expected incidence of an event is low.(41) Therefore, composite outcomes are important as they allow RCTs to be more feasible to conduct.(42) However they do have limitations: composites can lead to a loss of clarity over the mechanism of the effect, make comparability between trials more challenging, and clinical interpretation less straightforward.

1.3.2.1 Heterogeneity in component selection

Both the use of composites and their components in cardiovascular outcome trials have increased over time.(43) Increasing the number of components of a composite will also lead to a higher overall event rate. Notably there is wide heterogeneity in component selection of composites, even when investigating similar interventions of the same disease process.(44) This can make it challenging to interpret the conclusions of a study, especially when 'soft' outcomes with high event rates (such as urgent outpatient visits) are grouped together with 'hard' outcomes with fewer events (such as mortality).(45) Some 'soft' outcome measures may be harder to standardise, less important to healthcare providers and patients and are more subjective such as urgent outpatient visit whereas 'hard' outcomes such as all-cause mortality are more important to patients and objective.(45) The Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction (DELIVER) trial reported a primary composite of cardiovascular death and worsening heart failure, which was defined as either an urgent outpatient visit or an unplanned hospitalisation for heart failure.(46) Urgency of outpatient visits is subjective, with some clinicians favouring a more proactive role in managing a patient symptoms than others and therefore it is difficult to define. This in turn may lead to higher event rates which may influence the overall result of the trial.

A recent cross-sectional study of composites illustrated that as many as half of all composites for primary outcome measures incorporated a ‘soft’ outcome.(45) Additionally, these ‘soft’ or less clinically relevant outcome measures (such as revascularisation in both MI and stable angina trials) are more likely to determine the results of an overall composite outcome whereas ‘hard’ outcome measures (such as MI) were shown to contribute the least.(45) The decision to revascularize and its mode may differ between healthcare professionals and may contribute to higher event rates than an objective outcome measure such as MI.(9) It may be possible for two studies ostensibly investigating the same topic but differ in their conclusion due to the component selection and the subtleties of their outcome definition of their primary composite outcome measure as occurred between the EXCEL trial and the Nordic-Baltic-British-Left Main Revascularisation Study (NOBLE), which will be explained later in **section 1.3.2.3**.(39, 47)

Studies that incorporate ‘soft’ and ‘hard’ components may therefore be misinterpreted and hinder comparison between similar RCTs that investigate the same topic.

1.3.2.2 Meta analysis

Heterogenous outcome definitions may also alter meta-analysis findings and may skew the overall treatment effect concluded in a meta analysis. Bias in overall effect estimates may be introduced if the studies use the ‘same’ outcome measure that is inconsistently defined between studies,(48) especially if some definitions are more sensitive than others leading to artificially higher event rates, such as MI as discussed (**section 1.3.2.1**).The resulting variance between studies may also make pooled estimates of an intervention and hence the overall result of a meta-analysis less reliable.(9, 37)

1.3.2.3 Inconsistent findings

Using the same components within a composite such as MACE may lead to different results when definitions of MACE differ. This is illustrated in the NOBLE trial which, like EXCEL, randomised patients with coronary artery

disease to either PCI or CABG surgery. In both trials, all-cause mortality and stroke were components of MACE. Procedural MI was added in EXCEL, and non-procedural MI and repeat coronary revascularisation also formed part of the MACE composite in NOBLE. By five years, MACE was reported for 28% of the PCI group and 18% of the CABG surgery group (HR 1.51, 95%CI 1.13-2.00, p = 0.0044).(47) In contrast to EXCEL, the authors concluded that CABG surgery was superior to PCI despite using ostensibly the same primary composite outcome measure. It has been proposed that MACE should not be routinely used as a cardiovascular outcome measure – and if it is used, then the accompanying definitions must be standardised.(45)

1.3.3 The use of pre-defined outcome measures

The potential for bias is further increased if outcome measures are not pre-specified and fully reported. The Centre for Evidence Based Medicine Outcome Monitoring Project (COMPare) trial illustrated that overall outcome reporting in the manuscript was poor amongst publications in five reputable journals, with wide variation in the completeness of reporting pre-specified outcome measures.(49) Furthermore, on average five novel outcome measures were added during the conduct of the study without declaration. These issues may be mitigated through complete and transparent reporting of prespecified outcome measures.(9) To this end the 'Consolidated Standards of Reporting Trials' (CONSORT) statement was produced to improve the transparency of outcome reporting of trials by recommending a minimum set of items to be included in a report of a trial by way of a checklist.(23) The CONSORT checklist was recently updated to include the rationale behind the primary outcome selection and whether their definitions were in alignment with a pre-defined core outcome set (COS) within the methods section of a trial.(23)

1.3.4 Standardisation as the solution

There is an argument in favour of reporting cardiovascular outcomes in a manner that is more meaningful to clinicians, regulators, and patients. The standardisation of clinical variables and their definitions is central to this. Having a core outcome set of key cardiovascular outcome measures, carefully defined

and underpinned by the available evidence and aided by international support would enable more efficient evaluation and interpretation of the safety and efficacy of drug and device development and overcome reporting bias.(50)

An example is the Valve Academic Research Consortium (VARC) pre specified outcome measure definitions for transcatheter aortic valve implantation (TAVI).(51) A meta-analysis soon after its release demonstrated its wide adoption in the TAVI research community. This illustrates a desire for standardised definitions, and the potential speed of implementation.(52) Having a minimum core outcome set would not deter the use of more nuanced outcome variables and definitions to address specific populations and interventions.(50) But for studies investigating similar CVD processes there is an opportunity to standardise outcomes measures for wider use.(9)

1.3.5 Outcomes across different study designs

Standardised outcome measures may also be used for pragmatic trial designs such as registry-based trials. Outcomes for CVD morbidity and mortality has improved significantly over recent decades,(1, 3) predominantly due to the implementation of interventions and therapy tested in RCTs.(5) High quality RCTs continue to play a major role in evidence development primarily due to randomisation, which minimises bias and confounding of variables to allow a fair and meaningful comparison between therapies as mentioned in **section 1.2.3**.(42) However large RCTs are often complex and expensive to run which drives the use of composite outcome measures on highly selected patient populations. This limits the studys generalisability to real world patients.(42, 53)

In some circumstances registry based trials may be a feasible alternative as they embed randomisation into real world clinical registries to collect patient baseline characteristics, follow up period and outcomes leveraging existing registry platforms and electronic health records.(31) This allows for data to be generalisable at a much lower cost than running a traditional RCT. In order to run registry based trials that cover multiple geographies (and therefore multiple national registries), standardised outcome measures for CVD are needed.(31, 54)

1.3.6 Summary

- Primary outcome measures evaluate the efficacy and safety of a proposed intervention in RCTs. Implementation of such trials significantly improves CVD morbidity and mortality.
- Multiple definitions of the same CVD CRO, such as MI, may result in inconsistent findings in similar RCTs and therefore uncertainty over the effectiveness of a proposed intervention.
- Outcome measure definitions can therefore determine the overall result of an RCT which can impact guideline recommendations and therefore real-world patients.
- Inconsistent outcome definitions may also skew meta-analysis findings making them less reliable.
- Composite outcome measures use is increasing and allow CVD RCTs to be more feasible especially when the expected event rate of individual components is low.
- However common composite outcome measures such as MACE have wide heterogeneity in its component selection, even when investigating similar interventions of the same disease process. This makes interpretation and comparison between studies difficult.
- Furthermore, outcome measures are, sometimes, not pre-specified and fully reported in studies published in reputable journals which increases bias.
- Using a pre-specified minimum set of standardising CVD CROs may enable more efficient evaluation and interpretation of the safety and efficacy of drug and device development and overcome reporting bias.
- Standardising outcome measures that are internationally derived may facilitate the use of registry based trials that may be more feasible to run and provide more generalisable results than traditional RCTs.

1.4 Patient Reported Outcome Measures

In this section, I will discuss the different types of PROMs that exist, why they are important to measure and implement.

1.4.1 Types of PROMs

PROMs can be classified as generic or disease specific questionnaires. Generic PROMs evaluate general health concepts such as self-care or mobility and can therefore be used in a broad range of medical conditions. A well-known example of a generic PROM is the EuroQoL-5 dimension (EQ5D) questionnaire,(55) and the results assess overall HRQoL, quality of care and cost effectiveness of a treatment.(56) Results from generic PROMs may be aggregated to compare PROM data across different patient populations such as comparing patients with CVD with healthy controls which may not be possible for disease specific PROMs.(57)

Conversely disease specific PROMs are more detailed and nuanced to a particular patient population and investigates how aspects of a specific condition impacts specific outcomes such as symptom burden and are more sensitive to clinically meaningful change that a generic PROM may not detect.(27, 58) A well-known example within cardiology is the Kansas City Cardiomyopathy Questionnaire (KCCQ) that typically evaluates the specific impact of heart failure (HF) on important patient reported outcomes such symptoms (shortness of breath) and HRQoL.(59)

Both generic and domain specific PROMs provide a summary score that reflects the overall health status of the patient. If a PROM covers multiple domains (such as symptom burden, emotional wellbeing or HRQoL, then domain specific scores can be provided to provide further granularity. These scores may be used longitudinally in the same patient to assess the change in overall health status (or domain specific status) which can be of use in clinical monitoring.(60)

1.4.2 Health related quality of life

HRQoL refers to the impact that a disease or disorder has on a patient's overall perceived health and is a type of PROM that covers multiple domains. These

domains include physical, emotional and mental wellbeing and its scope in evaluating a patient's overall quality of life is more broad.(61) HRQoL PROMs may be generic or disease specific.(62)

HRQoL is important, as there is evidence that patients value better overall quality of life over additional life years gained from a CVD intervention.(62, 63) Consequently, patient advocacy groups such as the Patient-Centered Outcomes Research Institute (PCORI) advocate the measurement of HRQoL PROMs in clinical care and research.(64)

1.4.3 Why PROMs matter

1.4.3.1 Standardising patient outcome collection

There are multiple definitions for patient outcomes in the literature,(65, 66) but for the purpose of this MD it will be defined as the impact of the disease or intervention on outcomes that patient's care most about and in line with previous conceptual models posited by Wilson and Cleary that broadly encompasses three domains; symptom burden, functional health and HRQoL.(67) Existing methods to ascertain patient outcomes include PROMs and a clinician assessment or interpretation based on a patient's history.(24, 68)

Patient outcomes are increasingly important to trialists and regulators as the number of patients living with CVD has increased, driven in large part due to the success of guideline indicated treatment.(5) Chronic CVD can often deteriorate with significant symptoms affecting a patient's quality of life with the condition, also known as HRQoL,(69) and alongside clinical markers of disease inform a clinician's management plan across the common cardiovascular conditions. For example, significant angina burden, symptomatic atrial fibrillation (AF) and shortness of breath in HF that affects a patient's daily life may lead to interventional treatments such as PCI in obstructive coronary artery disease (CAD), catheter ablation in AF and cardiac resynchronisation therapy (CRT) HF as per clinical guidelines.(30, 70, 71) PROMs represent a more accurate, reliable and reproducible method of evaluating patient outcomes in comparison to a clinician's interpretation which will be demonstrated below.

1.4.3.2 Heterogeneity in a clinician's interpretation

Currently in routine practice outcomes for patients with CVD such as chest pains and shortness of breath are evaluated by clinicians and their interpretation of a patient's history during an episode of care. This is further classified using common scoring systems such as the Canadian Cardiovascular Score (CCS) classification.(72) Yet clinicians are poor at discerning the impact of a condition on a patient's daily life during a single episode of care(11) and often fail to recognise important symptoms such as angina.(73) For example, when comparing the angina scores using the CCS by both patients and clinicians, clinicians overestimated a patient's angina burden at baseline but underestimated the symptoms at twelve months follow up post revascularisation compared to the patient's evaluation.(73) This suggests bias in interpreting patient symptoms that can directly influence a patient's management both at baseline and at follow up, potentially leading to inappropriate use of guideline indicated care.(73). This may lead to over-treating such patients inappropriately at baseline but also not escalating care at follow up.

The subjectivity in reporting patient's symptoms may be compounded as such scoring systems have limited longitudinal reproducibility, even when scored by the same clinician,(12) and is subject to significant interobserver variability.(74) Previous studies have therefore cautioned against the use of scoring systems, such as the New York Heart Association (NYHA) classification, in assessing symptom burden and physical function alone, and advocate for researchers using the NYHA classification to also publish their inter and intra rater variability.(12)

In summary, using a clinician interpretation in evaluating patient outcomes may lead to heterogenous results, limited reproducibility, and is subject to bias.(73, 75)

1.4.3.3 Reliability of PROMs

PROMs represent a more standardised and reliable assessment of patient outcomes in comparison to a clinician's interpretation. For example, it is established that clinical guidelines for CRT implantation within heart failure are informed by a poor NYHA score (as well as imaging and biochemical

markers).(70) However, the NYHA is a clinician interpretation of the patient's HRQoL with HF and, alongside imaging and biochemical markers, can influence CRT implantation. Yet NYHA imprecisely assesses symptoms across the HF spectrum whereas the HF specific PROM was considered significantly more reliable as shown in a recent study.(75) This is concerning as current methods of ascertaining patient outcomes potentially lead to an underuse of evidence based HF therapies. Therefore, routine implementation of validated PROMs may reliably influence morbidity and mortality in clinical care.

1.4.3.4 Clinical monitoring and interpretation

The use of PROMs allows clinicians and patients to evaluate any change in patient scores relating to symptoms or limitations to their HRQoL over time. Once PROMs are embedded into routine care then multiple scores may be longitudinally collected for a single patient that demonstrates any change in health status scores from baseline which could more accurately reflect an improved or reduced HRQoL, for example.(60) This would be informative for clinical monitoring of patients and identifying those that require more intensive clinical surveillance and management compared to those that require less.(76) Use of PROMs may facilitate a more tailored approach to healthcare and improving clinic efficiency.

Obtaining patient's own views directly in routine clinical practice may better inform management practices as well as promoting share decision making in a more value based healthcare system.(58, 77) This may improve health inequalities at the individual but also at an organisational / regional level. At the individual level, feedback from PROMs scores can unmask symptoms that may have been missed in routine clinical history taking, especially mental health symptoms.(78) At the regional level comparing aggregated PROMs scores from various regions may drive further analysis of the cause of differing scores and complement existing quality improvement efforts to address the health inequalities.(79) There is therefore a need to incorporate standardised, easily reproducible PROMs in routine care, complimentary to existing investigations, that can accurately quantify patient concepts such as symptom burden and HRQoL. Providing international standards for the use of PROMs in CVD across Europe may improve patient care by reducing symptom burden for patients with chronic CVD.

1.4.3.5 Value based healthcare

Value based healthcare is a healthcare delivery model that encourages providers to improve patient outcomes relative to the cost of care provided and aims to enhance patient satisfaction, improve population health and ultimately reduce cost.(80) To achieve this, widespread adoption of PROMs is needed which will be explained in the section below.

1.4.3.6 Clinical registries and quality improvement

Moving to a more value-based healthcare system allows the patient perspective to be captured, by using PROMs, when evaluating quality and effectiveness of care by healthcare providers by way of patient reported outcome (PRO) performance measures or PRO quality indicators (QI).(81) Here PROM scores are embedded into routine care and collected nationally as part of a clinical registry and are usually portrayed as a percentage of attainment; the higher the percentage the better the care received. For example, in the United Kingdom (UK) the National Health Service (NHS) PROMs are employed routinely in elective hip and knee surgery and the aggregated scores are captured at baseline and in the post operative follow up period with the results informing healthcare provider performance to both patients and staff and support clinical decision making.(82) For departments with low percentage attainment of the QIs, and therefore presumed to be underperforming, there is evidence to suggest that publishing PRO performance measures led to quality improvement efforts.(83)

Furthermore, aggregating the overall PROMs scores of a population, known as group level, PROMs data may aid the interpretation of individual PROMs scores collected in routine care as it provides insight into what is considered normal for a general patient with that particular condition. This allows for comparison to the reference scores of the general population in terms of means and standard deviations.(60) One way to achieve this is through leveraging existing national and international CVD registries to incorporate widespread PROMs collection to aid quality improvement, benchmark quality across multiple healthcare providers and aid interpretation of individual PROMs score.

As such CVD clinical guidelines recommend incorporating PROMs collection to monitor and improve care across commonly treated cardiovascular conditions such as AF and HF.(4, 84-86) Furthermore, the ESC has begun to incorporate PROMs into the quality indicators for AF, HF and TAVI across Europe, which further solidifies the role of PROMs within clinical monitoring and quality improvement.(84-86) QIs are a method of measuring current practice against current standards of care and is an effective method of improving quality improvement.(87) However their uptake in routine practice is limited to individual hospitals and practices and is heterogenous across registries,(25, 88) there is therefore a need to incorporate PROMs in existing registries across Europe to improve CVD morbidity and mortality. There is also a need to establish a consensus on which PROM to use for each of the common CVD.

1.4.3.7 Role in research

1.4.3.7.1 As an outcome measure

Although PROMs may have multiple functions, their primary role is in evaluating patient outcomes for novel interventions as a primary or secondary outcome measure within clinical trials.(89) This is because typical CROs, such as cause-specific hospitalisation and repeat revascularisation, may differ in their goals in comparison to important patient outcomes such as symptom burden and quality of life, which influences clinical decision making.(26) As such trials that incorporate PROMs provide clinically meaningful results on an intervention's safety and efficacy from the patient's perspective.

A recent example demonstrating the impact of PROMs in trials was in a recent randomised placebo controlled trial that assessed a coronary sinus reducer in patients with stable coronary artery disease and treatment persistent angina (The Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia and Microvascular Resistance (ORBITA COSMIC trial).(90) The outcome measures used were a disease-specific PROM and a clinician interpretation of angina (CCS score) at baseline and at six months follow up. Interestingly, on average, the patient's angina PROM scores significantly improved in the intervention arm at follow up (OR 1.40 [95% CI 1.08 to 1.83]; (Benefit)=99.4%), yet the CCS scores (a clinician interpretation) showed no change (change in

CCS scores; −0·3 (−0.7 to 0.1). This correlated with a significant decrease in daily angina symptoms as directly reported by patients and highlights the central importance of PROMs (and relative weakness of a clinician's interpretation) in understanding the effectiveness of an intervention on important patient outcomes.(90)

As such PROMs use within clinical trials have steadily risen to over a quarter of all registered trials by 2013,(91) and just over half of all RCTs in HF by 2025.(92)

1.4.3.7.2 Independent predictor of poor outcomes

Although PROMs are important outcome measures themselves, they are also a strong independent risk factor for CROs such as mortality and hospitalisation.(93, 94) For example, one study collected KCCQ scores in multiple outpatient clinics at baseline and at 12 month follow-up for patients with HF and a reduced ejection fraction (EF). Of those patients with a KCCQ score of less than 25 that persisted at follow up, 37% had been admitted for HF and 20% had died, compared with 7% (HF admissions) and 5% (death) of those with a KCCQ score ≥75 (33% of patients, $p < 0.0001$ for both comparisons). (94) This demonstrates the strong association between KCCQ summary scores and all-cause mortality and HF hospitalisation, and therefore a low summary KCCQ score is an independent predictor of poor prognosis at 12 months.(94) Similar findings were found in a recent UK study that demonstrated poor mobility, pain, HRQoL and self care at baseline that persisted at follow up after MI was significantly associated with mortality, (HR 1.43, 95% CI 1.31-1.58; 1.21, 1.11-1.32; 1.20, 1.10-1.32; 1.44, 1.30-1.59, respectively).(93)

Therefore, PROMs are strongly associated with CROs and may be used to help quantify the risk posed to a patient from their CVD in conjunction with existing traditional assessments such as patient demographics, biological markers and anatomical investigations. Such an approach could lead to the development of risk prediction tools across the common CVD that allows for a more tailored and patient centred approach to healthcare. A recent example is the development of a futility risk score that calculates the risk vs benefit analysis of undergoing TAVI.(95) Here, a 10-fold cross validation was applied to a logistical regression

analysis that was performed on all patients who underwent a TAVI, did not have any peri-procedural complications and experienced a composite of outcomes, that was termed futility (all-cause mortality, stroke, lack of functional improvement and hospitalisation).(95) The final logistical regression model included important baseline characteristics such as diabetes and baseline functional assessment (using NYHA class), biomarkers as well as valve characteristics such as valve gradient. The area under the curve was 0.71 after validation (which suggests a good performance in predicting futility in patients undergoing TAVI) with a 97% specificity using single cutoffs.(95) When dividing patients into low, middle or high risk groups, the risk vs benefit analysis could identify futility in 6%, 19% and 59% of patients respectively.(95) This is an example of using important patient outcomes such as functional wellbeing, albeit assessed by clinicians over a direct patient report, into risk prediction scores.

1.4.3.8 PROMs in regulatory affairs

Given the expanding use of PROMs in recent high impact CVD trials,(92) regulatory bodies such as the FDA and the European Medicines Agency (EMA) have incorporated the use of PROMs in supporting pharmaceutical labelling claims.(24, 96) Pharmaceutical labelling claims are the information provided alongside the product that informs both patients and healthcare providers about the correct dosing and its desired effect. The accuracy and verification of these claims are of paramount importance for regulators as it directly impacts the patient safety and their health outcomes. (97)

The relative importance of PROMs to regulators has increased over time. In 2009, the FDA guidance advocated for the inclusion of PROMs in CVD trials,(24) which was strengthened in 2019 to allow new drugs for HF to attain FDA approval on the basis of improving patient outcomes such as physical function or symptoms alone, without demonstrating any beneficial effect on CROs such as hospitalisation or mortality.(98) EMA guidance also advocate for the use of multidimensional PROMs such as HRQoL as a secondary outcome measure for HF trials but specified that in particular circumstances relevant

patient outcomes such as symptom burden could be acceptable as a primary outcome.(96)

Incorporating patient outcomes generated from standardised, reliable and robust PROMs are recommended by the FDA in supporting high risk device labelling claims,(99) and the European Union now mandate surveillance of high-risk medical devices through annual safety reports that incorporate PROMs.(100)

Thus, the use of valid and psychometrically robust PROMs has a central role in regulatory approval in supporting pharmaceutical and device labelling claims.

1.4.3.9 PROMs in economic evaluations

To inform healthcare organisations and funders economic evaluations of novel interventions are required to prioritise and aid the allocation of finite resources.(101) Integral to such evaluations are generic PROMs, specifically HRQoL, that attempt to quantify the impact of an intervention on patients' overall quality of life. The EQ5D measure is the most common health utility measure used in such evaluations.(102)

The quality adjusted life year (QALY) incorporates both quantity and quality of life measures, where one QALY equates to one year lived in perfect health.(101) They can be used to compare and contrast differing healthcare interventions across populations. Thus QALYs are considered by national bodies such as National Institute of Clinical Excellence (NICE) in the UK and the US panel of cost effectiveness in health and medicine prior to the implementation of a new intervention.(101, 103) The role of PROMs therefore extends beyond routine clinical care and research.

1.4.3.10 Advocates of PROMs

Due to the wide ranging benefits of PROMs and guidance from regulators such as the EMA and FDA,(97, 104) multiple international organisations with key stakeholders such as patients, clinicians and trialists have advocated for their use in routine cardiology care and research.

The ESC has released position statements advocating for the comprehensive integration of PROMs within CVD across both research and routine clinical practice.(105, 106) This would allow for meaningful patient contribution to their care and research. Similar recommendations have been made by The American Health Association (AHA) in their position paper on PROMs within CVD(89) and by prominent patient advocacy groups such as PCORI (**section 1.4.2**).(64)

Although there is general guidance on using PROMs within CVD there are key steps to ensure that they are employed appropriately, such as the qualitative assessment of any prospective CVD PROM and anticipating potential barriers such as feasibility concerns to ensure that integration is streamlined and any PRO data generated is reliable.

1.4.3.11 Summary

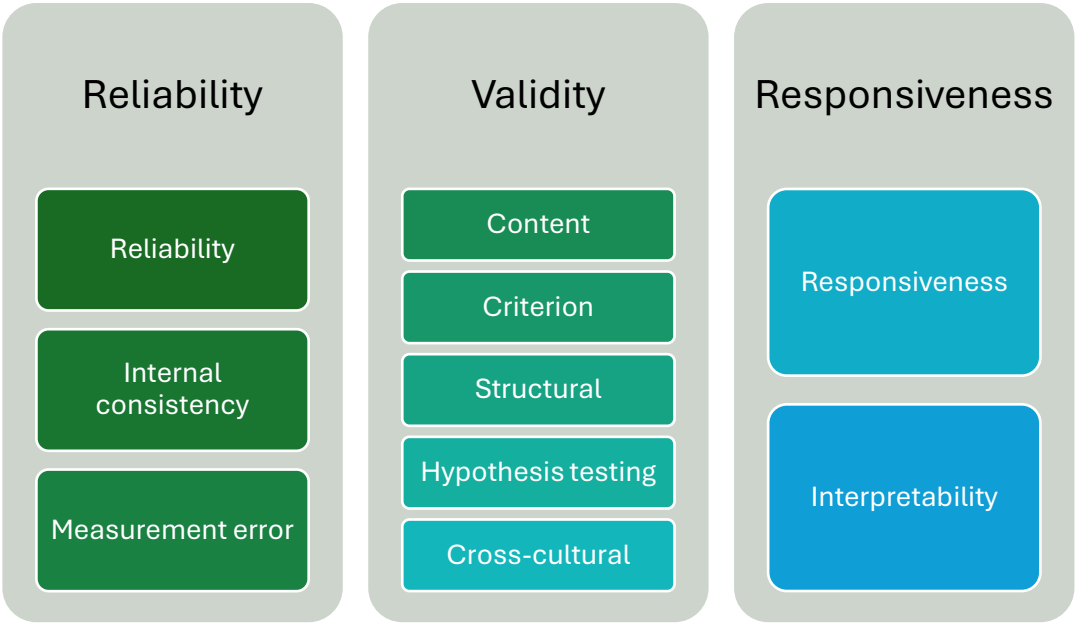
- Patient outcomes may be ascertained by both a clinician's interpretation and PROMs.
- PROMs represent a standardised method of evaluating patient outcomes that is more reliable, reproducible and less prone to bias compared to a clinician's interpretation of a patient history.
- Multiple types of PROMs exist but those that evaluate HRQoL have been identified as the most preferred by patients and regulatory bodies such as the EMA.
- The benefits of using PROMs extend to clinical practice, quality improvement and clinical registries, economic evaluation of new healthcare technologies, within research as a patient centred outcome measure and as an independent predictor of poor outcomes and is recommended to use routinely by international regulatory bodies such as NICE, EMA and the FDA.
- The wide-ranging benefits of PROMs is recognised and is advocated for use within clinical practice and research by patient advocacy groups such as PCORI and international cardiovascular societies such as the ESC and AHA.

- There is therefore a need to develop guidance on which CVD HRQoL PROM to use within CVD across Europe.

1.4.4 Qualitative assessment of PROMs

In contrast to CROs there are no standardised scales or scores across the spectrum of PROMs. Therefore, assessing the quality of each PROM in specific domains and populations are essential. The Consensus -based standards for the selection of health measurement instruments (COSMIN) represents the gold standard in assessing the methodological quality and validity of each PROM which spans 116 points across multiple domains, **Figure 1.1**.(107-109)

Figure 1.1. COSMIN domains that fall into three main categories.



These domains are content validity, structural validity, internal consistency, cross cultural validity / measurement invariance, reliability, measurement error, criterion validity, hypothesis testing and responsiveness.

These domains can be further distilled into four main concepts of validity, reliability, responsiveness and interpretability, which I will discuss in turn.

1.4.4.1 Validity

Validity is broadly defined as the degree to which the PROM or instrument measures the intended construct (such as pain, functional ability or HRQoL).This includes how accurately a PROM reflects the target disease

(content validity), measures the underlying construct appropriately (construct validity), is validated in other languages and cultures (cross cultural validity) and is correlated with an external criterion that is a gold standard for the target condition (that could include a biological marker for heart failure for example or a widely validated PROM).(107, 108) Therefore patient involvement is essential in the development of a PROM and a lack of patient involvement weakens the validity of a PROM(107) and contravenes FDA requirements in evaluating pharmaceutical labelling claims.(98) A recent review found a significant proportion of validated PROMs had either no involvement or limited patient involvement in its development and validation (from feedback forms to extensive cognitive interviews) suggesting that the content validity of most questionnaires may not accurately reflect what patients care most about.(110)

1.4.4.2 Reliability

Reliability evaluates the degree to which a stable patient's PROMs score remains the same despite repeated testing under several circumstances. These include when tested over time (test-retest), by different people during the same occasion (inter-rater) and using different dimensions within the same PROM (internal consistency). Therefore, reliability broadly assesses if a PROM score is free from random error or bias (measurement error) and that a change in score is a true reflection of a patient's condition.(108)

1.4.4.3 Interpretation

Responsiveness broadly assesses the ability of a PROM to detect a change over time and is linked with measurement error. Interpretability relates to the ability to assign a clinically understood meaning to an instrument's score or its change which includes minimally important difference (MID).(107, 108) MID is defined as smallest difference in PROMs scores that is perceived as beneficial or harmful by patients that would prompt a clinician to alter management.(111)

However assigning a clinically relevant meaning to longitudinal changes in PROMs score is challenging as there is rarely a consensus as to what represents a meaningful change to both patients and clinicians. Furthermore, if

a study sample is large enough, then small changes in PROMs scores between patients may naturally exist and be statistically significant but not meaningful to patients and therefore clinicians.(112) A common method to overcome this barrier is ‘anchoring’.(67) This refers to assigning patients into the following categories:

- those with no change in PROMs scores,
- small or large negative changes and small or large positive changes in health status and linking them to an external clinical variable or a PROM with known MID.(113)

Another aspect of interpretation, that is linked to responsiveness but distinct, is hypothesis testing. Hypothesis testing attempts to correlate one proposed PROMs score either with another known and tested PROMs score that is validated in the target population or an objective measure such as a biomarker.(109) A common method of anchoring in HF, for example, would be to link PROMs scores with 6 minute walk test or a CRO such as VO2 max that have clear objective results that are linked with adverse clinical outcomes.(94, 113)

Another method of identifying meaningful changes in PROMs scores is through distribution-based methods or analysing the distribution of PROMs scores within the population of interest (**section 1.4.3.6)**. This involves estimating clinical change based on the distribution of sample longitudinal scores for a given population such as using ½ standard deviation (SD) estimates from the mean in the absence of any clinical anchors to signify clinically relevant change.(114) Although this is an indirect way of statistically estimating MID in a target population, most MID effect sizes fall within this estimate.(113, 114) A systematic review into the magnitude of MID found that over three quarters of MID estimates were close to ½ SD from the mean (mean = 0.495, SD = 0.155) regardless if the PROM was a disease specific or generic questionnaire and if MID was calculated using anchoring or distribution based methods.(114) However some MID estimates were as low as 0.25 SD and although the distribution methods may identify meaningful change it may not be the minimal change needed to elicit a change in management.(111, 115)

Therefore some authors recommend the use of both methods to estimate MID to ensure responsiveness and interpretation of scores are accurate, reliable and minimal.(111, 113)

1.4.4.4 Summary

In summary, a COSMIN analysis provides a comprehensive evaluation for existing PROMs in CVD that assess whether the questionnaire investigates the target patient from the target population accurately, can differentiate changes in PROMs scores and attempt to ascertain whether these changes are clinically meaningful. Furthermore, any analysis of existing PROMs requires a comprehensive COSMIN score.

1.4.5 Limitations of PROMs

There are, however, recognised limitations and biases associated with PROMs that are important to consider. I will briefly mention some relevant limitations in the section below.

1.4.5.1 Patient representation

The first is a lack of appropriate patient representation during the development of a CVD PROM. As mentioned in **section 1.4.4.1** a significant proportion of PROMs were developed without or with limited patient input.(110) This is important, as patients value some outcomes differently to clinicians, and so without patient involvement then current PROMs may not be constructed in a way that is meaningful and important to patients with CVD and weakens the validity of a PROM.(107, 116) This is compounded if the sample of patients originally tested during a questionnaire's development is not representative of the clinical population in terms of age, sex or ethnic background.

The importance of a representative demographic is illustrated by a recent electronic PROM that demonstrated a statistically significant difference between the sexes in what each considers important for good quality of life.(117) Women reported that they considered the ability to do housework, being less of a

burden on others and insomnia as important health items to evaluate. In contrast, men reported the ability to drive a car, cycle, engage in physical exercise, eating and sexual activity as more important. The proportion of items that were considered important also differed by age and the specific cardiovascular condition such as AF or HF within the same study.(117) Other individuals experience or perceive good health that differ according to age, sex, type of CVD that they lived with; and there are even variations by country. A longitudinal survey evaluating CVD patients' outcomes and experiences of the COVID-19 pandemic highlighted significant country specific differences such as social stigma and rejection amongst patients from South Korea compared to Norway.(118)

A lack of representation of all groups during a PROMs development could lead to underreporting of health items considered important to one group over others. There could be a missed opportunity to enhance patient care using existing PROMs that are not truly representative of a typical patient.(110, 116, 117) This aspect is considered during a comprehensive qualitative assessment of a PROM's content validity using the COSMIN analysis.

1.4.5.2 Response shift

Over time (and medical treatment) some patients change their perception of their own HRQoL and response shift is defined as measuring the change in how an individual perceives (or their internal standard) their disease.(119) Response shift accounts for the stabilisation of HRQoL scores over time despite objective positive or negative changes in a patient's health,(120) and this occurs when a patient develops a new scale for measuring their own HRQoL (recalibration) and reprioritise some values over others.(121) Subsequently changes in longitudinal HRQoL scores, therefore, may not be entirely due to an intervention and response and is subject to bias. Furthermore, PROMs are inherently subjective, and some responses may be influenced by other factors such as mood, significant life events (such as bereavement) and expectations which may lead to varied outcomes.(122, 123) A PROM's ability to detect change in a patient's health status may evaluated through a qualitative assessment of its interpretability as outlined above.

1.4.6 Barriers to PROM implementation

Despite their advantages, the implementation of PROMs in clinical practice is variable.(124) This is due to barriers that exist on all levels; patient, clinician, service and systems wide.(125, 126) Anticipating and overcoming such barriers may allow PROMs to be integrated more comprehensively in a single healthcare system and eventually allow PROMs to be used across multiple healthcare systems internationally to evaluate and reduce CVD morbidity (and potentially mortality) on a large scale.

1.4.6.1 Patient level

These barriers refer to patient level factors that impede the completion of a questionnaire, that is also referred to as respondent or patient burden.(127) This is important because as patient burden increases, the likelihood of the patient completing the questionnaire in full decreases, and therefore missing PROM data increases.(128) This will impact the overall quality of patient data from a trial, which may introduce bias with an impact the overall trial result.(128) Important patient level factors identified in a recent systematic review included the duration of the questionnaire, poor understanding of the questions asked, lack of available validated translations of the PROM, and being too unwell to complete the questionnaire.(129) Other patient level barriers include a perception that the PROM has limited value to their care and difficulty in using electronically delivered PROMs. Therefore, healthcare providers and trialists need to carefully consider patient factors prior to implementation that include an appropriate duration, available translations, user friendly electronic PROMs and informing patients of the value of PROMs.

1.4.6.2 Healthcare provider

These barriers refer to healthcare provider level factors that impede the uptake and analysis of PROMs amongst healthcare providers.

Recent reviews highlight healthcare providers' scepticism towards PROMs as a major barrier to their use.(125, 130) This includes questioning the reliability and validity of PROMs, and therefore its inherent value, over a clinician assessment and the time taken to complete the questionnaires.(130) This is despite multiple reviews demonstrating that completing PROMs increases clinic efficiency and

saves time for clinicians, as they are unlikely to assess symptoms that have already been covered within the questionnaire.(125, 131, 132)

Other factors include the lack of training and ability to report, interpret, analyse and disseminate PROM scores to patients and other healthcare providers alike which may impede quality improvement.(132) This highlights the need to provide staff education and training early in PROM implementation to overcome these challenges.

1.4.6.3 Service level

Service level barriers refer to factors that affect the integration of PROMs across multiple departments within a hospital or network of hospitals.

Common barriers include the inability to integrate electronic versions of PROMs within existing IT infrastructures that allow easy data collection and storage, integrating PROMs into existing clinical workflows and limited resources to overcome these barriers whilst providing education and training in interpreting PROMs data for healthcare providers.(127, 129, 133)

1.4.7 Selecting the most appropriate PROM

Many healthcare organisations require guidance in designing, implementing and analysing PROM data to be meaningful in clinical care.(125, 132) The Patient-Reported Outcomes Tools: Engaging Users and Stakeholders (PROTEUS) consortium provide an introductory guide to support PROM use in clinical practice.(134) The PROTEUS guidance consisted of multidisciplinary experts that include PROMs methodologists, clinicians, trialists and patients and is divided into three sections; design, implementation and data management.(134) Importantly the guidance recognises that clinical workflows, healthcare resources as well as electronic healthcare records, target population and patient characteristics vary between healthcare organisations and addressing potential barriers proactively may ease implementation.

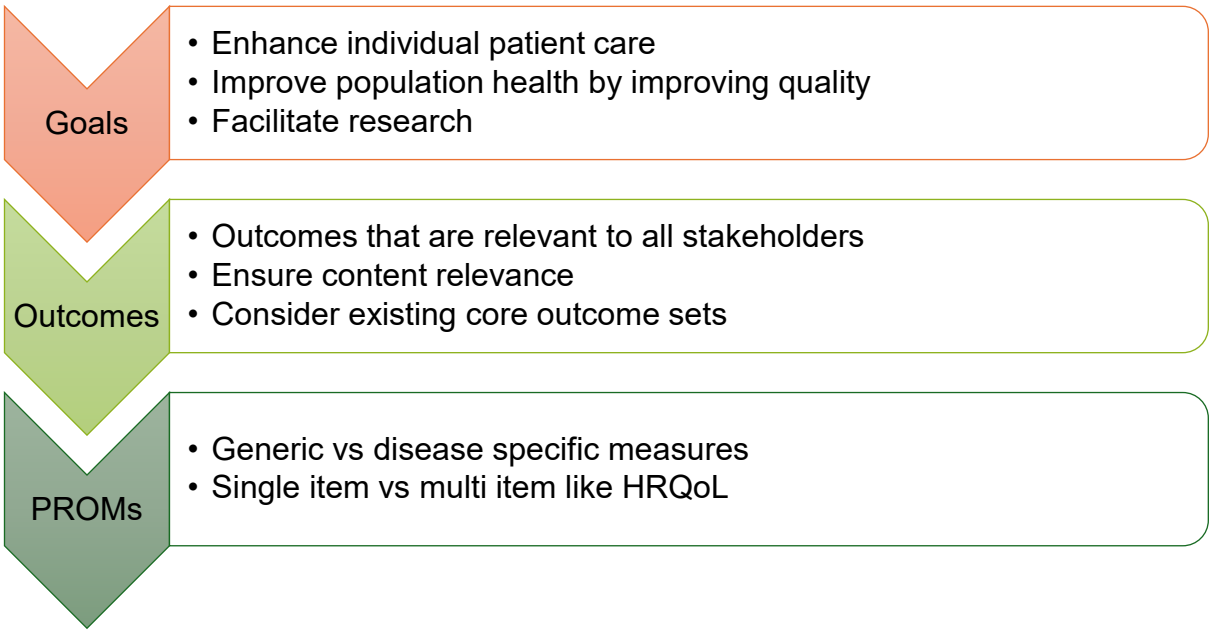
Currently the PROTEUS guidance on selecting the most appropriate PROM centres on a further three concepts:

1. Identifying the organisation's goals for using a PROM such as enhancing clinical care, quality improvement, population health or an outcome measure within a clinical trial.

2. Selecting existing validated PROMs with robust psychometric properties that are relevant to the target patient population (that includes evaluating if the PROM is feasible to implement).

3. Selecting a specific type of PROM (whether generic or disease specific, single item or multi-item etc).(134, 135) **Figure 1.2**

Figure 1.2. PROTEUS guidance on selecting PROMs.(134)



1.4.8 Feasibility of PROMs

Feasibility is defined as the intrinsic characteristic of a PROM that allows for ease of implementation that are not present or considered in qualitative assessments such as the COSMIN analysis.(108) There are over 7,000 validated PROMs spanning the range of medical diseases and interventions,(136) and it is possible to have more than one PROM with robust psychometric properties for the target condition that differ in feasibility characteristics. These characteristics are important to consider prior to implementation as they can serve to further differentiate the most appropriate PROM for the organisation and be an additional implementation barrier. These factors have been identified in the literature, yet some are absent from the

PROTEUS guide and do not feature within the COSMIN analysis.(129, 137, 138)

For example, most validated PROMs are owned by third party organisations and may be subject to high cost to use that may be prohibitive for trials or clinical practice.(133) This cost also extends to accessing subscription-based websites that contain some feasibility information on a given PROM.(136) Furthermore, operational costs such as obtaining valid translations, incorporating electronic PROMs into electronic health records, electronic data storage are important considerations that should be proactively accounted for.(138, 139) Other feasibility characteristics include complex licensing structures that could include terms and conditions unacceptable to healthcare providers such as direct access to patient data.(137)

The current PROTEUS guidance recommends assessing some feasibility items such as the cost of using a PROM, licencing (126, 140, 141) and the ability of a PROM to be understood by the user (125). However, additional factors such as operational costs including accessing more information of a PROM through subscription websites,(136) regulatory approval for the use of a PROM in a randomised clinical trial (142, 143) and metrics that interpret change in PROMs scores over time such as the MID that determines the ability of a PROM to be used in research, regulatory affairs and routine clinical care,(144, 145) but are not included in recommended assessment guides.

There is a need to develop a separate, formal, evaluation of a PROMs characteristics to identify the optimal CVD PROM for its specific use.

1.4.9 Summary

- CVD PROMs are distinct to CVD CROs, and there are key aspects to consider prior to their implementation.
- There are no standardised scores that exist across the spectrum of PROMs and one way to distinguish between one PROM over another is its qualitative assessment.
- The COSMIN analysis is a comprehensive qualitative assessment of PROMs, and contemporary COSMIN analysis would be needed for a prospective CVD PROM

- PROMs are inherently subjective and individuals experience or perceive good health that differ according to age, sex, type of CVD lived with and by country. Therefore, it is critical to achieve a diverse and wide patient involvement to ensure any consensus agreement is representative.
- There are barriers to PROMs implementation that exist on all levels; patient, clinician and systems wide. These barriers require consideration prior to any consensus agreement on CVD PROMs use to ensure the recommendations are pragmatic and easy to implement.
- User guides exist to navigate the complexities of PROMs implementation such as the PROTEUS guide. The guidance on selecting the most appropriate PROM emphasises establishing the goals, qualitative assessment and what type of PROM to use.
- However there are additional feasibility concerns to PROMs that is not covered in a qualitative assessment.
- There is therefore a need to develop a separate formal evaluation of a PROMs feasibility to be used in conjunction with the PROTEUS guidance on selecting the most appropriate PROM for a healthcare organization.

1.5 Current cardiovascular outcome sets

The need for standardising CROs and PROMs have been recognised by some organisations and in this section, I will discuss the existing cardiovascular outcome sets available and outline their scope, strengths and weaknesses. I will then discuss the existing international registries operational across Europe and discuss their strengths and weaknesses. I will describe what EuroHeart is, its scope and methodology in standardizing data variables and how this may be implemented into real world practice and potentially influencing CVD burden.

1.5.1 SCTI

The standardisation of CVD outcomes was formalised by the FDA in 2009 due to difficulty in comparing and contrasting outcomes from major trials due to a lack of uniform definitions.(9) The FDA established the Standardized data collection for Cardiovascular Trials Initiative (SCTI) explicitly to simplify the design of CVD trials in order to support pharmaceutical and device labelling claims with clear definitions for the major CVD outcomes.(146)

The SCTI document was published in 2017 and contributors included key stakeholders such as cardiovascular pharmaceutical and device manufacturers, academics, trialists and regulatory bodies and resulted in one document to cover all aspects of CVD. The proposed list of outcomes alongside their definitions covered major procedural and device CROs of interest to trialists and regulatory bodies.(146)

A recent systematic review screened 25,601 records identifying 254 outcome sets across all specialties developed for routine care and found that most outcome sets (n = 142/254; 54%), in general, lacked any patient involvement during their development.(147) The subsequent the SCTI dataset was no different to most of the outcome sets identified in the review and its Delphi process lacked patient validation, did not include recommendations for the use of PROMs within CVD and therefore may not be patient centred.(146) The aim of the SCTI dataset, however, was targeted for clinical trial use alone and is not tailored for routine clinical practice use within registries. Furthermore, the dataset has not been updated since its publication in 2017. As technology develops, traditional outcome measures such as MI could be surpassed with the advent of new biomarkers and or imaging modalities and hence impede

their implementation.(9) However, updating these outcome measures would be useful as part of a contemporary, wider framework of key cardiovascular endpoints. For example, the VARC has undergone two iterations with updated definitions of MI and implementation of new outcome measures such as valve thrombosis to accommodate the recent adoption of TAVI in younger patients.(9, 51)

1.5.2 Academic Research Consortium

The Academic Research Consortium (ARC) is an international collaborative that consists of academics, clinicians, regulatory bodies and industry that have developed, standardised and defined clear CVD outcome sets for clinical trial use.(148) The outcomes are detailed and cover important endpoints, and the set has been adopted widely within the TAVI field, as an example.(52)

However, there are limitations to ARC outcome sets. Similar to the SCTI, these outcomes have been developed with a focus on procedural or device outcomes rather than longitudinal disease outcomes that are important to a patient's HRQoL. Furthermore, important ARC outcome sets, such as TAVI, did not contain any patients in the modified Delphi process and lacks patient validation despite formally endorsing certain PROMs such as EQ5D to capture the patient perspective.(51) As such they are orientated more towards clinicians and trial use which may impede its real-world implementation.(148) Secondly, some proposed definitions were not endorsed by all key stakeholders such as international medical societies leading to a lack of consensus amongst trialists over the outcome sets.(149)

1.5.3 International Consortium for Health Outcomes Measurement

The International Consortium for Health Outcomes Measurement (ICHOM) is a United States based, nonprofit organisation that have developed and standardised outcome measures across a range of conditions including commonly treated CVD such as CAD,(150) AF,(151) HF(152) and heart valve disease.(153) The aim of such outcome sets was to promote patient centred healthcare for both trials and clinical practice.

These outcome sets have been developed through a modified Delphi process and involved multiple stakeholders, including patients.(154) The subsequent standardised outcomes contain CROs but differs to ARC and SCTI by providing specific guidance on PROM use for each CVD and data collection time points.(150)

However, ICHOM datasets recommend multiple PROMS for each CVD.(150-153) This may increase administrative and respondent burden, exacerbate existing healthcare scepticism on using PROMs within healthcare and may therefore hamper system-wide implementation. (124, 125, 127) For example, the ICHOM coronary artery disease dataset recommends three PROMs to evaluate three different symptoms; angina, depression and shortness of breath and therefore a patient may complete three different questionnaires in a single sitting, with clinicians interpreting three different PROM scores.(155) Furthermore, ICHOM lack a user-friendly IT platform that could allow healthcare providers to collect and interpret data seamlessly in real time which may facilitate implementation.

1.6 Existing international European registries

In this section I will discuss the existing quality of care systems that span multiple geographies within Europe. One way of assessing quality of care is by examining the clinical registries that span and impact multiple geographies which includes EuroHeart.

1.6.1 EURObservational Research Program

The EURObservational Research Program (EORP) was established by the ESC in 2009 to monitor implementation of guideline directed therapy in select centres. To date, over 180,000 patients have been enrolled in over 100 countries worldwide in 34 registries spanning 15 different CVD topics. These include common CVD domains such as HF,(156) acute coronary syndrome (ACS),(157) AF(158) and heart valve disease.(159)

EORP also established a unique program of observational research into the characteristics of patients with uncommon cardiovascular conditions and the

impact of contemporary treatments on outcomes. A recent example includes the EORP peripartum cardiomyopathy registry that demonstrated that bromocriptine, in addition to standard care, was associated with better maternal outcomes in such patients.(160)

However, EORP records data from select centres during a limited period of time from selected countries. Furthermore the definitions of outcomes between national registries were not harmonised thus raising concerns over the coverage and representativeness of the results but also the overall quality of data in patients with common cardiovascular conditions.(156, 158, 161)

1.6.2 Global Registries and Surveys Program

Similarly, the Global Registries and Surveys Program (GRASP) is an ESC program of observational, multicentre prospective and longitudinal study of initially inpatient and outpatient chronic coronary syndrome and heart failure as well as cardiac prevention. It was launched in 2024 with over 600 centres from 49 countries enrolled.(162)

Like EORP it is intended to capture a snapshot of care of selected patients in selected centres for a short period of time. Although providing longitudinal data on included patients and their adherence to guideline directed therapy there would likely be similar concerns over the overall quality of data.(8, 162)

1.6.3 The need for an international collaborative registry

International observational data from EORP and others highlight the collection and reporting of outcome measures differs across national registries.(157, 158) This hinders meaningful comparison and interpretation between countries and hampers quality improvement.(5) Incomplete capture of relevant outcomes can lead to missingness of data even within registries(163) and misclassification bias due to heterogenous definitions of similar outcomes.(164, 165) An international unified registry that overcomes these barriers allows for accurate capture of patients, improves outcomes for quality improvement and adherence to medical therapy which may improve CVD burden across Europe.(8)

1.6.3.1 EuroHeart

The European Unified Registries on Heart Care Evaluation and Randomized Trials (EuroHeart) is a ESC funded project that addresses this need. EuroHeart is an international collaboration of national registries that harmoniously collect and report data variables with standardised definitions across the common cardiovascular conditions.(54) The continuous individual patient data collection and reporting would provide more reliable, representative and generalisable data which will aid international quality improvement and once established provide a platform for registry based randomised trials.(8) This differs to the ICHOM, ARC and SCTI projects as EuroHeart aims to provide both the standardised variables and the infrastructure to implement them into a collaborative international registry that can impact CVD burden, a recent example of its relative success is the ACS/PCI international registry that has commenced recently.(166)

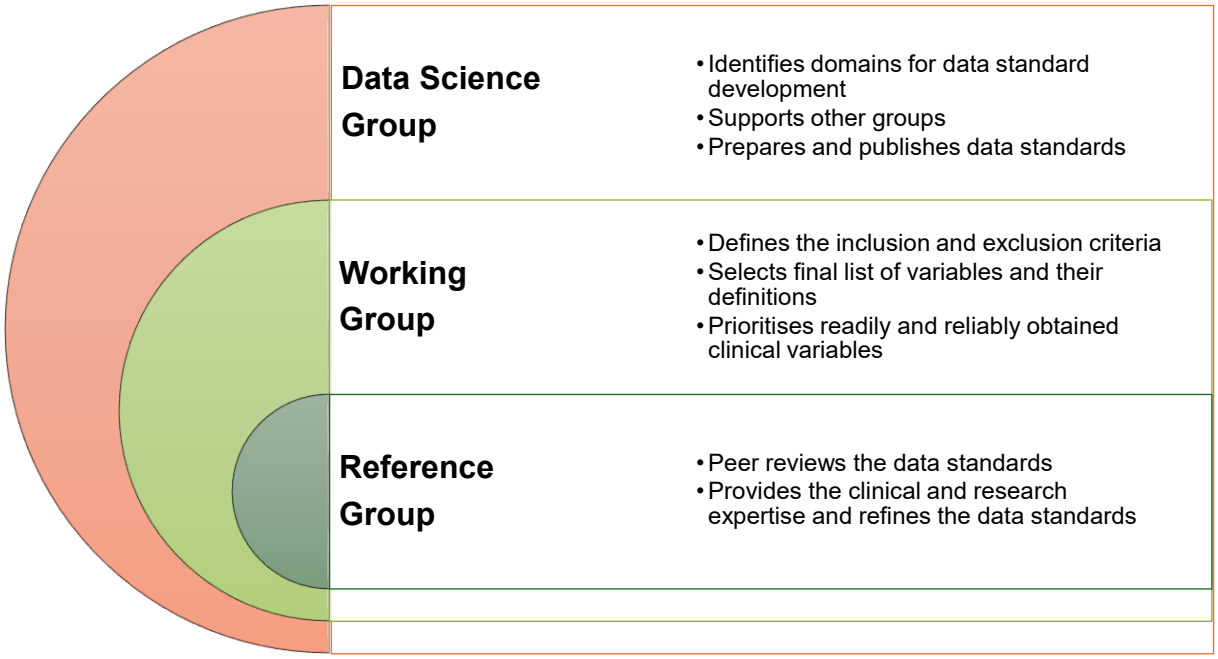
In doing so, EuroHeart aims to improve the quality of care and outcomes for patients with the following which will be referred to as the common cardiovascular conditions: ACS/PCI, HF, AF and TAVI.

EuroHeart has developed a suite of internationally derived standardised data variables for the common cardiovascular conditions using an established methodology by achieving consensus amongst international experts and stakeholders.(167-171) All standardisation of data variables and outcomes is led by the Data Science Group (DSG) of EuroHeart.

1.6.3.2 EuroHeart methodology

The established EuroHeart methodology for registry development requires the participation and interaction of three core groups; the DSG, a working group and a reference group under a recognised operational framework (**Figure 1.3**).(171)

Figure 1.3. Operation framework of the relevant EuroHeart groups



The DSG was responsible for identifying potential clinical domains to be developed, conducted the systematic review and translated the research findings into a unique candidate set of variables with permissible values and proposed definitions and working with the working and reference group in refining the set of variables and their definitions according to consensus. The DSG then prepared and published the data standards and undergo periodic review.(171)

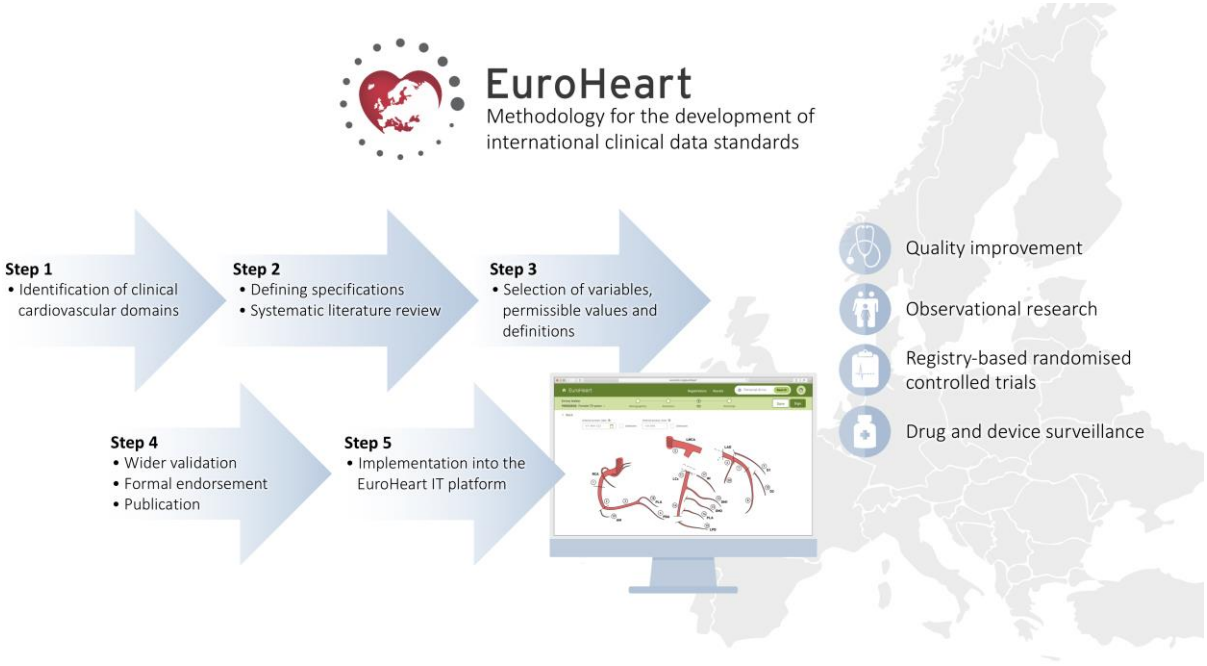
A working group was established for each cardiovascular condition and each member was nominated by relevant ESC working groups and associations and members of each national cardiac society. The working group was responsible for defining the inclusion and exclusion criteria for the data standards, clarifying the clinical setting to which these data standards apply to, agree on a final list of variables, permissible values and definitions that were clearly written and harmonised to ESC clinical guidelines and that such variables are pragmatic to collect in the real world in both high and middle income countries.(171)

The reference group comprised of members of each ESC affiliated organisation and working groups and was tasked to provide a more broad feedback on the

inclusion and exclusion criteria set, the final list of variables and their definitions and evaluated the applicability of these variables in clinical settings.(171)

When established for each cardiovascular domain the EuroHeart methodology comprised of five critical steps (**Figure 1.4**).

Figure 1.4 The five step EuroHeart methodology taken from (171)



1.6.3.2.1 Step 1: Identifying clinical domain

The DSG identified the clinical domain to be developed in conjunction with the Executive Committee.(54) This decision was based on either clinical need for data collection or lack of current registries.(171) Given the establishment of standardised data variables the next domain to be developed was the cardiovascular outcomes that included both CROs and PROMs across the common cardiovascular conditions.

1.6.3.2.2 Step 2: Constructing data standards and evidence synthesis

After conducting the systematic review of the identified clinical domain, the DSG liaised with the working groups to identify the target population and determine the clinical setting. For the purposes of the MD systematic review and the target population were patients with the common cardiovascular conditions and the clinical setting was outcomes that occurred during the follow up period post discharge. Each outcome was assessed according to their importance,

evidence base, feasibility, validity, reliability and applicability in accordance with user guides that evaluate patient outcomes in registries.(172)

1.6.3.2.3 Step 3: Selecting variables, their values and definitions

Each variable extracted from the systematic review was then presented to the working group to vote in a modified Delphi process to achieve consensus. The Delphi process involves a structured discussion and questions over a fixed issue and may be superior to the classical method in achieving consensus.(154) The variables were either excluded from the core outcome set or included as either a Level 1 or 2 variable. Level 1 variables are mandatory to collect whereas Level 2 variables are optional. Once variables were categorised the permissible values and their definitions was subsequently finalised.(171)

1.6.3.2.4 Step 4: Endorsement from Reference Group

Via online meetings and email correspondence the finalised list of variables was independently reviewed by each member of the reference group to ensure they were pragmatic to collect for EuroHeart member countries and to achieve external validation. Once achieved the outcome set was submitted for publication in peer reviewed journals.

1.6.3.2.5 Step 5: EuroHeart IT platform implementation

The data variables were then programmed into the unique EuroHeart IT platform that is available for EuroHeart member countries to use depending on their registry infrastructure. Alternatively the data variables may be implemented into the national registry’s existing IT platform.(171)

1.7 Conclusion

This project will investigate select outcome measures used within cardiovascular research and aim to standardise these outcomes across the four commonly treated cardiology conditions: ACS/PCI, AF, HF and TAVI. The relevant measures will include CROs such as all-cause mortality as well as PROMs.

This report highlights the work completed during the course of the MD. **Chapter 1** has highlighted the health and economic burden of cardiovascular disease, variations in care and outcomes for cardiology patients across Europe, why standardising CVD CRO and patient outcomes are important, existing CVD outcome sets and existing CVD registries across Europe. **Chapter 2** discusses the aims and objectives of the MD and outlines the methodology used to standardise outcome measures with the results obtained so far. **Chapter 3** provides the results of the systematic review and evidence mapping of contemporary cardiovascular outcome measures. The results from the systematic review formed the basis of the EuroHeart methodology in achieving consensus for CROs in the common CVD conditions and HF in **Chapter 4 and Chapter 5.** A scoping review of all HRQoL PROMs in the common CVD and their COSMIN analysis scores are provided in **Chapter 6,** which in turn will be used to establish a consensus as to which PROMs are preferred in each of the common CVD in Chapter 7. Due to the feedback taken from international experts, a feasibility checklist was distilled from a scoping review and modified Delphi exercise amongst key stakeholders in **Chapter 8.** The conclusion to the MD is provided in **Chapter 9.**

Chapter 2
Aims and Objectives

Aim

In this thesis I will utilise existing methodologies needed to standardise CROs and hierarchically rank existing HRQoL PROMs across ACS/PCI, HF, AF, TAVI and generic CVD for quality improvement and clinical research.

Objectives

1. To aid in completing a systematic review of cardiovascular outcomes across the common CVD conditions.

2. To develop a suite of internationally derived, standardised and defined outcome measures for HF utilising a modified Delphi method.

3. To aid the development of internationally derived and defined outcome measures for ACS/PCI, AF, TAVI and generic CVD utilising a modified Delphi method.

4. To aid in completing a systematic review of PROMs in CVD.

5. To develop a suite of internationally derived, hierarchical ranking of PROMs in ACS/PCI, HF, AF, TAVI and generic CVD utilising a modified Delphi method.

6. To develop an internationally derived checklist that evaluates the intrinsic barriers to implementing PROMs utilising a modified Delphi method.

Research question

1. What are the main outcome measures used within contemporary CVD research and are the definitions heterogenous?

2. What are the PROMs used within ACS/PCI, HF, AF, TAVI and generic CVD and what is the quality of each CVD PROM?

3. How can heterogenous CVD outcome definitions be harmonised for quality improvement and research for HF and the other domains?

4. What are the intrinsic barriers that exist for each PROM that are not found in qualitative assessments?

5. How can international consensus, COSMIN score and the checklist be used to establish a suite of preferred PROM in each domain of ACS/PCI, HF, AF, TAVI and generic CVD.

Chapter 3

Systematic Review of Cardiovascular Outcomes

Outcome measures for randomised clinical trials and multicentre observational studies of cardiovascular diseases published in major clinical journals: systematic review and evidence mapping

3.1 Contribution

My contribution to the systematic review involved: updating the search strategy and modifying the results to include any articles published from 1st January 2013 to the 6th of June 2024, reviewing articles for inclusion, cleaning subsequent data, categorisation and qualitative assessment of included articles, updating the risk of bias for RCTs and editing of the final manuscript. This systematic review involved multiple collaborators from inception which included formulating the review protocol, registration, initial data capture and exclusion and writing the original draft of the manuscript that was subsequently published. The publication details are:

Bhatty A, Wilkinson C, Aktaa S, et al. Outcome measures for randomised clinical trials and multicentre observational studies of cardiovascular diseases published in major clinical journals: systematic review and evidence mapping. Heart. 2025 Jun 27:heartjnl-2025-326045. doi: 10.1136/heartjnl-2025-326045. Epub ahead of print. PMID: 40533147.

3.2 Abstract

3.2.1 Background

Outcome measure choice and definition can determine the result of the study. We describe outcome measures and their definitions for cardiovascular studies in highly-cited medical journals.

3.2.2 Methods

Phase 3 or 4 RCT or multicentre observational studies in cardiovascular medicine that were published in the New England Journal of Medicine, Lancet

or Journal of the American Medical Association between 1st January 2013 and 6th June 2024 were identified from Embase and Ovid Medline. Two independent reviewers selected the studies and extracted the primary and secondary outcome measures from each publication.

3.2.3 Results

386 studies (83% RCTs; 17% observational) representing 10,699,147 participants were included. These studies investigated coronary heart disease (51%), cardiomyopathy / HF (22%), heart rhythm disease (15%), valvular heart disease (11%) and 'other' CVD (1%), with 45% investigating a device and 48% funded by industry. The most frequently reported primary outcome measure was a composite (63%), the most frequent component of which was MI (58%). The use of a composite for the primary outcome measure increased from 49% of studies in 2013 to a peak of 85% in 2018. From 2013 to 2023 the median number of secondary outcome measures per study increased for RCTs (3 to 8) and observational studies (0 to 7). Definitions for cardiovascular mortality, MI and stroke varied across the studies.

3.2.4 Conclusions

For cardiovascular studies published in highly-cited journals, there has been an expansion in the use of primary composite outcome measures and secondary outcomes measures, with heterogeneity in the definition of primary outcome measures. A standardised approach to the use of cardiovascular outcomes measures is required.

3.3 Introduction

As discussed in **section 1.2.3.**, outcome measures are fundamental in RCTs and observational studies by influencing the safety and efficacy of a proposed intervention and the sample size in RCTs.(22) A practice changing RCT may influence guideline recommendations and therefore impacts patients in routine clinical care.(173) However as shown in **section 1.3.1**, heterogenous definitions of the same outcome measure may alter the results of practice changing trials,(39) lead to inconsistent findings, and therefore making comparison between similar studies difficult.(40, 47) This also introduces clinical heterogeneity which makes meta analyses of a topic less reliable.(9, 37)

Furthermore, contemporary approaches to study design may have been influenced by the falling CVD mortality rates driven primarily by the success of guideline indicated care (174, 175). As mentioned in **section 1.4.3.1**, a consequence of falling CVD mortality rates is an increased prevalence of patients living with CVD and its impact on their quality of life, termed HRQoL.(69) This has led to an increased recognition of the importance of quality of life PROMs in CVD trials.(176) However using traditional CROs, novel therapies would require larger, and more expensive, trials to identify smaller event differences between prospective treatment arms using traditional RCTs, which may not be feasible.(22, 177) As mentioned in **section 1.3.2.**, to achieve statistical power investigators may have adjusted their approach to outcome design by expanding the use of composite outcome measures that contain more components,(44) and exploring pragmatic, cost effective alternatives to RCTs involving the use of routine data being employed for registry based trials.(175, 177, 178) Other cost effective measures include using secondary outcome measures to improve the power of a study without increasing its sample size as explained in **section 1.2.1.**(179) Secondary outcome measures are employed to help interpret the primary outcome measure and are often exploratory in nature.(180)

However, there are important limitations to consider when using composite outcomes such as MACE. These include heterogeneity in component selection and their definitions in composite outcomes even when investigating similar interventions of the same disease process as explained in **section 1.3.2** (44, 179, 181) This can make comparisons between studies difficult, lead to

uncertainty about the effectiveness of a treatment and is a potential signal of investigator bias.(9)

Consequently, there have been multiple efforts to standardise the commonly used CVD outcome measures and their definitions by organisations including the US FDA that first established the SCTI in 2009.(51, 146, 155) However, it is not clear whether these have had an impact on the consistent selection and definition of common outcome measures and their definitions in major studies of common CVD conditions, and any change over time.(146, 182)

There have only been a few studies, in the literature, that have provided an evidence map the use of CVD outcomes and their definitions employed in major trials. A recent descriptive analysis demonstrated wide heterogeneity in the consistency of outcomes employed by 50 large RCTs of atherosclerotic cardiovascular diseases (ASCVD) published in major journals.(181) The most common composite outcome measure employed was a 3 point MACE that consisted of non-fatal MI, non-fatal stroke and CV mortality (n=14 studies, 28%). The remaining studies reported a total of 29 different combinations of the components of MACE (n=36, 72%), which may complicate comparison, and therefore interpretation, between similar studies.(181) In addition, the authors found that the published and original outcomes (published in the trial protocol) changed in under half (n=23, 46%) of RCTs.(181) As mentioned in **section 1.3.2.**, this may introduce bias into the conclusions of a study and potentially compromise a trial's scientific validity. However, the review was limited to ASCVD and no other common CVD, did not focus on the use of PROMs in ASCVD and did not provide granularity on how the most common outcome measures used were defined.

Rahimi et al examined how PROMs were employed by RCTs across the common CVD in 10 general medical and cardiology journals between 2005 and 2008.(53) These outcomes were categorised as either patient important outcomes (death, PROM and morbidity) or non-patient important outcome (a surrogate outcome that did not have a direct impact on patients).(183) The review found that PROMs were reported in a small minority of trials (n=65, 16%) and the authors found that the results from a fifth of all included studies (n=81, 20%) would have benefited from reporting a PROM and therefore PROMs were underutilised and underreported according to their own analysis of the trial.(53)

This was determined by analysing all included studies using an algorithm that was developed and validated by the study authors.(53) This algorithm evaluated certain aspects of each trial that previous literature had deemed important to consider before reporting PROMs.(53, 184-186). Most of the non-patient important outcome studies (70%), according to their *post hoc* analysis, would have benefited from a PROM which included studies evaluating an intervention on symptoms, quality of life or functional status.(53) But, the review lacked granularity on distribution of individual outcomes (whether patient important or not) across the common CVD within RCTs, how they may have changed over time and their associated definitions. Furthermore, both reviews, mentioned above, lacked detail on the use of CROs and PROMs employed by large multi-centre observational studies.

Therefore, I aimed to describe and summarise the use of outcome measures and their definitions in contemporary RCTs and multicentre observational studies of common CVDs. I also aimed to investigate if the selection of outcomes differed by CVD condition, funding source of study, whether the overall result of the study was positive or not and whether the intervention was a device or not. Understanding the extent and depth of outcome measures in cardiovascular clinical studies helps improve the study design, conduct and result interpretability.

3.4 Methods

3.4.1 Search strategy and selection criteria

This systematic review was reported in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.(187) Briefly, this involves specifying the eligibility criteria, information sources, search strategy, selection process, data collection process, data items, risk of bias assessment and synthesis methods. The protocol was pre-registered: https://doi.org/10.25405/data.ncl.19264346.

3.4.2 Eligibility criteria

Similar to the previous reviews,(53, 181) a select number of highly cited cardiology journals will be investigated as they are more likely to publish practice changing trials with wide readership. These were the Journal of American Medical Association (JAMA), The Lancet and the New England Journal of Medicine (NEJM). Therefore, only studies published in these highly-cited journals were included.

Eligible studies were phase 3 or 4 RCTs or multicentre observational studies of adult patients (>18 years old) with established cardiovascular disease or tested a cardiovascular intervention that was published over the past decade (between 1st January 2013 and 6th June 2024) and was published in English. Phase 3 RCTs are sometimes referred to as the therapeutic confirmatory phase and are trials typically evaluating the safety or efficacy of an intervention prior to regulatory approval such as the FDA or EMA.(188) Phase 4 RCTs are conducted after regulatory approval and are post marketing or surveillance studies that aim to follow up patients who received the intervention for a longer period of time to ascertain any potential adverse reactions or side effects. These studies are sometimes referred to as post approval studies.(188) These RCTs were chosen as they are ones impacting patients the most and are influential in altering guidelines.(22) Multi centre observational studies were similarly chosen for its impact on patients.

Cardiovascular disease was pre-specified as common conditions typically managed by cardiologists: heart rhythm disease, coronary heart disease,

cardiomyopathy and HF, and valvular heart disease.(189) Excluded studies included any review articles, studies published in subsidiary journals, sub-studies of the main paper, secondary and meta-analyses, studies in which outcome measures were not reported or not disclosed and any cardiovascular study investigating children (under the age of 18).

3.4.3 Information sources and search strategy

Embase and Ovid Medline was searched using a search strategy developed with a research librarian (**Appendix A.1**). Recommended search filters for phase 3 and 4 RCTs and multi centre observational studies were used,(190, 191) and previously search strategies for heart disease were adapted and incorporated.(192-194)

3.4.4 Selection, data, and risk of bias

Two of the eight reviewers (CW, BB, PK, GB, SA, AT, AW, AB) independently selected studies distilled from the search strategy which involved screening the titles and abstracts of studies and assessing their full text in detail for eligibility. Decisions were recorded online using the Rayyan software.(195) Articles were selected if both reviewers agreed to its inclusion whereas disagreements were resolved through discussion with a third reviewer (CW). Seven reviewers contributed to study selection, and eight to data extraction.

3.4.5 Study characteristics

The following 14 study characteristics were extracted: title, journal, year of publication, continent(s) in which the study was delivered and the number of countries from which participants were recruited, the number of participants, the number of primary and secondary outcomes, study type (RCT or observational), follow-up duration, funding source of the trial (whether wholly industry, non-industry or combined/both), cardiovascular disease category (as mentioned in the introduction), intervention type (device, drug or other) and result type (statistically significant or not). A device / drug study was defined as any study

that investigated the safety or effectiveness of an interventional procedure, technique or medication. ‘Other’ was defined as anything that was neither a drug nor device study, such as investigating the impact of quality improvement toolkits on outcomes for ACS patients.(196) Statistically significant result was defined as any result that met the pre-defined threshold for significance in each trial which included non-inferiority trials.

Given the breadth of outcomes present, only the first primary outcome measure stated, its definition (as reported verbatim in the manuscript text by the study authors) and result (statistically significant or not) was extracted. The primary outcome measure was categorised as a composite if there was more than one outcome measure considered collectively for the analysis, for example, all-cause mortality and stroke. Other primary outcome measures were grouped according to their clinical topic. All study characteristics, outcomes and their definitions were tabulated and recorded in Microsoft Excel.

3.4.6 Data analysis

3.4.6.1 Risk of bias (quality) assessment

Studies were assessed for bias using the Newcastle-Ottawa score for observational studies and risk of bias 2 toolkit for RCTs and recorded in line with guidelines for reporting systematic reviews.(197, 198)

3.4.7 Data synthesis and statistical analysis

Study characteristics were summarised using counts and proportions for categorical variables, means with standard deviation (SD) for normally distributed and medians with interquartile range (IQR) for non-normally distributed data. The outcome measures reported (e.g. left ventricular EF) were thematically categorised, and these were used to classify subsequent studies, whilst remaining open to adding additional categories if further themes emerged. The data synthesis on outcome measures was stratified by year of publication, sample size, study design, cardiovascular disease type, intervention type, funding source and whether the result was statistically significant or not. The heterogeneity of outcome selection and definition was described

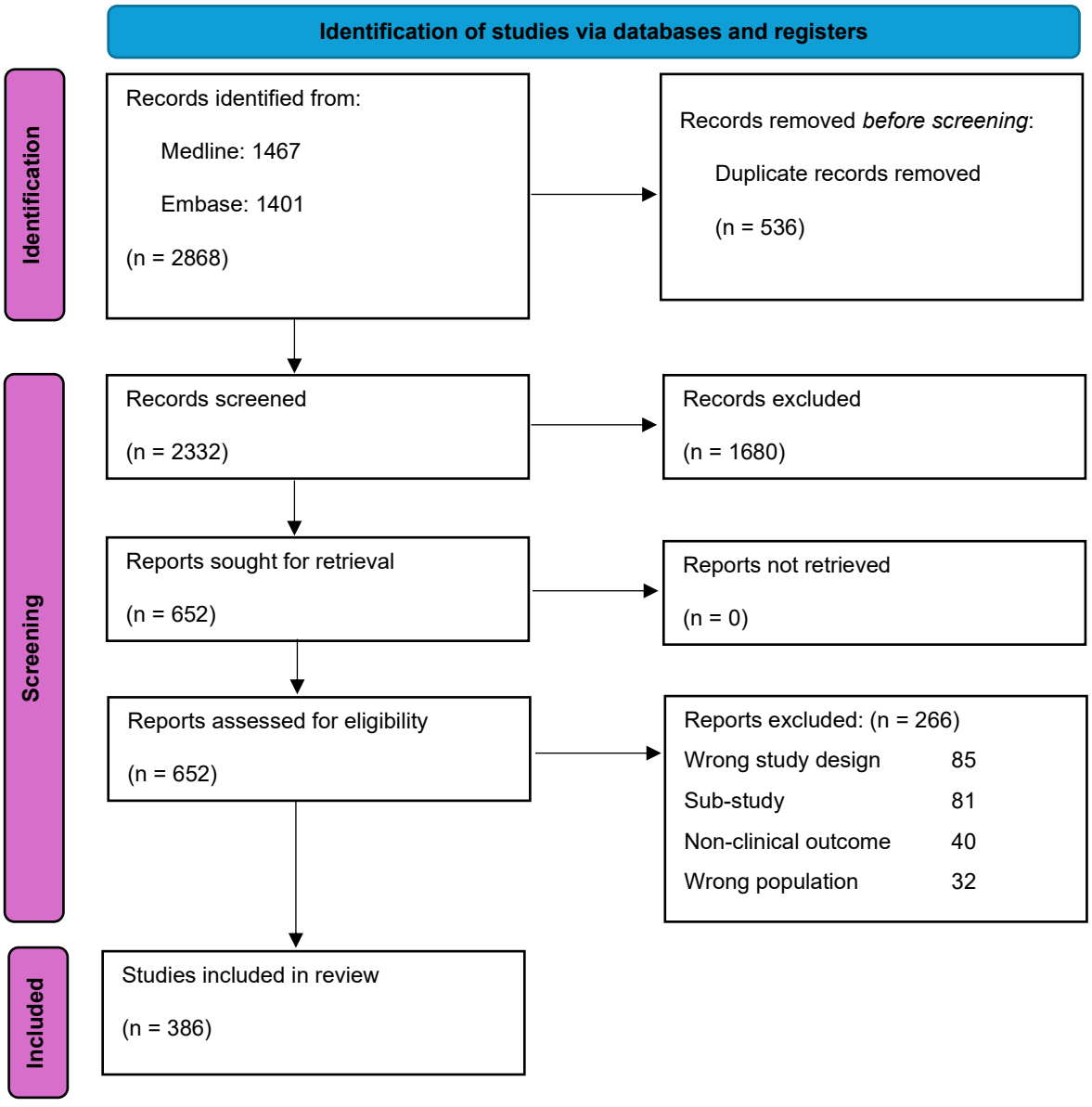
narratively. The most used outcome measure definitions were also synthesised narratively. Stata 17 MP was used for the analysis, and R for data visualisation.

3.5 Results

3.5.1 Study selection and characteristics

Of 2,868 unique citations screened, 386 were included in the review after full-text evaluation. (**Figure 3.1**). Of these, 168 (44%) were published in the NEJM, 112 (29%) in JAMA, and 106 (27%) in the Lancet, comprising 320 (83%) RCTs and 66 (17%) observational studies.

Figure 3.1. PRISMA diagram of included studies.



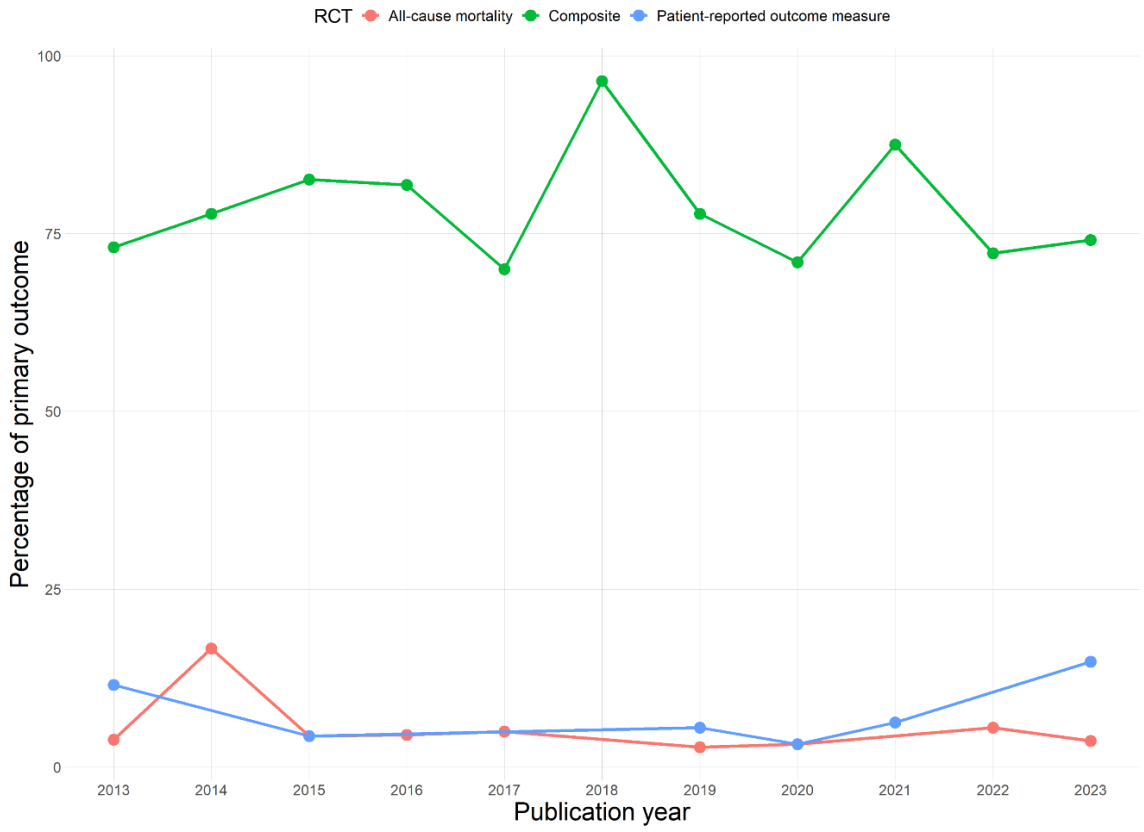
In total, there were 10,699,147 participants recruited from six continents. Studies included participants most commonly from Europe (n = 260, 67%) and/or North America (n = 222, 58%). Participants from Asia were included in 134 (35%), Australia/Oceania in 97 (25%), South America in 84 (22%), and Africa in 42 (11%) (**Figure 3.2**).

Figure 3.2. Temporal trends in numbers of published studies stratified by design according to continent

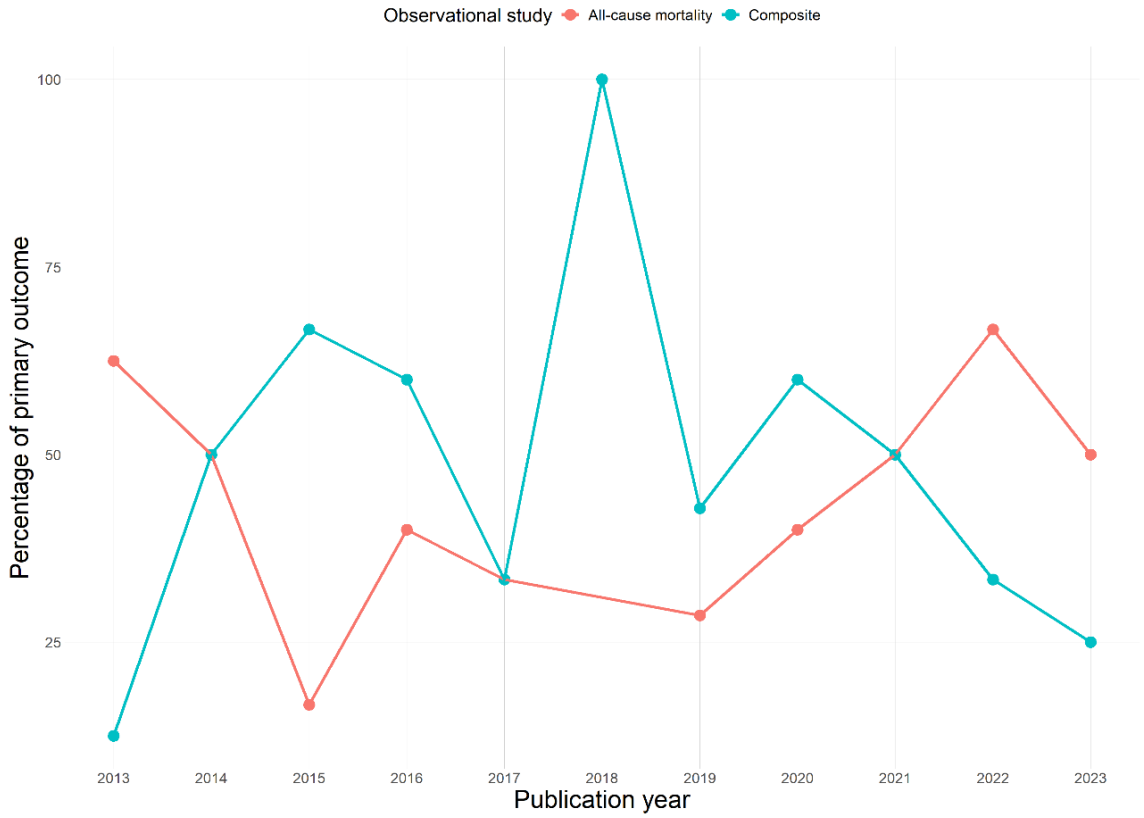
Most frequently, one country was included (n=162, 42%), and the maximum was 57 countries (median 3, IQR 1 to 12). Over the complete years of the review (1st January 2013 to 6th June 2024), the mean number of studies included was 35.1 (SD 3.4) per year, which appeared stable over time.

Overall, the most frequently reported primary outcome was a composite of two or more elements (243 studies, 63%), followed by all-cause mortality (35 studies, 9%) for both RCTs and observational studies. A PROM was the third most frequently employed outcome measure for RCTs alone (**Figure 3.3**).

Figure 3.3. Temporal trends in primary outcome measures for A) randomised clinical trials



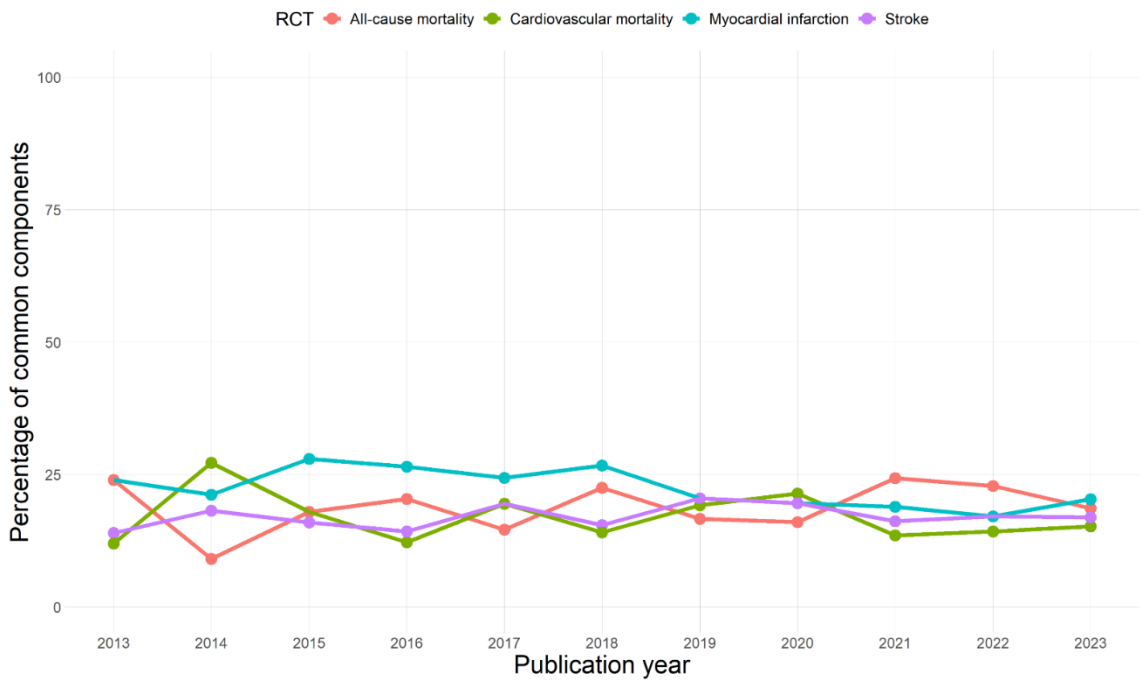
B) Observational studies



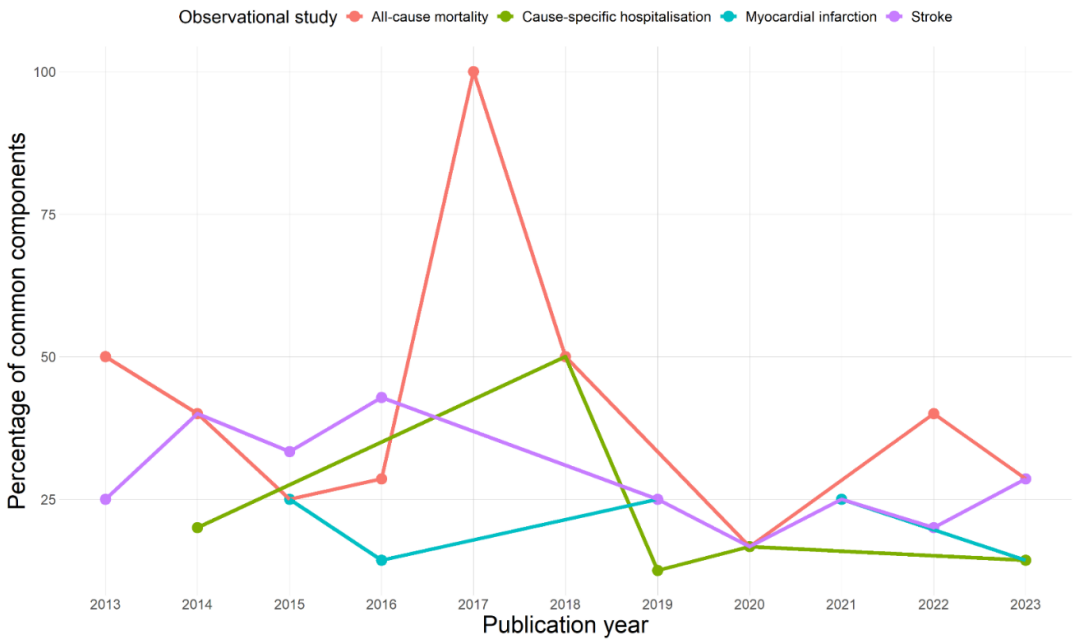
Where the primary outcome was a composite, the most common components overall were MI (142 studies, 58%), all-cause mortality (125 studies, 51%), stroke (116 studies, 48%) and cardiovascular mortality (104 studies, 43%). Overall, there was heterogeneity in the distribution of the components of the primary outcome measure included in the composite according to their frequency of use **(Figure 3.4)**.

Figure 3.4. Temporal trends in the most common components of composite outcome measures in A) randomised clinical trials and B) observational studies.

A)



B)



Most studies had a primary focus on coronary heart disease (n=197, 51%) followed by cardiomyopathy / HF (n=85, 22%), heart rhythm disease (n=58, 15%), valvular heart disease (n=42, 11%) and other cardiovascular diseases (n=4, 1%; **Table 3.1**).

Table 3.1. Characteristics of the included studies and their outcome measures by disease category.

Category	Study type	Number of studies	Number of participants		Number of primary outcome measures reported		Number of studies that report secondary outcome measures	Number of secondary outcome measures reported *	
		(% of category)	Total	Median (IQR)	Median (IQR)	Range		Median (IQR)	Range
Coronary disease and ischaemia	RCT	172 (87)	857,246	2,441 (1257 – 5,691)	1 (1 – 1)	1 - 8	164 (94%)	5 (2 - 9)	1 - 27
	Observational	25 (13)	6,857,735	28,304 (4,314 – 62,048)	1 (1 - 2)	1 - 4	13 (57%)	1 (0 – 4)	1 - 17
Cardiomyopathy and HF	RCT	74 (87)	156,541	888 (422 – 2,859)	1 (1 - 2)	1 - 5	41 (55%)	5 (3 - 7)	1 – 20
	Observational	11 (13)	694,440	5,816 (794 – 23,341)	1 (1 - 2)	1 - 4	4 (36%)	5 (3 – 5)	1 – 9
Heart rhythm	RCT	43 (74)	62,845	455 (300 – 1,902)	1 (1 - 2)	1 - 3	44 (98%)	4 (3 – 10)	1 – 26
	Observational	15 (26)	1,050,942	15,400 (526 – 51,496)	2 (1 – 3)	1 - 4	9 (69%)	1 (1 – 4)	1 – 7
Valvular heart disease	RCT	28 (67)	32,793	913 (375 – 1,535)	1 (1 – 2)	1 - 3	28 (100%)	7 (4 – 10)	1 – 38
	Observational	14 (33)	821,775	19,547 (1077 – 91,330)	2 (1 – 2)	1 - 4	12 (86%)	2 (1 – 3)	1 – 11
Other	RCT	3 (75)	10,834	321 (2709 – 8,126)	1 (1 – 2)	1 - 2	2 (67%)	3 (2 – 5)	3 – 6
	Observational	1 (25)	153,996	153,996 (N/A)	2	N/A	N/A	0	N/A

Abbreviations IQR: interquartile range; RCT: randomised clinical trial

* of those studies that report secondary outcome measures

3.5.1.1 Funding

Industry funded most studies (n=184, 48%) followed by non-industry funded (n=118, 31%) and some were funded by both (n=84, 22%, **Table 3.2**).

Table 3.2. Characteristics of observational studies and randomised clinical trials and their outcome by funding source.

Funding	Intervention (%)			Primary outcomes		Secondary outcomes	
	Device	Drug	Other	Median (IQR)	Range	Median (IQR)	Range
RCT							
Industry	74 (45)	59 (54)	3 (1)	1 (1 - 2)	(1 - 5)	5 (2 - 7)	(0 - 38)
Non-Industry	24 (31)	37 (48)	16 (21)	1 (1 - 2)	(1 - 4)	5 (1 - 8)	(0 - 27)
Both	44 (57)	28 (36)	5 (7)	1 (1 - 2)	(1 - 8)	5 (2 - 8)	(0 - 26)
Observational							
Industry	13 (72)	3 (17)	2 (11)	1 (1 - 2)	(1 - 5)	2 (2 - 4)	(0 - 11)
Non-Industry	14 (34)	9 (22)	18 (44)	1 (1 - 2)	(1 - 4)	1 (1 - 2)	(0 - 17)
Both	4 (57)	3 (43)	0 (0)	2 (1 - 2)	(1 - 3)	2 (1 - 3)	(0 - 7)

Abbreviations RCT: randomised clinical trials; IQR: interquartile range

3.5.1.1.1 Industry

Industry funded 184 of the studies (48%), most of which were RCTs (166 studies; 90%) and half of which investigated drugs (92 studies, 50%) followed by devices (87 studies, 47%). These studies reported between one to eight primary outcomes (median 1, IQR 1 to 2). The most frequently reported primary outcome was a composite (131 studies, 71%). A median of six secondary outcomes were reported in each study (range 0 to 27, IQR 2 to 8, **Table 3.2**).

3.5.1.1.2 Non-industry

Of 118 non-industry funded studies, 77 were RCTs (65%) and most investigated drugs (46 studies, 39%). These studies reported between one to four primary outcome measures (mean 1, median 1, IQR 1 to 2). The most frequently reported primary outcome was a composite (59 studies, 50%). A median of four secondary outcomes were reported by each study (range 0 to 27, IQR 1 to 7, **Table 3.2**).

3.5.1.1.3 Industry and non-industry

84 studies were funded by both industry and non-industry partners of which most (77 studies, 92%) were RCTs, and the majority investigated devices (48 studies, 57%). They reported between one to eight primary outcomes (median 1, IQR 1 to 2), and the most frequently reported primary outcome measure was a composite (53 studies, 63%). A median of five secondary outcomes were reported by each study (range 0 to 26, IQR 2 to 9, **Table 3.2**).

3.5.1.2 Device

Included studies were mostly either device related (n=173, 45%) or drug related (n=169, 44%) and a minority of studies investigated care processes or lifestyle measures that did not directly investigate a drug or a device (n=44, 11%, **Table 3.3)**.

Table 3.3. Characteristics of observational studies and randomised clinical trials and their outcomes reported by intervention**.**

Funding	Funding (%)		Study type (%)			Primary outcomes		Secondary outcomes	
	Industry	Non Industry	Both	RCT	Observational	Median (IQR)	Range	Median (IQR)	Range
Intervention									
Device	87 (50)	38 (22)	48 (28)	142 (82)	31 (18)	1 (1 - 1)	(1 - 5)	5 (2 - 8)	(0 - 38)
Drug	92 (54)	46 (27)	31 (18)	154 (91)	15 (9)	1 (1 - 2)	(1 - 8)	5 (2 - 8)	(0 - 20)
Other	5 (11)	34 (78)	5 (11)	24 (55)	20 (45)	1 (1 - 2)	(1 - 4)	3 (2 - 7)	(0 - 27)

Abbreviations IQR: interquartile range; RCT: randomised clinical trial

Of the 173 studies investigating devices, most were RCTs (142 studies, 82%) and a majority were industry funded (87 studies, 50%). The number of primary outcomes ranged from one to five (median 1, IQR 1 to 1). The most frequently reported primary outcome measure was a composite (108 studies, 62%). A median of five secondary outcomes were reported by each study (range 0 to 38, IQR 2 to 8, **Table 3.3**).

3.5.1.3 Drugs

Most included drug trials were RCTs (154 of 169 studies, 91%) and the majority were industry funded (92 studies, 54%). The number of primary outcomes ranged from one to eight outcome measures (median 1, IQR 1 to 2). The most frequently reported primary outcome measure was a composite (118 studies, 70%). Each study reported a median of five secondary outcome measures (range 0 to 20, IQR 2 to 8,**Table 3.3**).

3.5.1.4 Other

Most studies that were not classed as either drug or device trials were RCTs (24 of 44 in total, 55%). These studies were primarily funded by non-industry partners (34 studies, 78%). The number of primary outcomes ranged from one to four (median 1, IQR 1 to 2). The most frequently reported primary outcome measure was a composite (17 studies, 39%). Each study reported a median of three secondary outcome measures (range 0 to 27, IQR 2 to 7, **Table 3.3)**.

3.5.1.5 Statistically significant results

Most included studies reported a statistically significant result (n=254 studies, 66%, **Table 3.4**).

Table 3.4. Characteristics of observational studies and randomised clinical trials and their outcome measure by statistically significant results.

Results outcome	Study type (%)		Primary outcomes		Most common primary outcome		Most common components	Secondary Outcomes	
	RCT	Obs	Median (IQR)	Range		(n; % of studies)		Median	Range
Significant (254)	206 (81)	48 (19)	1 (1-2)	1 - 8	Composite	153 (60)	MI (94; 61) Stroke (76; 50)	4.5 (2-9)	0 - 38
Non-significant (132)	114 (86)	18 (14)	1 (1-2)	1 - 6	Composite	90 (68)	All-cause mortality (52; 58) MI (48; 53)	5 (2-7)	0 - 23

Abbreviations RCT: Randomised clinical trial; Obs: Observational studies; IQR: Interquartile range; MI: Myocardial Infarction;

Most of the included studies reported a statistically significant primary outcome (n =254 studies, 66%) and most of the statistically significant primary outcomes studies were RCTs (n = 206 studies, 81%, **Table 3.4**). The number of primary outcomes ranged from one to eight (median 1, IQR 1 to 2). The most frequently reported primary outcome was a composite (n=153 studies, 60%) with MI and stroke being the most frequently used components. Each study reported a median of 4.5 secondary outcome measures (range 0 to 38, IQR 2 to 9).

3.5.1.6 Non statistically significant results

Of the 132 studies that reported a non statistically significant result most were reported by RCTs (n = 114 studies, 86%, **Table 3.4**). The number of primary outcomes employed ranged from one to six (median 1, IQR 1 to 2). The most frequently reported primary outcome was a composite (n= 90 studies, 68%) with all cause mortality and MI being the most common components. Each study reported a median of 5 secondary outcomes (range 0 to 23, IQR 2 to 7).

3.5.2 Temporal trends

Over time, there was a trend towards a less frequent use of all-cause mortality as the single primary outcome measure **(Figure 3.3)**. Moreover, the proportion of studies using composites as a primary outcome measure increased from 49% in 2013 to a peak of 85% in 2018 to 55% in 2023. The most frequently used components of those composites remained relatively stable, with an increase in the reporting of all-cause mortality and hospitalisation in recent years **(Figure 3.4)**.

During the study period, the median number of participants enrolled appeared to decline overall but not consistently across all subgroups. For example, in non-industry funded RCTs and observational studies, the median number of participants enrolled increased from of 519 and 8,188 in 2013 to 2,859 and 23,341 in 2023 respectively. However, the median number of participants enrolled in RCTs generally declined from 1,811 to 764 in 2013 to 2023, respectively (**Figure 3.5 and Table 3.5**).

Figure 3.5. Temporal trends in the median number of participants recruited by funding source in observational studies and randomised clinical trials

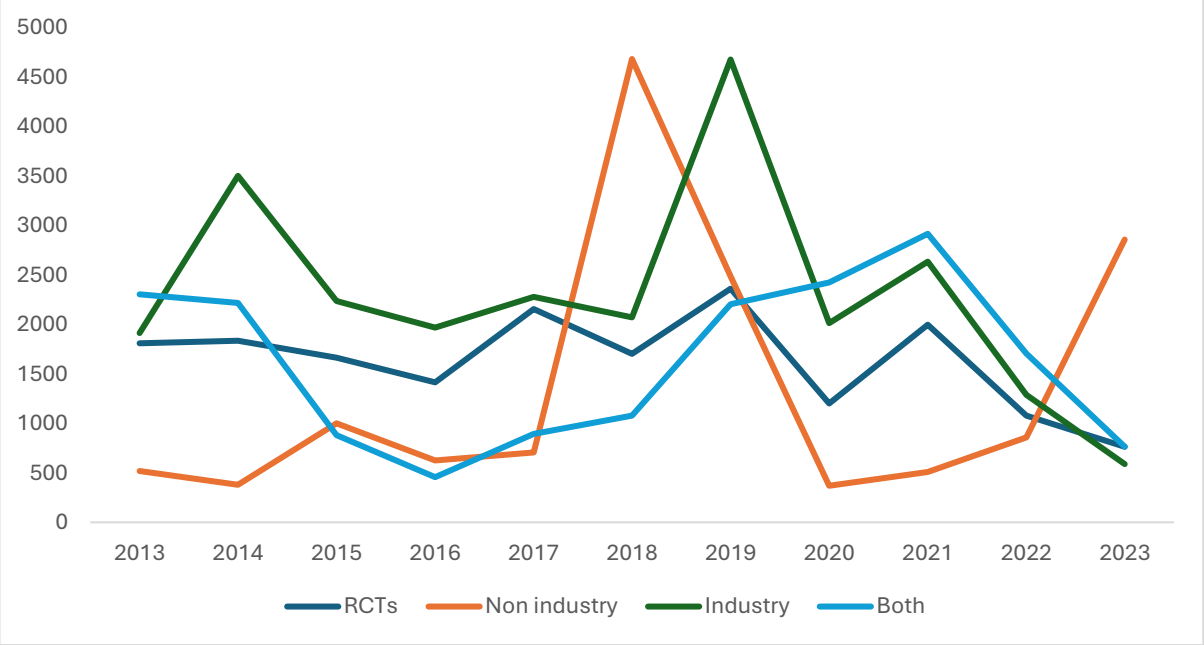


Table 3.5. Median number of participants by funding source and intervention over time for randomised clinical trials and observational studies per year of publication

Intervention	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
RCT	1811	1837	1666	1416	2157	1704	2362	1201	1999	1078	764
Industry	1915	3504	2237	1969	2281	2071	4679	2014	2635	1289	589
Non-industry	519	380	1000	627	706	4684	2488	370	509	860	2859
Both	2304	2219	880	457	894	1078	2204	2425	2917	1706	764
Drug	1811	716	1666	1208	1316	900	1368	942	663	1286	418
Device	1963	6186	2854	2199	6318	5022	3532	2168	2697	1108	2962
Other	1921	552	710	100	894	21374	6120	140	349	1002	3157

Observational	8188	13719	15314	21339	91330	21312	1563	9106	33181	114871	23341
Industry	6848	459	9486	22672	1000	0	794	0	3629	477	186966
Non-industry	24169	24317	40616	20006	92902	21312	107546	5541	62048	2227502	1118976
Both	1021	0	10318	0	0	0	0	31290	0	114871	303
Drug	7710	1790	11250	10542	1000	0	1563	5541	3629	57674	19088
Device	5031	24317	51294	22672	91330	21312	794	31290	581451	0	0
Other	16417	37674	22369	119735	609735	0	113662	0	33181	2227502	121103

The number of secondary outcome measures per study increased from a mean of 3 in 2013 to a mean of 8 in 2023 and peaked at 9 in 2022. The median use of secondary outcomes per study and by study type also increased (RCT = 3 in 2013 to 6 in 2023 with a peak of 7.5 in 2018; observational studies = 0 in 2013 to 7 in 2023 (**Figure 3.6, Figure 3.7 and Table 3.6)**. Non-industry funded observational studies demonstrated the greatest increase in the use of secondary outcomes from a median of 0 in 2013 to 6.5 in 2023 with a peak of 9 in 2019 **(Figure 3.6 and Table 3.6).**

Figure 3.6. Median number of secondary outcome measures by study design and funding.

Figure 3.7. Temporal trends in the median number of components of primary and secondary outcomes by study type.

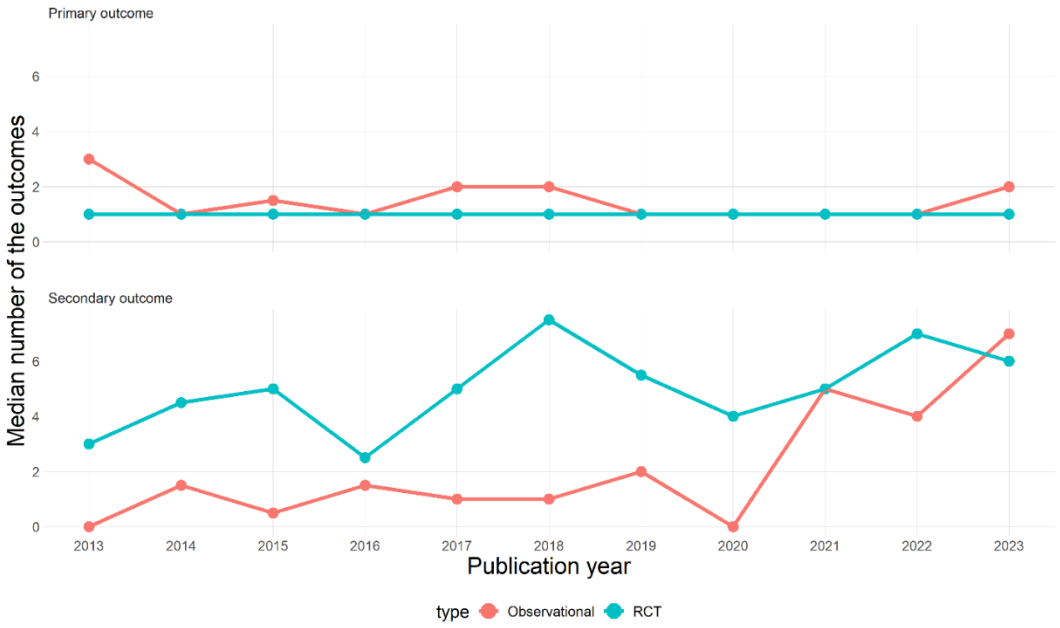


Table 3.6. Median number of secondary outcome measures per year, per funding source and intervention for randomised clinical trials and observational studies by year of publication

Intervention	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
RCT	3	4.5	5	2.5	5	7.5	5.5	4	5	7	6
Industry	3	4.5	5.5	3	5	7.5	5.5	5	6	5.5	6
Non-industry	6.5	5	5	3	4	7	5	3	5	11.5	5
Both	2	3	4	1	7	8.5	8	4	6	7	8
Drug	3	5	5.5	3	6.5	9	8	2	5	11.5	7
Device	3	4.5	5	2	4.5	5	5	5	7	5	5
Other	6.5	0	4	0	7	7	6.5	6	3	27	4

Observational	0	1.5	0.5	1.5	1	1	2	0	5	4	7
Industry	0	1	2	5	1	0	3	0	1	9	5.5
Non-industry	0	2	0	0	1	1	1	0	7	4	6.5
Both	2	0	0	0	0	0	0	7	0	0	7
Drug	0	0.5	0.5	1.5	1	0	2	0	1	4.5	7
Device	0	0	0.5	5	1	1	5	7	3	0	0
Other	0	2	0.5	0	1	0	1	0	12	4	4.5

3.5.3 Coronary heart disease

Of the 197 studies of coronary heart disease, 172 (87%) were RCTs (**Table 3.1**). These included a total of 857,246 participants (median 2,441, IQR 1,257 to 5,691, **Table 3.5)**. Of these, between one and eight different primary outcome measures were reported (median 1, IQR 1 to 1). The most frequently reported primary outcome was a composite (142 studies, 82%). The composites included between two and ten components, and the most common components were MI (125 studies, 88%), cardiovascular mortality (77 studies, 54%) and revascularisation (74 studies, 52%). The next most frequently used primary outcome measure was bleeding (8 studies, 5%), followed by all-cause mortality (6 studies, 3%). Secondary outcome measures were reported in 164 studies (94%) with a median of five secondary outcome measures per study (range 1 to 27; IQR 2 to 9, **Table 3.1**).

In the 25 (13%) observational studies, there were 6,857,735 participants (median 28,304, IQR 4,314 to 62,048). Among these, between one and four different primary outcome measures were reported (median 1, IQR 1 to 2). The most frequently used primary outcome measures was all-cause mortality (11 studies, 48%), followed by a composite (7 studies, 30%). The composites included between three and five components, and the most common components were MI (6 studies, 86%), cardiovascular mortality (5 studies, 71%). Stroke and revascularisation were included in the composites of 4 studies each (57%). Secondary outcome measures were reported in 13 studies (57%), and one secondary outcome was reported as median (range 1 to 17; IQR 0 to 4).

3.5.4 Cardiomyopathy / HF

Of the 85 reported studies of cardiomyopathy and HF, 74 (87%) were RCTs with a total of 156,541 participants (median 888, IQR 422 to 2859, **Table 3.5**). Between one and five primary outcome measures were reported (median 1, IQR 1 to 2). The most common primary outcome was a composite (45 studies, 61%). The composites included between two and ten

components, and the most common components were cause-specific hospitalisation (28 studies, 62%), all-cause mortality (26 studies, 58%) and cardiovascular mortality (18 studies, 40%). The next most frequently used primary outcome measures were physiological parameter (11 studies, 15%) and patient reported outcome measure (5 studies, 7%). Secondary outcome measures were reported in 41 studies (55%) with a median 5 secondary outcome measures per study (IQR 3 to 7; range 1 to 20).

In the 11 (13%) observational studies, there were 694,440 participants (median 5,816, IQR 794 to 23,341). Between one and four primary outcome measures were reported (median 1, IQR 1 to 2). The most commonly used primary outcome measures were all-cause mortality (5 studies, 46%), followed by a composite outcome (2 studies, 18%). Secondary outcome measures were reported in 4 studies (36%) with a median five secondary outcomes (IQR 3 to 5; range 1 to 9).

3.5.5 Heart rhythm

Of the 58 studies on heart rhythm, 45 (74%) were RCTs with a total of 62,845 participants (median 455, IQR 300 to 1,902). Between one and three primary outcome measures were reported (median 1, IQR 1 – 2). The most frequently used primary outcome measure was a composite (14 studies, 31%). The composites included between two and five components, with the most frequently used components being stroke (8 studies, 57%), systemic embolism (6 studies, 43%) and cardiovascular mortality (4 studies, 29%), recurrence or relapse of arrhythmia (11 studies, 24%), and a patient-reported outcome measure (5 studies, 11%). Secondary outcome measures were reported in 44 studies (97.8%) with a median number of four secondary outcome measures per study (IQR 3 to 10; range 1 – 26).

In the 15 (26%) observational studies, there were 1,050,942 participants (median 15,400, IQR 526 to 51,496). Between one and four primary outcome measures were reported (median 2, IQR 1 to 3). The most frequently reported primary outcome was a composite (7 studies, 54%). The composites included between two and six components, and the most common components were all-cause mortality (5 studies, 71%) and then stroke (4 studies, 57%). Recurrence

or relapse was the next most frequently reported primary outcome (2 studies, 15%). Secondary outcome measures were reported in 9 studies (69%) with a median of one secondary outcome measure per study (IQR 1 to 4; range 1 to 7).

3.5.6 Valvular heart disease

Of the 42 studies on valvular heart disease, 28 (67%) were RCTs with a total of 32,793 participants (median 913, IQR 375 to 1,535). Between one and three primary outcome measures were reported (median 1, IQR 1 to 2). The most reported primary outcome was a composite (18 studies, 64%). The composites included between two and ten components, and the most common components were all-cause mortality (17 studies, 94%), stroke (13 studies, 72%), and cause-specific hospitalisation (6 studies, 33%). All-cause mortality was the next most frequently reported primary outcome (4 studies, 14%), followed by bleeding (2 studies, 7%). Secondary outcome measures were reported in all 28 studies (100%) with a median of seven secondary outcome measures per study (IQR 4 to 10; range 1 – 38).

In the 14 (33%) observational studies, there were 821,775 participants (median 19,547, IQR 1077 to 91,330). Between one and four primary outcome measures were reported (median 2, IQR 1 to 2). The most reported primary outcome was a composite outcome (6 studies, 43%), followed by all-cause mortality (4 studies, 29%). The composites included two or three components, and the most common components were both stroke (5 studies, 83%), and all-cause mortality (5 studies, 83%). Secondary outcome measures were reported in 12 studies (86%) with a median of two secondary outcome measures per study (IQR 1 to 3; range 1 to 11).

3.5.7 Other cardiovascular diseases

Four studies (three RCTs and one observational study) were eligible for inclusion in more than one category. These studies included 164,830 participants (median 5,141, IQR 2,787 to 79,628). One to four primary outcome measures were reported (median 1, IQR 1 to 3). Secondary outcome measures

were reported in two RCT studies (67%), with a median of three secondary outcome measures per study (IQR 2 – 5; range 3 to 6).

3.5.8 Summary of results

- Most studies (n=184, 48%) were industry funded, and most investigated devices (n=173, 45%).
- The majority of studies, when stratified by funding or intervention, were RCTs that employed a composite as the primary outcome measure (n=124 studies, 75%; n=44 studies, 57%; n=52 studies, 68%; n=96 studies, 68%; n=111 studies, 72%; n=13 studies, 54%; for industry, non-industry combined/both funding, device, drug and other intervention respectively).
- Of these the most frequently used components of the composites were all cause mortality (in non-industry, combined funding / both, device, drug and other intervention trials) followed by MI (in industry, non-industry, combined funding / both and device trials)
- Most studies reported a statistically significant primary outcome (66%) and a composite primary outcome was most frequently employed across the three journals and whether the primary outcome reported was statistically significant or not. The most common components were commonly all-cause mortality and MI.
- Most studies concerned coronary heart disease (n=197, 51%) followed by cardiomyopathy / HF (n=85, 22%).
- Overall, the most frequently reported primary outcome across each CVD category was a composite. These ranged between two and ten components and the most common components, across all studies, were MI (142 studies, 58%) and all-cause mortality (125 studies, 51%). All-cause mortality and stroke were the most common components in the domains except for coronary heart disease.
- Overall, the distribution of the components of the primary outcome measure included in the composite varied according to their frequency of use by study design.

- The most frequently used components of composites remained relatively stable over time, with an increase in the reporting of all-cause mortality and hospitalisation in recent years.
- The frequency of use of secondary outcome measures varied, with a high proportion of studies reporting them in heart rhythm, valvular heart disease and coronary heart disease studies and lower rates in cardiomyopathy studies.

3.5.9 Outcomes and their definitions.

3.5.9.1 Mortality

All-cause mortality formed the primary outcome measure in 158 studies (125 as part of a composite). The definition of all-cause mortality was consistent across all relevant studies.

Cardiovascular mortality was reported in 107 studies (104 as part of the composite), and there was wide variation in the definitions used. The definitions of what constitutes cardiovascular mortality were not always reported in the study manuscript, and were often absent from the protocol or supplementary materials (34%)(199-201) or partially defined to include unexplained death only with no other details (15%).(202) Partially defined studies employed bespoke study specific definitions: presuming all deaths to be cardiovascular unless there was a clear demonstration of a non-cardiac cause.(203, 204) In another example, cardiovascular mortality was the first of two primary outcome measures.(199) This was added *post priori* following the publication of the Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) trial and the definition was not stated in the manuscript (although adjudication by an independent Clinical Events Committee was undertaken).(205) The majority of studies employed one consensus-based definition of cardiovascular mortality (51%). Half of these studies (47%; 24% of total) employed a broad definition of cardiovascular mortality in line with consensus documents published in 2018.(206, 207) This included: MI, pump failure, pulmonary embolism, stroke, presumed and confirmed sudden death, post procedural death and presumed cardiac death.(208) These definitions did not include death of unknown causes in contrast to others studies (53%; 27% of total studies) which aligned with other consensus documents.(209-211)

3.5.9.2 Myocardial infarction

MI formed the primary outcome measure for 143 studies (in 142 as a component of a composite) and definitions were not universally reported. In some studies (17%), no definition was provided.(212, 213) In one paper, definitions were not provided in the manuscript, and the supplementary material stated that definitions would be provided in the 'MACE Clinical Events Committee charter',(214) which is not published.

Where MI was defined, definitions varied. In some studies (20%), study-specific criteria were used, which were sometimes complex and bespoke. One study employed two definitions of MI, one for the primary outcome measure and the other for its secondary outcome measure; to capture all types of MI.(215) Another study changed the definition used since its protocol had been published to a more contemporary definition(216) with the adjudicating committee still blinded to the group allocation and results.(217) Using differing definitions of MI may alter event rates and therefore the overall result of the study as explained in **section 1.3.1.** More recently, consensus definitions such as the Third and Fourth Universal Definition of MI were employed and were the main definition used in studies (63%).(218-222) The definition of a peri-procedural MI was inconsistent – for example, one required higher biomarker thresholds for defining an MI compared to the traditional type 1 threshold, citing data that a more stringent definition 'had greater prognostic significance than the universal definition types 4a and 5'.(218)

3.5.9.3 Stroke

Often (50%) stroke was defined as a 'non-traumatic focal neurologic deficit lasting greater than 24 hours',(223) and was classified as ischaemic, ischaemic with haemorrhagic transformation, haemorrhagic or of uncertain type. A transient ischemic attack was defined as a non-traumatic abrupt onset of a focal neurologic deficit lasting less than 4 hours.(223) In some studies (14% of all), stroke was not defined.(224)

Consensus definitions included those by the VARC.(225) Stroke was further classified using the modified Rankin score into disabling (2 or more) or non-disabling (<2) at 90 days.(226)

3.5.9.4 Bleeding

Bleeding was used as a primary outcome in 42 studies (29 as part of a composite). Consensus definitions included the International Society on Thrombosis and Haemostasis,(227) Thrombolysis in Myocardial Infarction,(228) the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria(229) and the Bleeding Academic Research Consortium (BARC).(228) The most commonly used consensus definition was BARC (81%). One manuscript that used its own study-specific criteria also reported consensus-based criteria.(230)

3.5.10 Risk of bias

Most (78%) of the included RCTs and observational studies had a low risk of bias. There were some areas of concern particularly in deviations in assignment and adherence (22%). There were no areas of high concern in any of the studies. (**Appendix A.3 and A.4)**.

3.5.11 Summary

- All cause mortality was defined consistently in all included studies

- The definitions employed for CV mortality was inconsistent across included studies. Over a third (34%) of studies did not provide a definition within the main manuscript or trial protocol.

- Over half of included studies that employed CV mortality gave a definition (51%) that was aligned with a consensus definition with the remaining studies providing a partial definition only (15%).

- Of the studies that provided a clear definition of CV mortality, half aligned with the SCTI definitions in 2018 (47%, 24% of total) whereas the other half aligned with contrasting consensus documents (53%).

- Most studies provided a clear definition for MI (63%) that aligned with either the Third or Fourth Universal Definition of MI and a minority of studies provided no definition (17%).

- A fifth of studies provided study specific definitions for MI (20%) that were bespoke.

- Stroke and bleeding were defined were more consistently across the included studies.

- The risk of bias for the majority of included studies was low (78%).

3.6 Discussion

In this systematic review of 386 RCTs and observational studies of CVD published in three highly-cited international medical journals during the past decade, the primary outcome measure employed was a composite in more than half of studies. The use of a primary composite outcome increased and by 2018 eight in ten studies were using composites as the first stated primary outcome measure. In parallel, the number of secondary outcome measures per study increased. These findings were consistent across both RCTs and observational studies, journals, outcome results, sources of funding, disease area and study design. Furthermore, we found wide variation in the number and type of outcome measures, and their definitions were often incomplete or not reported in the primary results manuscript.

Outcome measure definitions, where reported, were inconsistent between studies which challenges the interpretation of studies and limits their comparisons with similar studies. (9) For example, the definitions of MI, if given, varied over the past decade. Some, but not all, variability is expected given that common consensus definitions have updated over time that are not aligned, such as the 3rd and 4th universal definition of MI.(221, 231-233). In contrast bleeding was an infrequent primary outcome (11% of all studies) with most definitions opting for BARC.(228) This could be because bleeding is becoming a less important outcome in intervention studies given the safety and efficacy of contemporary anti-thrombotic therapies.(234) When bleeding was reported, it was frequently part of a composite, which may suggest that low absolute event rates associated with advanced medical therapy were anticipated, or that patients with low risk of bleeding were investigated.

Previous studies have demonstrated heterogeneity in how MACE is defined and classified. (44, 179) In this work, the components of composites were not limited to MACE, and up to six components were included. This may be problematic as inappropriate combinations of composites may introduce bias because each component differs in clinical significance, (235, 236) particularly if they are not separated into safety and efficacy composites.(179) Subsequently, elevated event rates and treatment effects associated with less important components may ‘result in misleading impressions of the impact of treatment’.(237) As cardiovascular morbidity and mortality decline, studies need to be larger or

combine outcomes measures to reach sufficient statistical power to detect a meaningful difference between groups where it truly exists. Given that large studies incur additional delivery complexity and cost, our finding that the trend to use more composite and secondary outcomes over time is unsurprising.

Our finding of trials employing an increasing number of secondary outcomes matches previous trials on CVD outcomes published in highly cited journals.(180) Interpreting statistically significant secondary outcomes presents a challenge for trialists especially if the primary outcome was not statistically significantly different between groups, as it may increase the risk of type 1 statistical error. (238) Type 1 error occurs when the null hypothesis is incorrectly rejected, such as the intervention has no effect, and is more likely to occur when a trial employs multiple outcome measures. This may be problematic as employing multiple outcome measures (or multiple components of a composite) may increase the risk of falsely detecting a difference where there truly is none. As a result, a trial may falsely imply the efficacy or safety of an intervention, increase reporting bias and complicate the interpretation of multiple studies of a similar intervention.(9, 180, 238)

Reporting bias can be compounded if outcome measures are not pre-specified and fully reported. Previous work found that only half of papers published in high-profile journals reported all of their specified outcome measures and on average each study added five new outcome measures during the conduct of the study.(49) This may have impacted the included studies and therefore our analyses. To this end, the cardiovascular and stroke outcome definition for clinical trials was published but there has been a small uptake in its use since their publication in 2018 (n = 11 studies, 9%).(206) This may occur because changing outcome definitions midway through a trial is unlikely to occur (as this may differ to its original trial protocol) and could account for these small changes as well as the presence of alternative consensus definitions that are not aligned for the common cardiovascular conditions. (225, 231, 239) Eventually, there may be higher uptake of the SCTI definitions in due time (or others) given the lifecycle of large trials may be long (from trial planning, delivery and eventual publication of results).(206) Nonetheless the criteria for outcome definition for participants of studies for valvular heart disease are more

consistently employed – suggesting opportunities to utilise standardised outcome definitions internationally.(9, 240, 241)

The *a priori* selection of patient-relevant, clinically-meaningful and standardised study outcome measures is fundamental to the delivery of high quality clinical research and innovation.(190) Novel methods are employed to plan, conduct and interpret RCTs and observational studies, that include routinely collected data from electronic health records and registries.(242) Accurate use of such datasets for recruitment and in follow-up for RCTs, including registry-based trials, necessitates the mapping of finite outcomes and their definitions to commonly used coding frameworks,(243) as historically outcomes such as MI have limited specificity and sensitivity in administrative data.(244) The 'Aspirin Dosing: A Patient Centric Trial Assessing Benefits and Long Term Effectiveness' (ADAPTABLE) trial used a common data model as the outcome measure ascertainment without adjudication, and found that the positive predictive values for hospitalisation for MI, stroke, and major bleeding, compared to adjudication were 90%, 72%, and 93% respectively.(245) Whilst adjudication of outcome measures is considered important to minimise noise and mitigate bias,(246) there are increasing data to support the use of routinely collected health data for outcome measure ascertainment.(246, 247) Recent work has sought to meet the need for standardised outcome measures and their definitions in order to improve the quality and generalisability of outcome reporting across registry and study designs.(241)

3.6.1 Strengths of the review

This was a carefully constructed systematic review that had a number of strengths that guide improvements in the design and conduct of clinical CVD research.

The review was methodologically robust and followed the PRISMA guidelines,(248) with transparency in the aims, conduct and reporting. The search strategy employed was built on previous work on outcomes and, after consulting with a research librarian, was appropriate and comprehensive. The included articles, therefore, are an accurate portrayal of the design and conduct of contemporary CVD trials published in highly-cited journals.

Furthermore, both the inclusion criteria and study characteristics of the included articles investigated were thorough. The review included articles from the past 11 years of CVD research and extracted 14 study characteristics from each article.

This is the first review, to our knowledge, that examined definitions of outcomes across a range of CVD such as CV mortality and MI, how this may have changed depending on key study characteristics such as funding and their temporal changes. Therefore the result from this systematic review has implications for research design across the major CVD and gives a good overview of the published literature that are available to clinicians.

3.6.2 Limitations of the review

There are limitations to this work. We focused on only three, albeit highly-cited and respected journals that limited the number of included trials, which were mainly RCTs (83%), in our analysis. Other journals with wide readership were not considered and these may include more observational trials or other major RCTs and the resultant analysis is therefore subject to publication bias. Publication bias is a type of reporting bias and refers to the tendency for journals to publish studies with positive findings (or in this case statistically significant results). (249)This may distort the ability to accurately synthesise and describe the evidence in each area. This is especially true for this systematic review, where two thirds of included studies reported a statistically significant finding (n =254 studies, 66%) However, the included studies provide an overview of the clinically relevant literature in which practice-changing work is presented to clinicians.

Our analysis majored upon the first primary outcome measure stated, which may have been subject to outcome reporting bias,(49) with limited analyses for outcomes that listed more than one primary outcome and of secondary outcome measures, for the main CVD states. We therefore lack detail on outcomes that frequently appear as the second primary outcome, secondary outcome measures such as PROMS, and on outcomes for other cardiovascular diseases. However, the median number of primary outcomes employed for most trials was 1. This suggests that the impact of reporting the subsequent

primary outcome(s) stated could have a limited impact on the overall trends reported in this analysis.

The outcome definitions examined were restricted to the most frequently reported five outcomes only (all-cause mortality, CV mortality, MI, stroke, bleeding) with limited analysis of the relationship between heterogenous outcome definitions with study characteristics such as funding, intervention type and CVD condition which would be noteworthy but lengthy to complete. Furthermore, our analysis did not examine important disease specific outcome definitions such as AF burden, HF event or HF hospitalisation. However the five outcomes stated above were the most frequently employed outcomes across all conditions (either as primary outcomes or as part of a composite) and their definitions have therefore broad applicability.

3.7 Conclusion

This investigation of outcome measures in RCTs and multicentre observational studies in cardiovascular disease published over a decade in major international clinical journals found evidence for the increasing use of composite outcome measures, an expansion in the number of secondary outcome measures employed per study, and variation in the primary outcome measures reported and their definitions. This heterogeneity has the potential to contribute to biases and potentially makes interpretation and cross-study comparisons problematic. The adoption of robust, internationally agreed and standardised outcome measure definitions for cardiovascular studies by trialists, funders, and regulatory bodies has the potential to improve the quality of clinical research.

3.8 Summary of chapter 3

- Outcome measures are fundamental to trial design and conduct. MACE are often used as a composite outcome measure in clinical studies of cardiovascular diseases.
- There is, however, limited literature about the nature and definitions of outcome measures in cardiovascular studies, and how this may have changed over time.
- For clinical studies of CVD, a composite is the most frequently reported primary outcome measure, the use of which has increased almost two-fold over the last decade.
- The number of secondary outcome measures also increased at least two-fold over this period.
- Primary outcome composite measures were inconsistently defined and classified, particularly for common primary outcome measures such as cardiovascular mortality and MI, making comparisons between studies difficult.
- The increasing use of composite outcome measures, expansion in the number of secondary outcome measures employed per study, and variation in the primary outcome measures reported and their definitions contributes to biases and potentially makes interpretation and cross-study comparisons problematic.
- The adoption of robust, internationally agreed and standardised outcome measure definitions for cardiovascular studies by trialists, funders and regulatory bodies has the potential to improve the quality of clinical research.

Chapter 4
Standardising HF Outcomes

Standardised and hierarchically classified HF and complementary disease monitoring outcome measures: European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart)

4.1 Contribution

This chapter is a summary of the standardised and hierarchically classified HF outcomes that I led and is built on the findings of **Chapter 3**. These definitions are part of a larger piece of work on standardising cardiovascular outcomes across the common CVD that I assisted on that involved multiple collaborators.

My contribution to this chapter was extracting the HF outcomes and their definitions from existing CVD guidelines, prominent HF registries and the systematic review findings from **Chapter 3**. These outcomes were then presented to the Working Group (WG) for comments after which I reviewed and amended the agreed upon existing definitions. I wrote the first draft of the manuscript and subsequent versions after comments from co-authors which was published

The publication details are:

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4.2 Abstract

Aims

The lack of standardised definitions for HF outcome measures limits the ability to reliably assess effectiveness of HF therapies. EuroHeart aimed to produce a catalogue of internationally derived data definitions for HF outcome measures.

Methods

Following the EuroHeart methods for the development of cardiovascular data standards, a WG was formed of representatives from the ESC HF Association and other leading HF experts. A systematic review of observational and RCTs identified current outcome measures, which was supplemented by clinical practice guidelines and existing registries for contemporary definitions. A modified Delphi process was employed to gain consensus for variable inclusion and whether collection should be mandatory (Level 1) or optional (Level 2) within EuroHeart. In addition, a set of complementary outcome measures were identified by the WG as of scientific and clinical importance for longitudinal monitoring for people with HF.

Results

Five Level 1 and two Level 2 outcome measures were selected and defined, alongside five complementary monitoring outcomes for patients with HF.

Conclusion

I developed and published a structured, hierarchical catalogue of internationally derived HF outcome measures. This will facilitate quality improvement, high quality observational research, registry-based trials, and post market surveillance of medical devices.

4.3 Introduction

HF is increasingly common with an estimated prevalence of 64.3 million patients diagnosed with the condition worldwide and in some HIC this translates to 1 - 2% of the general adult population.(174, 250, 251) These numbers are forecasted to increase due to an aging population and guideline indicated therapy leading to improved survival after MI (particularly ST-elevation MI, STEMI). (1, 30, 250)

Most patients with HF are diagnosed with at least three other co-morbidities (250) and is therefore associated with substantial morbidity but also mortality. Co-morbidity with HF has been shown worsen HF symptoms which leads to a reduced quality of life for patients, worsens overall prognosis and subsequently leads to increased HF associated hospitalisations and high economic burden.(5, 251-253) Therefore advances in medical and interventional therapy for HF as well as the co-morbidities that accompany HF is of particular importance for patients, clinicians and policymakers.

As shown in **section 1.3**, advances in research study design, generalisability of results, and their translation into clinical practice is contingent upon consistent, clear definitions of clinical outcomes that are widely applicable.(9) Inconsistent outcome measures and definitions in studies of the same intervention hinders interpretation of the effect of the interventions being tested.(9) Furthermore, a fifth of all included studies in the systematic review investigated HF and cardiomyopathy (85 studies, 22%) and evidence for the heterogeneity in the use of outcome measures and their definitions have been provided in **section 3.5.** Therefore, there is a need to standardise important outcome measures for HF.

As mentioned in **section 1.5,** major international CVD working bodies have sought to standardise outcomes measures and their definitions for CVD such as ARC and SCTI (146, 239, 254). However, there are several limitations with these catalogues of outcome measures. First, some catalogues are not specific to HF management.(232) Of the initial CVD outcomes published in 2018 only two relate to HF (HF hospitalisation and HF event) which potentially underserves patients with HF in both trials and registries.(232)

Secondly, some outcome catalogues are not suited for contemporary HF diagnosis and management.(232, 239) HF classification has traditionally been

categorised according to EF due to the efficacy of guideline indicated therapy.(252) However this classification has evolved to incorporate three distinct categories of left ventricular systolic dysfunction to ensure guideline indicated therapy is implemented correctly; HF with reduced EF (≤ 40%), HF with mildly reduced EF (41-49%) and HF with preserved EF (≥50%).(255) Consequently the definition of HF was broadened and updated to incorporate both the various categories of systolic dysfunction and the use of biomarkers, such as brain natriuretic peptides (BNP), in the diagnosis of HF.(255) These categories were agreed upon through international consensus of leading HF experts and stakeholders in 2021.(255) But previous outcome sets have not updated the definition of HF nor the classification of important HF subtypes such as HF with preserved EF (232, 239, 255) and a recently described phenomenon of HF with improved ejection fraction (HFiEF) which is defined as an improvement in EF with medical therapy.(255)

Thirdly, these outcome measures lacked hierarchical grading of the perceived importance of the outcome measure to health care providers, trialists and regulators that is a hallmark feature of the standardised data standards previously published by EuroHeart. (146, 167-170, 239) As mentioned previously in **section 1.5**, an important limitation is the outcome sets previously published were mainly focused on trial design and methodology and not curated for real world evidence generation from registries. (146, 239, 254) Lastly, other outcome sets are catered to investigate patients with acutely decompensated HF that require hospitalisation only.(254)

EuroHeart has previously published a suite of internationally derived data standards for cardiovascular diseases using an established methodology as mentioned in **section 1.6.3.2**. (167-171) EuroHeart is prospectively and continuously capturing patient data across participating countries as part of a collaborative international registry of patients with acute coronary syndrome,(166) and will now expand to other cardiovascular disease areas including HF. EuroHeart will facilitate harmonised country-level quality improvement and will generate the basis for international observational and registry-based randomised controlled trials, and post-marketing surveillance of devices and pharmacotherapies. Robust, internationally agreed, and

standardised clinical outcome measures and their definitions are therefore required.(9)

I therefore aimed to identify and define a catalogue of hierarchically classified standardised HF outcome measures and their definitions that is contemporary for use both in trials and real-world patients in collaboration with the ESC HF Association (HFA) and other international HF experts.

4.4 Methods

4.4.1 Data Science Group

As explained in **section 1.6.3.1,** the DSG was formed and comprised of a project chair (CPG), medical experts (CW, AB, GB), project manager (CR), statistician (ABS) and data manager (SC).

4.4.2 Methodology

We followed the EuroHeart methodology for the development of data standards as mentioned in **section 1.6.3.2**.(171) Briefly, this involved: i) a systematic review of the literature to compose a list of 'candidate' outcome measures for HF composed from the results from **Chapter 3** led by the medical experts (AB); ii) the selection and prioritisation of variables by domain experts in the WG using a modified Delphi method conducted by the medical experts (CW and AB); iii) the synthesis of outcome measure definitions based upon the existing literature, with critical review by the WG.

EuroHeart has already set out 'generic' cardiovascular outcomes measures in **Chapter 5** that are applicable to all patients with CVD and therefore in addition to those specified for HF.(256) These include all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, and new onset HF. The outcome measures agreed upon for HF should be considered in concert with these EuroHeart generic outcome measures that will be described in **Chapter 5**.

4.4.3 Systematic review

We performed a systematic review of the literature on primary and secondary outcome measures reported in cardiovascular studies relevant to HF published between 1st January 2000 and 7th September 2023. This was an earlier version

of the more comprehensive systematic review that is reported in **Chapter 3** and was used to identify commonly reported outcome measures for HF. This included peer reviewed randomised clinical trials and observational studies published in highly cited medical journals (Lancet, JAMA, and NEJM). Outcome measures alongside their definitions from existing HF registries, previous consensus documents and contemporary guidelines were also screened, (146, 239, 252, 254) and synthesised. A collated list of candidate variables were presented to the WG members during the modified Delphi process.

A WG was formed to identify clinically relevant outcome measures for the management of HF and agree upon their definitions for the variables via virtual meetings and polls. The WG was comprised of international experts and included members of the EuroHeart Data Science Group, representatives from prominent international HF groups such as the HFA and ESC WGs. External HF experts were approached to provide further validity to our findings. The ESC WGs included: ESC Patient Forum, Association of Cardiovascular Nursing and Allied Professions, European Association of Cardiovascular Imaging, ESC Committee for Young Cardiovascular Professionals, WG on Aorta and Peripheral Vascular Diseases, WG on Atherosclerosis and Vascular Biology, WG on Cardiovascular Pharmacotherapy, WG on Cardiovascular Surgery, WG on Cellular Biology of the Heart, WG on Coronary Pathophysiology and Microcirculation, WG on e-Cardiology, WG on Myocardial Infarction, WG on Pulmonary Circulation and Right Ventricular Function and WG on Thrombosis.

In total the WG included 42 clinical experts spanning 16 countries across Europe and North America with expertise in conducting trials and authoring HF guidelines. (**Appendix B.1**)

4.4.4 Hierarchical grading

The WG classified outcome measures as Level 1 that should be collected for all participants, and Level 2 that may be selected by participating centres depending on their own requirements.

4.4.5 Modified Delphi process

By means of a poll, each member of the WG independently reviewed the list of outcome measures derived from the literature review and voted to classify them as either a Level 1 (mandatory), Level 2 (optional), or to exclude the variable.

This judgement was based upon the respondent's expertise concerning the importance, supporting evidence base, validity, reliability, feasibility, and applicability of each variable.

The threshold for inclusion as a Level 1 variable was at least 75% of participants voting for selection of the variable as Level 1.(257) The threshold for inclusion as a Level 2 variable was at least 75% of participants selecting for the variable either as Level 1 or Level 2. The results of the poll were presented and discussed among the WG during an online meeting held on 28th October 2023. Participants were invited to provide feedback during voting and there was a proposal made by the experts that additional variables to monitor disease progression and response to therapy over time would be valuable. These additional variables were termed complementary outcomes and will be expanded on further in **section 4.5.1.3 and 4.6.** This resulted in a re-vote on the newly defined complementary outcomes by means of an online poll. The agreed list of variables and their definitions were then reviewed by the WG for ratification.

4.4.6 Implementation and application

The final set of Level 1 HF outcome measures will be programmed into the EuroHeart IT system by the EuroHeart Registry Technology Group. Data recorded on the IT platform will have an associated date of outcome occurrence and outcome multiplicity is allowed (except for the occurrence and date of death). The expected target population will be patients hospitalised after an index presentation of HF at a participating centre in EuroHeart countries. Data reporting and its statistical analysis will be in accordance with a statistical analysis plan.

4.4.7 Patient involvement

Patients were not invited to the vote on the candidate list of variables as per their request as they advised us that the process was too technical. They did express interest in reviewing the final list of outcomes. The results of the poll have been presented to the ESC patient forum, alongside the other CVD outcomes, on 5th December 2023. They expressed support for the work as well as encouraging the inclusion of PROMs into each CVD domain. This was developed into a separate project outlined in **Chapter 7.**

4.5 Results

The systematic review retrieved 4,728 studies of which 861 (18%) met the inclusion criteria. Of these, 176 (20%) studies concerned HF. The candidate outcome measures were extracted by members of the Data Science Group and were supplemented by those used in existing registries. In total, 18 candidate outcomes measures for HF were presented to the WG for independent voting on 16th July 2023 to be included as either Level 1 or 2 or excluded (**Table 4.1**).

Table 4.1. List of HF outcomes considered for Level 1 inclusion and their vote distribution (n= 35 participants).

Outcome measure	Mandatory (%)	Optional (%)	Exclude (%)
HF re-hospitalisation	96	4	0
EF	84	12	4
All-cause re-hospitalisation	76	24	0
Heart transplantation	76	20	4
LVAD	76	24	0
CRT implant	68	28	4
ICD implant	68	24	8
NYHA class	64	24	12
Serum BNP	56	36	8
Serum potassium	44	40	16
Resuscitated ventricular arrhythmia	40	48	12
Change in NYHA class	40	44	16
Change in serum BNP	20	76	4
Change in EF	20	72	8
Attendance at cardiac rehabilitation	12	68	20
Peak O2 consumption	8	76	16

Abbreviations: LVAD**:** Left ventricular assist device; CRT: Cardiac resynchronisation therapy; ICD: Implantable cardioverter defibrillator; BNP: brain natriuretic peptide; EF: ejection fraction; NYHA: New York heart association; O2: oxygen

The WG proposed additional HF outcome measures, during the first meeting on 16th July 2023, which may be used for monitoring patients with HF, supplementary to the Level 1 and Level 2 outcome measures termed 'complementary outcomes.' The WG subsequently voted on 16 outcomes to either be included as either complementary, Level 2 outcome measures or excluded (**Table 4.2**). The final set of outcome measures were selected after a series of meetings and online polls between 16th July and 28th October 2023.

Table 4.2. List of HF outcomes considered for complementary outcome inclusion (Level 2) and their vote distribution (n = 30).

Outcome measure	Optional (%)	Exclude (%)
Presence of concurrent AF	96	4
NYHA class	92	8
Serum BNP	92	8
Change in EF	92	8
Serum creatinine	72	28
EF	72	28
6-minute walk test	72	28
KCCQ score	68	32
Attendance at cardiac rehabilitation	68	32
Serum potassium	68	32
Change in NYHA class	64	36
Days in hospital after discharge	56	44
Change in serum BNP	56	44
Serum lactate	24	76
Peak O2 consumption	16	84

Abbreviations: NYHA: New York heart association; EF: ejection fraction; KCCQ: Kansas City Cardiomyopathy Questionnaire; O2: oxygen; AF: Atrial Fibrillation; BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate.

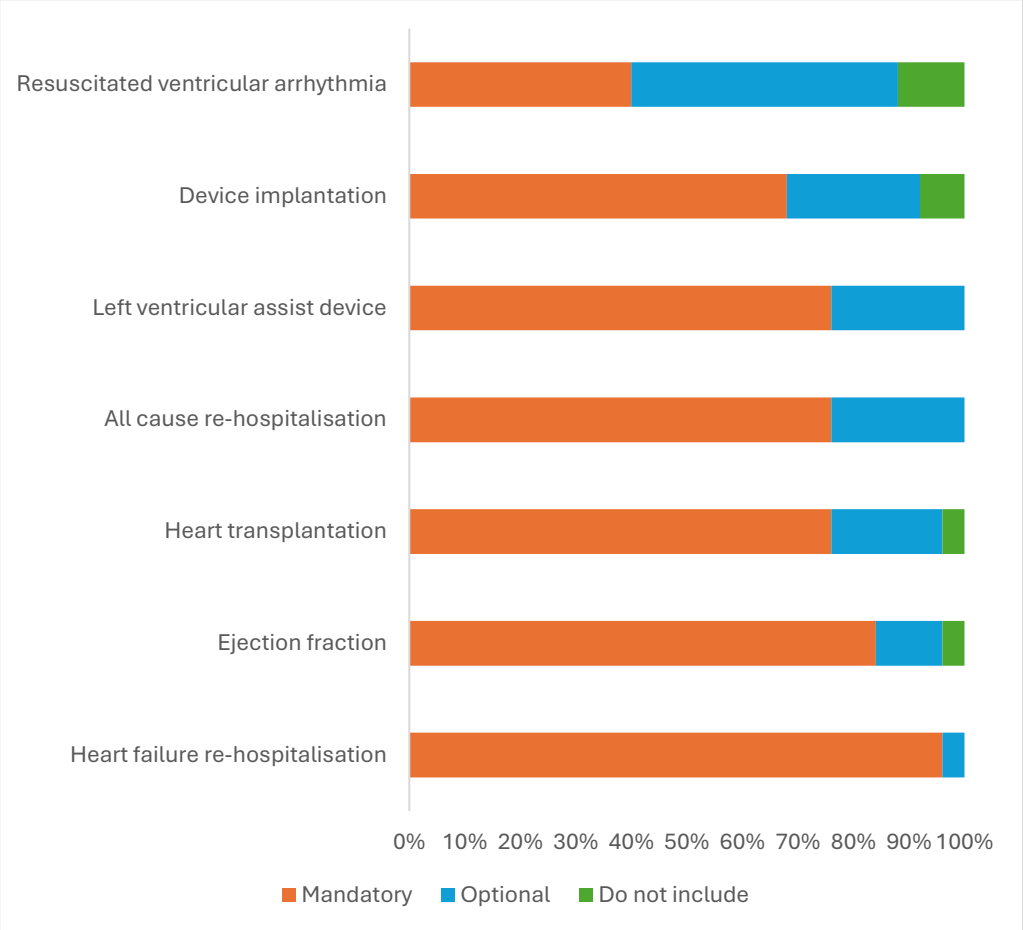
4.5.1 Hierarchical outcomes

4.5.1.1 Level 1 (mandatory) outcome measures

There were five outcome measures specific to HF that were deemed mandatory to collect and defined as Level 1 by the WG. These were in addition to the EuroHeart generic Level 1 cardiovascular outcome measures.

There was agreement between experts on these outcome measures. These were: i) capture of left ventricular ejection fraction as a percentage. Where this is not possible, the category reported should be according to ESC guidance,(258) ii) all-cause hospitalisation, iii) HF hospitalisation, iv) implantation of left ventricular assist device and v) heart transplantation (**Figure 4.1**).

Figure 4.1. Distribution of votes for Level 1 and Level 2 HF outcome measures.



A total of 42 HF experts attended the virtual meetings with 35 experts voting on the above outcome measures. Device implantation refers to leadless, single and dual chamber pacemakers, subcutaneous, extravascular and subcutaneous defibrillators and cardiac resynchronisation therapies.

4.5.1.2 Level 2 (optional) outcome measures

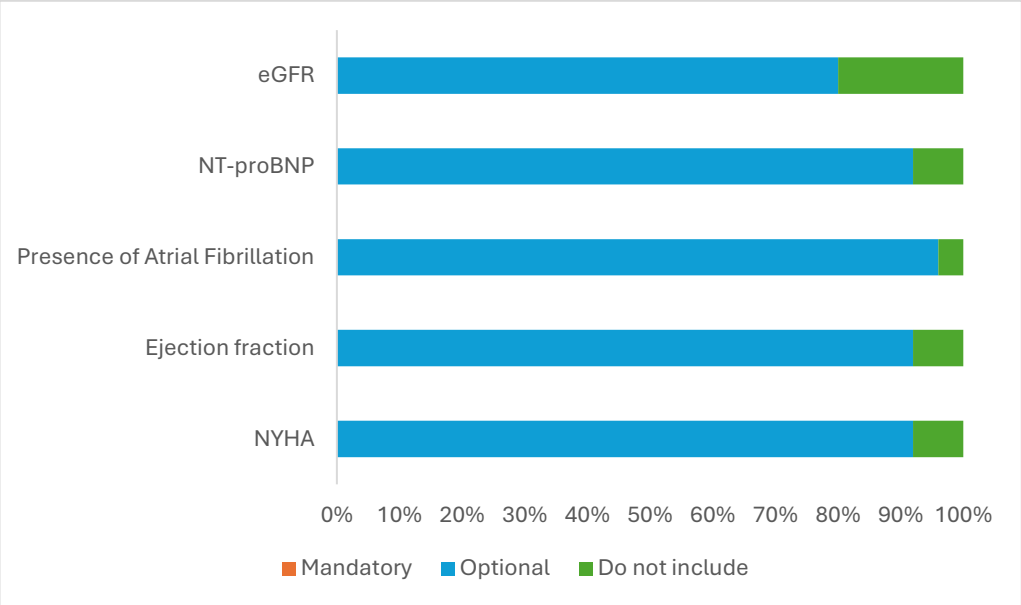
There were two outcome measures that were deemed optional to collect and defined as Level 2 by the WG (**Figure 4.1**).

These were device implantation that included: transvenous pacemakers; leadless pacemakers; transvenous; subcutaneous ICDs; CRT - pacemaker; and CRT- defibrillator and resuscitated ventricular arrhythmia.

4.5.1.3 Complementary monitoring outcome measures

The WG proposed additional HF outcome measures that may be used for monitoring patients with HF, supplementary to the Level 1 and Level 2 HF outcome measures. These were: i) concurrent presence of AF, classified as first diagnosed AF, paroxysmal, persistent or permanent as defined by ESC guidelines(259)); ii) N-terminal proBNP); iii) estimated glomerular filtration rate (eGFR); iv) change in left ventricular EF (i.e. the difference in the left ventricular EF (%) be measurement using the same imaging modality for calculating left ventricular EF); and v) NYHA class (**Figure 4.2**).

Figure 4.2. Distribution of votes for the HF complementary outcomes**.**



A total of forty two international HF experts attended the virtual meetings with thirty experts voting on the above outcome measures. NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate.

4.5.1.4 Expert feedback on Level 2 outcomes.

The HF WG agreed to capture the change in EF as an important complementary variable in order to capture those patients with HFiEF. Despite the subjectivity associated with NYHA the WG felt that capturing a clinicians' interpretation of the impact of the disease on quality of life was an important variable to record. Reporting its longitudinal changes over time was felt also to be important and may influence clinical practice.

6 minute walk test, KCCQ score and peak O2 consumption provide important prognostic information but did not meet the threshold for inclusion as the WG felt they were not easy and pragmatic to capture across multiple geographies especially the feasibility concerns over the KCCQ PROM.

Serum potassium and lactate were not considered to be clinically meaningful to capture for patients with chronic HF as well as days in hospital after discharge.

The definitions for the Level 1 and 2 HF outcomes are provided in **Table 4.3**.

Table 4.3. Level 1 and 2 HF outcome measures and definitions.

HF: Level 1 variables	
All-cause rehospitalisation	Unscheduled hospitalisation for any cause, defined as a being admitted for more than 24 hours or past a calendar day.(51, 232)
HF rehospitalisation	Hospital admission primarily related to HF (HF). HF is a clinical syndrome characterised by typical symptoms (e.g., dyspnoea) and/or signs (e.g., ankle swelling), caused by a structural and/or functional cardiac abnormality (e.g., left ventricular hypertrophy or impairment), and associated with elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion from a cardiogenic origin at rest or with exercise Unplanned HF hospitalisation is defined as a patient requiring an unscheduled hospital admission for a *primary diagnosis* of HF with a length of stay that either exceeds 24 h or crosses a calendar day (if hospital admission and discharge times are unavailable). To satisfy the criteria for a HF hospitalisation, the patient must be admitted primarily for HF with signs, symptoms, and diagnostic testing results identical to those already described above. The patient must also require treatment for HF such as significant augmentation of oral diuretics, intravenous diuretics or mechanical or surgical intervention for HF. (51, 233, 252, 255)
Left ventricular ejection fraction	Let ventricular ejection fraction, ideally measured with echocardiography.
Heart transplantation	Receipt of surgery in which a failing, diseased heart is replaced with a healthier donor heart.(260)
Left ventricular assist device	Implant of a left ventricular assist device (LVAD).
HF: Level 2 variables	
Device implantation	Implantation of:

	• Transvenous permanent pacemaker is an electronic device that is implanted in the subcutaneous tissue and gives the heart an electrical stimulation through transvenous wires. • Leadless pacemaker is an electronic device that is implanted directly into the right ventricle. • Transvenous implantable cardioverter defibrillator (ICD) is a device that is used to correct abnormal heartbeat through transvenous wires. • Subcutaneous ICD is an ICD with a presternal lead and is positioned between the latissimus dorsi and serratus muscle within the subcutaneous tissue. • Extravascular ICD is an ICD with a substernal lead and the device in the subcutaneous tissue of the lateral thorax. • Cardiac resynchronization therapy (CRT) device and pacemaker (CRT-P) is defined as a biventricular pacemaker that sends electrical stimulation to both ventricles. • CRT-D is a biventricular pacemaker and defibrillator.(261, 262).
Resuscitated ventricular tachyarrhythmia	The patient was successfully resuscitated and had return of spontaneous circulation from a ventricular tachyarrhythmia.
NYHA class	NYHA class I: no limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnoea. NYHA class II: slight limitation of physical activity. The patient is comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnoea. NYHA class III: marked limitation of physical activity. The patient is comfortable at rest. Less than ordinary activity causes fatigue, palpitations, or dyspnoea.

	NYHA class IV: inability to carry on any physical activity without discomfort. HF symptoms are present even at rest or with minimal exertion. (252, 255)
Change in left ventricular ejection fraction	Left ventricular ejection fraction, ideally measured with echocardiography.
Atrial fibrillation	Patient has a concurrent diagnosis of any type of atrial fibrillation with HF. Atrial fibrillation is defined as a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. The minimum duration of an ECG tracing of atrial fibrillation required to establish the diagnosis of clinical atrial fibrillation is at least 30 seconds, or the entire 12-lead ECG. Atrial flutter is defined as a supraventricular tachyarrhythmia with coordinated but overly rapid atrial electrical activation, usually with some degree of atrioventricular (AV) node conduction block. The minimum duration of an ECG tracing of atrial flutter required to establish the diagnosis of clinical atrial flutter is at least 30 seconds, or the entire 12-lead ECG.(263)
NT-proBNP (ng/L)	Serum NT-proBNP in ng/l.
Estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2)	Estimated glomerular filtration rate (eGFR) in ml/min/1.73 m^2.

4.6 Discussion

Through a structured and collaborative international expert-led process, we have identified and defined a catalogue of hierarchical outcome measures for patients with HF, including a complementary suite of monitoring variables. These will be used to measure the clinical outcomes for participants in EuroHeart and have wider utility for RCTs, prospective observational cohorts, and clinical registries outside of EuroHeart.

The identification and optimal clinical management of HF is critical, given its increasing prevalence and represents a significant health burden across Europe.(5) Recent advances in guideline directed care have been associated with improved symptoms, better quality of life, reduced all-cause mortality, and fewer readmissions.(20, 264) Nonetheless, translating clinical guidelines into real world practice can be challenging. Previous work has shown that provision of guideline directed care for HF is variable between and within the European countries and suboptimal provision of care may be associated with adverse outcomes.(18, 265) One possible cause for this could be variability in defining key outcome measures (9) which can impact HF hospitalisation rates.(266)

The EuroHeart HF outcome measures build upon existing cardiovascular outcomes relevant to patients with HF, including those by the ARC.(239, 254) There are similarities between these outcome sets: like ARC, all-cause and cardiovascular-specific mortality were included as mandatory variables within EuroHeart. These are important safety outcomes that are necessary for regulatory approval of device and pharmacological interventions within cardiology.(252) Similarly, all-cause and HF hospitalisations were included, and are predictors of mortality and disease severity.(267) They are also important for patients,(267) and health services,(265) and in research are often components of a composite outcome.(268) LVAD and heart transplantation likewise was included within both EuroHeart and ARC given their importance in advanced disease management and increasing within Europe.(251, 252)

Both organisations provide similar definitions for HF hospitalisation, with emphasis on the admission to hospital being attributed primarily to HF and that the hospitalisation must exceed 24 hours or cross a calendar day. For worsening HF to be defined as an outcome measure, both organisations agree

upon the requisite for clinical, biomarker and radiological markers and augmentation of medical therapy from baseline.

Categorising and defining HF outcomes in hierarchical fashion is a hallmark feature of EuroHeart data standards, (167-170) which differs from previous work on HF outcomes set out by the ARC.(239) Previous studies within HF have graded outcomes hierarchically based on their importance to both clinicians and regulators, which reflects an ambition from researchers and regulators to adopt a more pragmatic approach to analysis within research.(269, 270)

In contrast to ARC, recording left ventricular EF is a Level 1 outcome in EuroHeart and as mentioned in the introduction, the ARC classification of HF due to left ventricular systolic dysfunction has not been updated to align with a recent consensus documents.(255) Current guidelines stratify HF according to left ventricular ejection fraction categories due to differences in the benefit of HF therapies and the association of worsening outcomes with declining left ventricular ejection fraction.(18, 258) However, HFiEF is increasingly recognised after implementing guideline-directed therapy and is associated with better long term outcomes.(271) Therefore, the WG agreed that left ventricular ejection fraction should be included both as a stand-alone variable and a variable that can be used for monitoring HF.

We also define complementary outcomes that may be used for the longitudinal evaluation of patients with HF, beyond traditional ‘hard’ outcomes.(272) These variables are either mechanistic or surrogate outcomes that if collected prospectively could form the basis of further research. For example, the Valsartan Heart Failure Trial (Val-HeFT) investigated left ventricular EF as a surrogate outcome in patients with an ejection fraction below 35% that were randomised to valsartan or placebo. Compared to placebo, patients taking valsartan demonstrated an improvement in left ventricular ejection fraction, improved survival at 12 months especially if EF was above 40% and a decreased NT-proBNP level.(271) Some of the patients receiving valsartan (9.1%) demonstrated an improvement in their EF at 12 months (28.7% ± 5.6% to 46.5 ± 5.6%). After a 3 year follow up period, the mortality rate was 2.9 per 100 person-years (95% confidence interval, 1.8–4.5) in the HFiEF group and 5.8 per 100 person-years (95% confidence interval, 5.3–6.4) in the group with persistent HF with reduced EF fraction despite taking valsartan.(271) Given the

advances in optimal medical therapy in HF, monitoring the left ventricular EF as well as other complementary variables could form the basis of observational research in real world settings. The WG emphasised the need for consistency in the method of measurement, for example serial echocardiogram scans or cardiac magnetic resonance imaging where applicable.

The relationship between AF and HF is complex, because AF can be either the cause or consequence of HF.(273) Studies have shown that catheter ablation in patients with symptomatic paroxysmal or persistent AF in the context of severe left ventricular systolic dysfunction improves outcomes compared to medical therapy alone.(274, 275) This highlights the importance of recognising and considering AF as a potentially therapeutic target in HF in contemporary registries or a surrogate marker for deterioration in HF.(276)

Other outcomes such as eGFR was included given renal impairment is well known to be greatly associated with mortality in patients with HF.(277) In previous meta analyses, the prevalence of chronic kidney disease (CKD) occurring with HF was 32% and was associated with all-cause mortality [odds ratio (OR) 2.34, 95% CI 2.20–2.50, $P < 0.001$)].(277) And even moderate CKD was demonstrated to be an independent predictor of mortality [hazard ratio (HR) 1.59, 95% CI 1.49–1.69, $P < 0.001$]. (277) Therefore renal outcomes have featured in some contemporary HF trials. (278, 279) For example, in the Canagliflozin and Cardiovascular and Renal Events in Type 2 diabetes (CANVAS) trial participants were randomly assigned canagliflozin or placebo and were followed up for 188.2 weeks. (278) Patients that received canagliflozin demonstrated a 40% reduction in the composite renal outcome of eGFR, the need for renal replacement therapy or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77) as well as a signal that canagliflozin may improve albuminuria, although it was not statistically significant (hazard ratio, 0.73; 95% CI, 0.67 to 0.79). (278) Therefore eGFR was voted to be an important renal outcome to collect longitudinally.

Contemporary ESC HF guidelines recommend quantifying the impact of HF symptoms on a patients quality of life by using NYHA class and is routinely used, alongside EF and biomarkers, to guide management especially the use of CRT.(252) The ESC quality indicators of care for HF recommend capturing serum BNP as an important diagnostic and assessment tool for HF.(85)

Therefore they both feature as longitudinal complementary HF outcomes to be captured.

EuroHeart aims to reduce the burden of cardiovascular disease across Europe. The publication of these variables and their definitions will allow us to better understand the outcomes for people with HF. They will be integrated with the existing registries, (167-170) and incorporated into the EuroHeart IT platform. This will allow the patterns of clinical care and outcomes of patients to be evaluated longitudinally across Europe, and provide a platform for international quality improvement to address any unwarranted variation in care,(5, 258) and facilitate quality benchmarking.(167) It is therefore important to health care providers, funders, and patients to integrate and optimise provision of guideline-indicated care, whilst monitoring outcomes for patients. By harmonising data collection from distinct European HF registries into an international collaboration together, EuroHeart can better inform clinical care by highlighting regional / international health inequalities. (31) This can be feedback to individual countries to promote local or regional quality improvement and therefore improve cardiovascular care continuously.(31) Integral to this process however is the adoption of a catalogue of standardised definitions of cardiovascular outcome measures that allows for research to be more externally generalisable and potentially more efficient in its delivery.(9, 31)

4.7 Strengths

We followed a robust methodology in achieving consensus on HF outcomes using an established method of developing data standards with a transparent and organised approach in establishing consensus between international experts.(171) This method has been consistently used for all the previous EuroHeart projects in standardising the data standards for the common CVD. (167-170)

For this project, a systematic review on HF outcomes was completed that compiled a list of contemporary and applicable outcomes relevant to HF trials and clinical practice. This provides a scientific basis to the subsequent modified Delphi process that harnessed the expertise of a wide range of international experts in HF to identify appropriate HF outcomes alongside their definitions. To

improve geographical representation, we approached external experts as well as those nominated by all ESC affiliated institutions. The HF outcomes and their definitions were endorsed by the ESC Patient Forum as well as the ESC Committee for Young Cardiovascular Professional that provided an additional layer of validity in our findings.

4.8 Weaknesses

However, we recognise the limitations of this work. Although the outcome measures and their definitions were distilled from a systematic review, the final selection of outcomes were agreed upon by consensus of the international experts within the WG and are therefore subject to selection bias. Nevertheless, the experts that composed the WG were taken from a broad range of countries with a wealth of experience and knowledge within registry work and trials. Although patients were approached to participate and vote during the modified Delphi they declined, and we were unable to capture the patient's perspective.

And, although the importance of PROMs and PREMs is increasingly recognised,(280, 281) our remit for this project was limited to clinical outcomes that was decided by international consensus of the WG. A further project involving PROMs use within HF and other cardiovascular conditions is anticipated.(241)

4.9 Conclusion

This document provides a structured, hierarchical catalogue of HF outcome measures that are internationally derived that includes complementary outcomes. For EuroHeart this will facilitate quality improvement, prospective observational research and RCTs across Europe.

4.10 Summary of chapter 4

- HF is a common long-term condition that is associated with significant morbidity and mortality.
- Existing consensus documents have sought to standardise HF outcome measure for use in trials. However, they are not specific to HF, not aligned with contemporary diagnosis, classification and management of HF, address acute decompensated HF or lack hierarchical specification
- A structured and hierarchical catalogue of HF outcome measures that are internationally derived by ESC affiliations and WGs including the HF Association.
- These include five Level 1 outcomes (mandatory within EuroHeart), two Level 2 outcomes (optional) and five complementary outcomes (optional).
- Addition of complementary HF outcomes that are useful to monitor in patients with HF.

Chapter 5
Standardising Cardiovascular Outcomes

Derivation and definitions of clinical study outcome measures for cardiovascular diseases: the European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart)

5.1 Contribution

Below is a summary of the internationally derived, standardised outcome measures listed for inclusion for ACS/PCI, AF, TAVI and generic CVD in addition to the HF outcomes outlined in **Chapter 4**. Similarly, a systematic review, adapted from my findings in **Chapter 3**, was completed that informed the modified Delphi process. In addition to the HF outcomes highlighted above this project completes the first half of my MD in standardising the selection and definitions of key CROs for CVD.

Similar to the HF outcomes this project involved multiple collaborators. My contribution involved collating the outcomes and their outcome definitions from existing CVD guidelines, registries and the provisional findings of the review that completed in **Chapter 3.** After WG comments, I reviewed and amended existing definitions until they were agreed upon and provided critical feedback on the subsequent publication.

The details of the publication are:

Wilkinson C, **Bhatty A**, Batra G, et al. Definitions of clinical study outcome measures for cardiovascular diseases: the European Unified Registries for Heart Care Evaluation and Randomized Trials (EuroHeart). *Eur Heart J*. 2025;46(2):190-214. doi:10.1093/eurheartj/ehae724

5.2 Abstract

Background and aims

Standardised definitions for outcome measures in randomised clinical trials and observational studies are essential for robust and valid evaluation of medical products, interventions, care and outcomes. The EuroHeart project of the ESC aimed to create international data standards for cardiovascular outcomes.

Methods and results

We followed the EuroHeart methods for data standard development. From a Global Cardiovascular Outcomes Consortium of 82 experts, five WGs were formed to identify and define key outcome measures for: CVD (generic outcomes), ACS/PCI, AF, HF and TAVI. We conducted a systematic review of the literature and used a modified Delphi method to reach consensus on a final set of variables. For each variable, the WG provided a definition and categorised the variable as mandatory (Level 1) or optional (Level 2) based on its clinical importance and feasibility. Across the five domains, 25 Level 1 (generic: 5, ACS: 8, AF: 2; HF: 5, TAVI: 4) and 50 Level 2 (generic: 18, ACS: 7, AF: 6, HF: 2, TAVI: 15) outcome measures were defined.

Conclusion

We present internationally derived definitions for outcome measures for a range of common CVD and their interventions. These may be used for data alignment to enable high-quality observational and randomised clinical research, audit, and quality improvement for patient benefit.

5.3 Introduction

Careful selection and use of clinical outcome measures is of paramount importance to enable valid and reliable scientific quantification of the benefits and harms of treatment as set out in **section 1.3.4** (282, 283) Translating these results into clinical guidelines and therefore practice is dependent on consistent, clear definitions of clinical outcomes that are widely applicable.(9) Inconsistent outcome measures and definitions in studies of the same intervention hinders interpretation of the effect of the interventions being tested.(9)

The definitions of cardiovascular outcomes measures employed in observational research have been inconsistent and heterogeneous,(44) yet an increasing proportion of RCTs are using routinely-collected healthcare systems and/or clinical registry data for outcome evaluation.(178, 284-286) Registry-based RCTs now span multiple geographies.(284) It is therefore increasingly important that consistent, internationally derived and robustly defined clinical outcome measures are developed.(9)

Outcome measure sets have been proposed for a range of cardiovascular conditions by major international organisations such as the SCTI, ARC and ICHOM but there are limitations to using them.(151, 152, 155, 287, 288) In general, some of these outcome measure sets are focused on single pathologies and therefore limits their applicability to other CVD as some outcomes are generalisable and important to report across all CVD, such as MI, heart failure hospitalisation and CV mortality.(151, 152, 155, 289) However, there are limitations to the single pathology outcome sets. In particular, the most recent outcome set for coronary artery disease was published in 2015 by ICHOM and is yet to be updated to incorporate important changes to ACS diagnosis and management such as the universal definition of MI in 2018.(155) As previously mentioned for HF, some outcome sets are not specific to HF management,(232) with only two outcomes relate to HF (HF hospitalisation and HF event).(232)

A significant proportion of outcome sets also are catered for RCTs (51, 146, 287, 289, 290) and are not constructed to use within existing CVD registries for real world data generation. Other outcome sets lack a structured hierarchy of the perceived importance of the outcome measure to health care providers,

trialists and regulators that is a hallmark feature of the standardised data standards previously published by EuroHeart. (146, 151, 152, 155, 167-170) Other sets often lack patient stakeholder involvement (288) and some catalogues offer differing definitions of a singular, although important, outcome such as bleeding.(227-229, 290) As reported in **Chapter 3,** this has resulted in a mixed uptake of all bleeding definitions which may obscure interpretation and comparison between trials with one study of note employing multiple bleeding definitions.(230)

The EuroHeart project of the ESC has previously published data standards for four common CVD domains: ACS/PCI, AF, HF, and TAVI.(167-170) These were developed using a standardised, evidence-based method,(171) which we now use to select and define cardiovascular outcome measures for assessments in common CVD and interventions. This catalogue of cardiovascular outcome measures will provide a 'common language' to facilitate federated, pooled, comparative and meta-analyses of independent yet harmonised clinical studies, and support the delivery of international registry-based RCTs. This will facilitate improvements in clinical outcome reporting, making clinical studies more robust, generalisable and applicable, and so improve our understanding of cardiology care and clinical outcomes and the care that we provide to patients.

5.4 Methods

Cardiovascular outcome measures were classified as either generic or domain-specific. Generic measures were defined as those outcomes with potential applicability to all patients with CVD. Domain-specific variables were defined as those applying to patients following diagnosis of ACS, AF, or HF, or after a TAVI procedure. A participant would be eligible for the collection of generic outcomes in addition to specific domains.

5.4.1 EuroHeart method

We followed the EuroHeart method for cardiovascular data standard development.(171) This involved: (i) completion of a systematic review of the literature **(Chapter 3)**, to synthesize a list of 'candidate' variables; (ii) selection

and prioritisation of some variables over others by domain experts in the WG using a modified Delphi method; and (iii) WG feedback.(171)

5.4.2 Systematic literature review

The protocol was pre-registered.(291) We searched Embase and Ovid Medline for studies published in the three medical journals with the highest impact factor: NEJM, Lancet or JAMA on or after 1st January 2000 until 12th October 2021. The inclusion dates were broadened to include as many 'candidate' outcomes for the WG consideration. Studies were included if they reported results from a phase 3 RCT or a multicentre observational study, and included adults with CAD, ACS, PCI, heart rhythm disease, cardiomyopathy, HF, or valve disease, to ensure coverage of all five domains. Conference abstracts or review articles were excluded, as were sub-studies where the main paper was included in the review, and studies in which clinical outcomes were not reported or not defined. The search strategy was developed with a research librarian (**9.8A.1**). Outcome measures and their definitions that were included in the existing domain registries were reviewed,(167-170) and outcome measure variables were included for Delphi voting. These were presented to the WG participants, who were able to suggest additional variables based upon clinical expertise.

5.4.3 Working Groups

We approached all of the ESC associations and WGs to nominate clinical and academic experts to join a Global Cardiovascular Outcomes Consortium, alongside existing members of the EuroHeart team. Additional international clinical experts were approached directly for additional specific expertise. From this Consortium, five WGs were assembled: one for the generic cardiovascular outcome measures, and one for each of the four EuroHeart domains of ACS/PCI, AF, HF and TAVI. Some experts served in more than one group, depending on their experience and availability (**Appendix C.1**).

5.4.4 Variable level

WG members were asked to take part in a Delphi process to consider three options for each proposed cardiovascular outcome measure variable: include as a mandatory (Level 1) variable; include as an optional (Level 2) variable; or do not include. Voting was conducted in an online poll. Level 1 cardiovascular outcome measure variables are intended for collection in all participants in the registry, whereas Level 2 variables are discretionary and may be useful and available in some (but not all) settings and countries, depending on the purpose of the registry.

The threshold for inclusion as a Level 1 variable was at least 75% of participants voting for selection of the variable as Level 1.(171) The threshold for inclusion as a Level 2 variable was at least 75% of participants selecting for the variable either Level 1 or 2. Where a cardiovascular outcome measure variable was already included as a Level 1 variable in the generic domain, this was not considered again by the other domain groups (as it would already apply to all registry participants). Where a variable was already included as a Level 2 variable in the generic domain, it could be re-considered by the WG for upgrade to Level 1 within that specific domain.

5.4.5 Selection of the final set of variables

The results of the Delphi voting were presented in an online meeting, and the results of each cardiovascular outcome measure variable were discussed. Where a Level 1 confirmatory vote had been made already, these results were presented for information only – because the threshold for inclusion had been made. Where the threshold for Level 1 or 2 inclusion had not been reached, participants could request for this to be rephrased based upon their clinical expertise, and this could proceed for a second vote with the same thresholds employed as in the first round.

5.4.6 Definitions

The proposed definitions for each variable were collated from the literature and shared with the invitees from every WG for comments and clarification. These

were agreed by consensus. The previously published variables and definitions for each domain included various classification systems for bleeding,(167-170) but for the outcomes domain participants were clear that a single harmonised classification for bleeding outcome measure was essential. Thus, an online poll was circulated to all participants to vote on their preference for the VARC,(292) BARC,(290) or International Society On Thrombosis and Haemostasis (227) classifications of bleeding that would then be employed across all of the cardiovascular outcome domains.

5.4.7 Patient and public involvement

The ESC patient forum was invited to contribute to this project from its inception. Their feedback was that the development of data variables and standards for cardiovascular outcomes measures was too technical for their meaningful contribution. Instead, they suggested that the results of the Delphi polls were presented to the forum for their discussion and comment, which took place in December 2023 prior to the finalisation of the catalogue of cardiovascular outcome measures. Representatives from the ESC patient forum are part of the research team for the development of CVD PROMs that is detailed in **Chapter 7.**

5.5 Results

5.5.1 Systematic review

Of 4,728 publications that were screened, 801 (16.9%) were included in the review after full-text evaluation. Of these, 320 (40.0%) were published in the NEJM, 284 (35.5%) in JAMA, and 197 (24.6%) in the Lancet, comprising 620 (77.3%) RCTs and 181 (22.6%) observational studies. The most frequently reported primary outcome measure was a composite (449 studies, 56.0%), followed by all-cause mortality (109 studies, 13.6%). Where a composite was the primary outcome measure, the most frequent components were MI (273 studies, 60.8%), all-cause mortality (242 studies, 53.9%), stroke (190 studies, 42.3%) and cardiovascular mortality (178 studies, 39.6%).

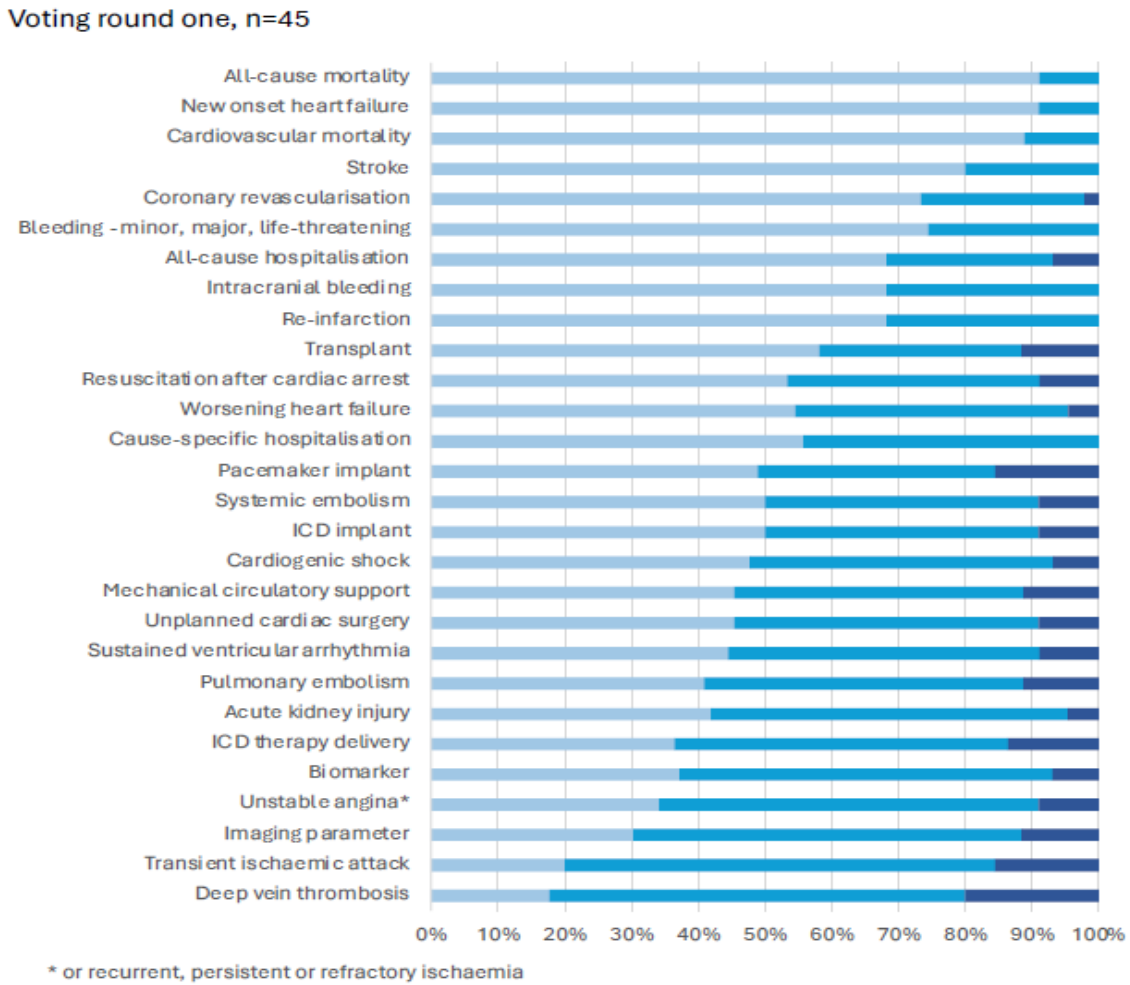
5.5.2 The Working Group process

The extracted clinical outcome measures were presented to the five WG for consideration as candidate variables for inclusion.

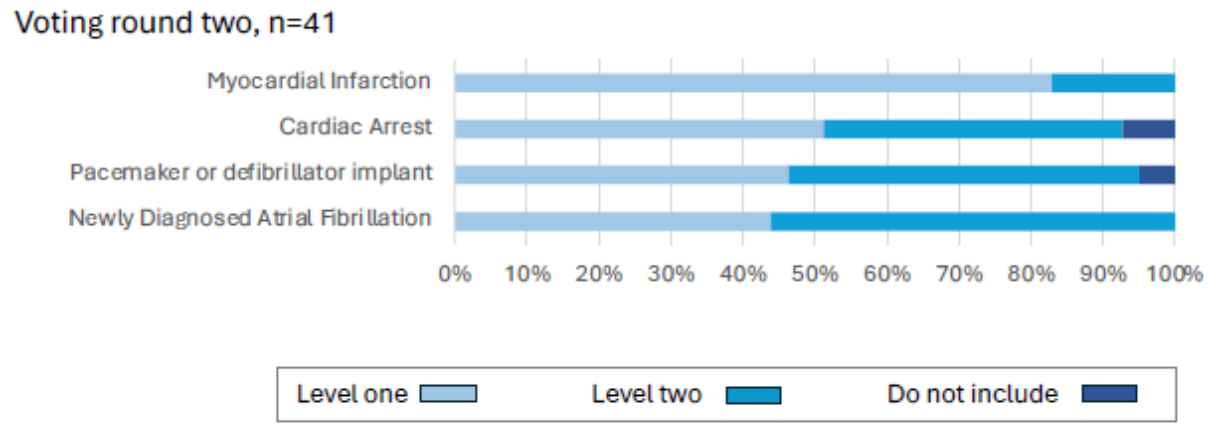
In the first round, 28 candidate variables were considered for the generic cardiovascular outcome measures domain by 45 experts **Figure 5.1**. Following discussion, a further four variables were considered by 41 experts (51 individuals contributed in total, **Figure 5.1**).

Figure 5.1. Distribution of votes in the generic domain; A) in the first round, B) in the second round.

A)



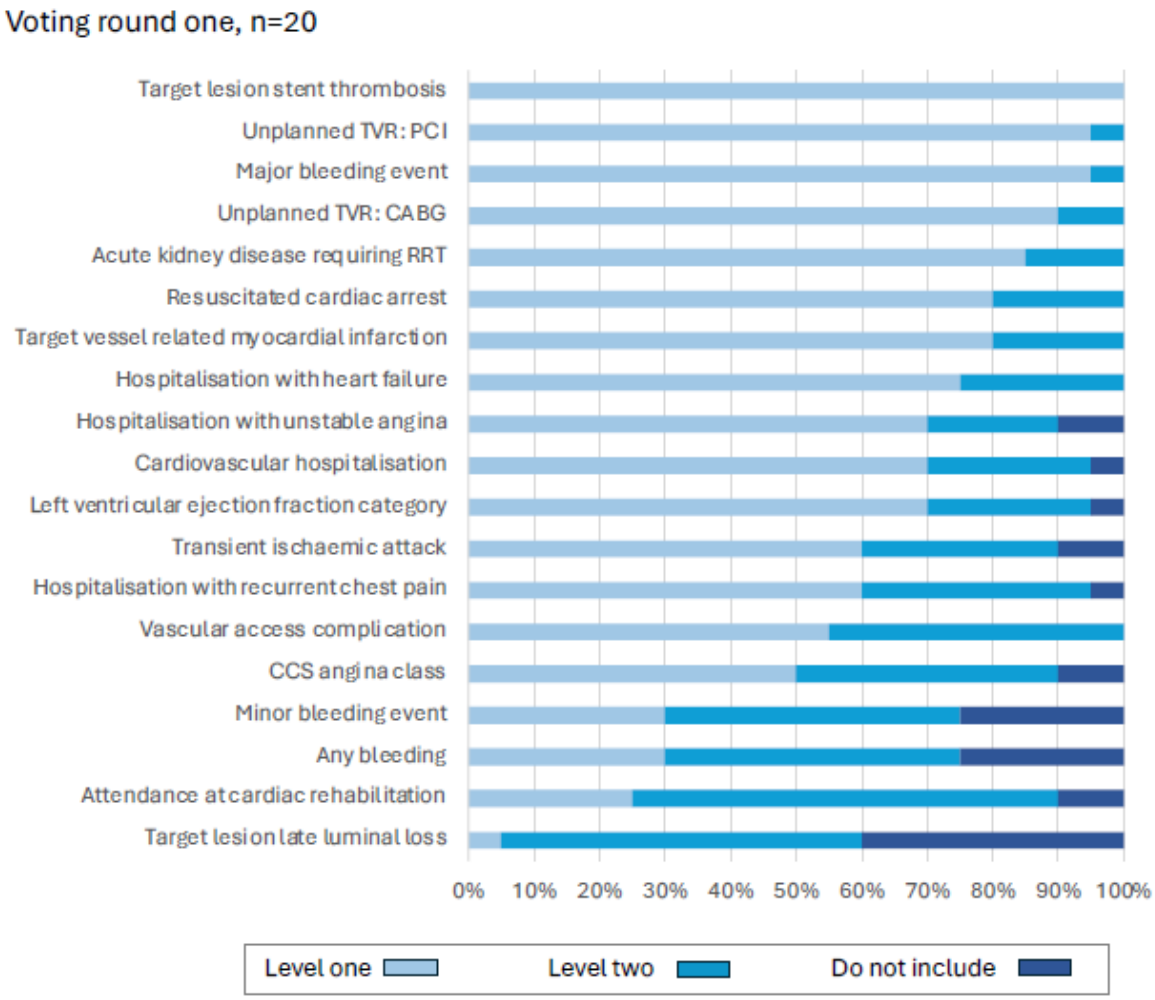
B)



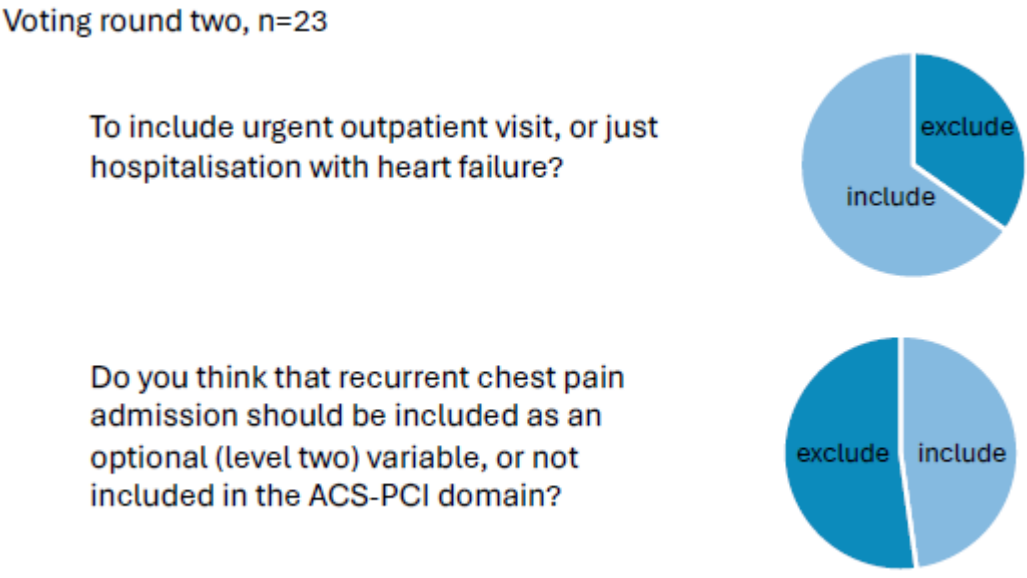
For the ACS outcome measures domain, 26 experts reviewed 19 candidate variables in two rounds of voting (**Figure 5.2**). Of these, 23 experts voted on whether to include recurrent chest pain as a Level 2 variable and clarity over HF event or hospitalisation was required.

Figure 5.2. Distribution of votes in the ACS/PCI domain, A) in round 1, B) in round 2.

A)

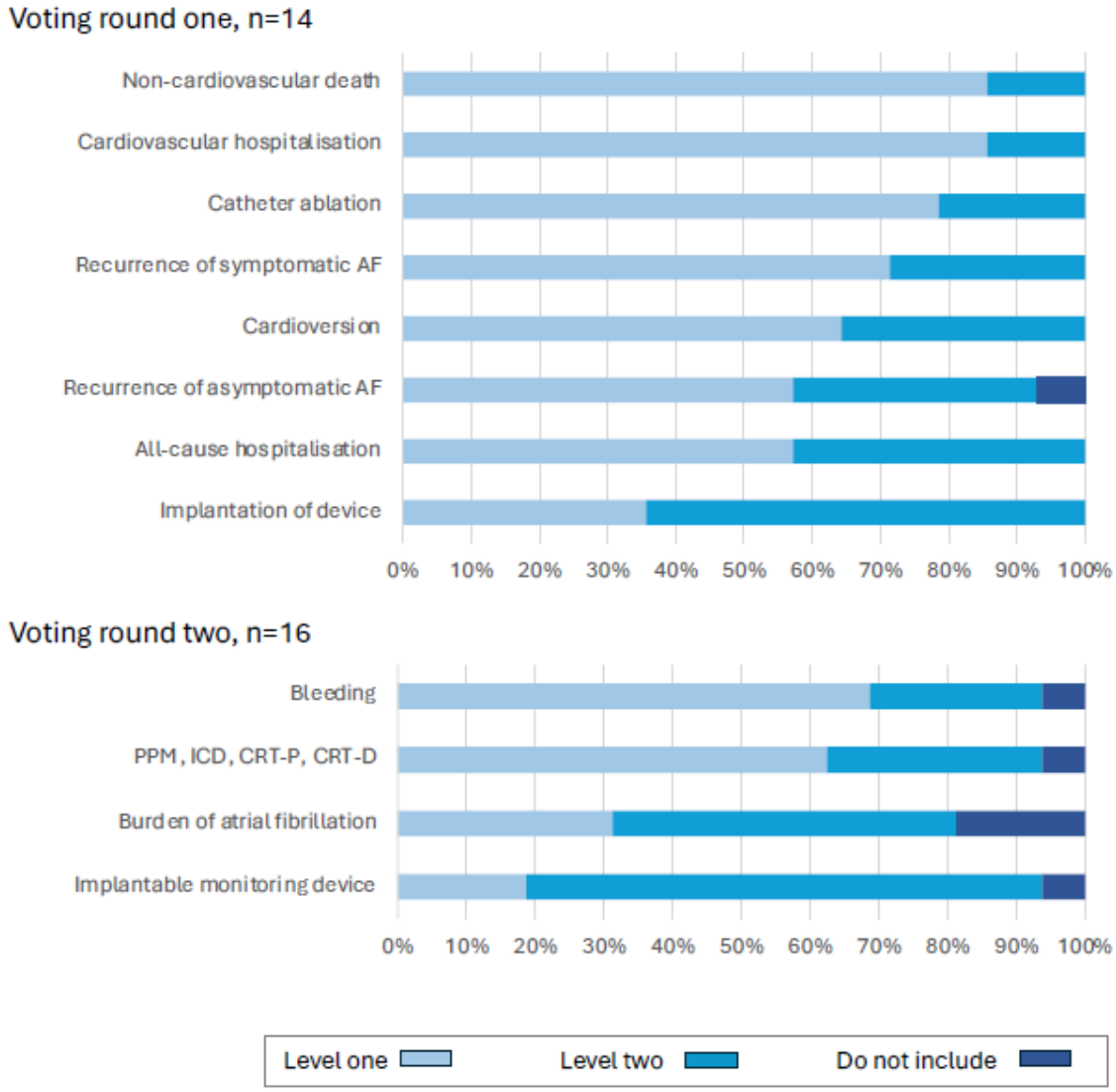


B)



For the AF outcome measures domain, 18 experts reviewed 12 variables in two rounds of voting (**Figure 5.3**).

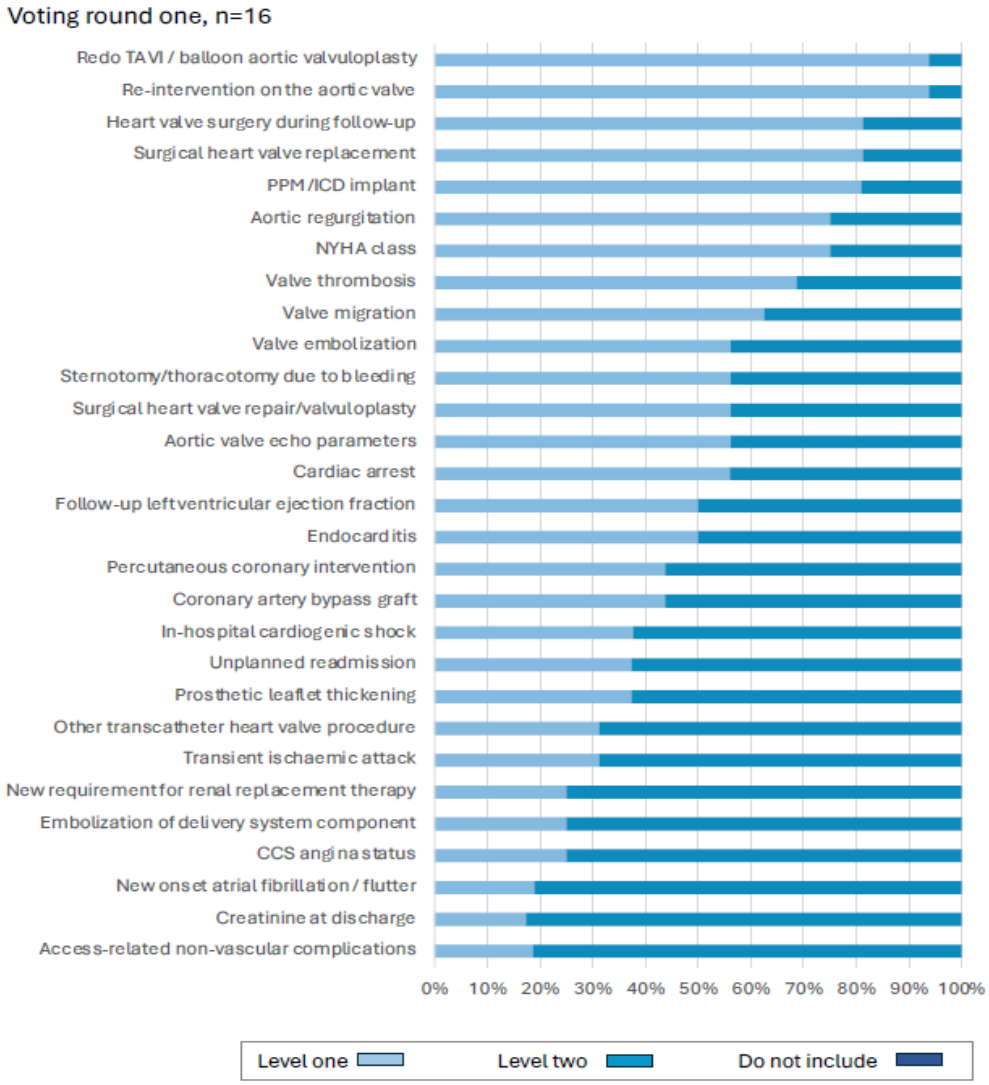
Figure 5.3. Distribution of votes for the AF domain.



For the HF outcome measures domain, 35 experts reviewed 19 variables in two rounds of voting (**Figure 4.1 and Figure 4.2**).

In the TAVI outcome measures domain, all 29 variables were already included in the TAVI registry, and so the reference group were asked to consider whether these should be considered as Level 1 or 2 outcomes, and then the list refined during the meeting, during which 16 experts reviewed 29 variables in one round of voting (**Figure 5.4**). The complete list of variables and their definitions was reviewed by all contributors (n=82). The definitions for each variable are detailed in each section.

Figure 5.4. Distribution of votes for the TAVI domain



5.5.3 Generic domain: Level 1 variables

For the generic cardiovascular outcome measures domain, five Level 1 variables were agreed: all-cause mortality, cardiovascular mortality, MI, stroke, and new-onset HF.

5.5.4 Generic domain: Level 2 variables

For the generic cardiovascular outcome measures domain, 18 Level 2 variables were agreed: transient ischaemic attack, worsening heart failure, cardiogenic shock, mechanical circulatory support, heart transplant, bleeding events, device implantation (including transvenous pacemaker, leadless pacemaker, transvenous ICD, subcutaneous ICD, CRT pacemaker or defibrillator), ICD therapy delivery (for example cardioversion or anti-tachycardia therapy), systemic embolism, pulmonary embolism, deep vein thrombosis, cardiac arrest, hospitalised ventricular tachycardia, newly diagnosed AF, all-cause re-hospitalisation, cause-specific hospitalisation, unplanned cardiac surgery, acute kidney injury. **Table 5.1** provides the full list of definitions.

Table 5.1. List of generic CVD outcomes and their definitions.

Generic domain: Level 1 variables	
All-cause mortality	Death from any cause
Cardiovascular mortality	Death that is primarily from a cardiovascular (CV) cause: • Related to heart failure, cardiogenic shock, native, mechanical or bioprosthetic valve dysfunction, myocardial infarction, stroke, thromboembolism, bleeding, tamponade, vascular complication, arrhythmia or conduction system disturbances, cardiovascular infection (e.g., mediastinitis, endocarditis), or other clear cardiovascular cause. • Intraprocedural death – caused by immediate/latent complications of a cardiovascular procedure. • Sudden death – Sudden natural death presumed to be of cardiac cause that occurs within one hour of onset of symptoms in witnessed cases, and within 24 hours of last being seen alive when it is unwitnessed. In autopsied cases it is defined as the natural unexpected death of unknown or cardiac cause. • Death of unknown causes.(287, 293, 294)
Myocardial infarction	Myocardial infarction, as defined according to the latest universal definition of MI, currently: a rise and/or fall of cardiac troponin with at least one value above the 99th percentile and/or symptoms suggestive of ischaemia, new significant ECG changes, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology or identification of a coronary thrombus by angiography/intracoronary imaging or by autopsy. History of myocardial infarction also includes episodes of symptoms suggestive of myocardial ischaemia which are accompanied by presumed new ischaemic ECG changes or ventricular fibrillation; coronary intervention-related myocardial infarction; and coronary artery bypass graft-related myocardial infarction.(295)
Stroke	An acute episode of focal or global neurological dysfunction (lasting for ≥ 24 hours or until death) caused by an infarction or haemorrhage in the brain, spinal cord, or retina resulting in cell damage based on pathological, imaging, or other objective evidence. Stroke does not include nonvascular neurological deficits. • **Ischaemic stroke** is defined as an acute episode of focal, cerebral, spinal, or retinal dysfunction that is caused by central nervous system infarction, where the neurological dysfunction lasts for ≥ 24 hours. Ischaemic stroke may result in haemorrhage (haemorrhagic transformation). • **Haemorrhagic stroke** is defined as an acute episode of focal or global neurological dysfunction of the brain, spinal cord or retina that is caused by a spontaneous (not traumatic) collection of

	intraparenchymal, intraventricular, and/or subarachnoid blood, where the neurological dysfunction lasts for ≥ 24 hours. Haemorrhagic stroke does not include subdural hematomas. • **Unspecified stroke** is defined as an acute episode of focal or global neurological dysfunction that is caused by a presumed infarction or haemorrhage to the central nervous system, where the neurological dysfunction lasts for ≥ 24 hours but with insufficient information to allow categorisation as either ischaemic or haemorrhagic stroke.(296)
New onset heart failure	A new clinical diagnosis of heart failure made by a healthcare professional. Heart failure is a clinical syndrome characterised by typical symptoms (e.g., dyspnoea) and/or signs (e.g., ankle swelling), caused by a structural and/or functional cardiac abnormality (e.g., left ventricular hypertrophy or impairment), and associated with elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion from a cardiogenic origin at rest or with exercise.(255)
Generic domain: Level 2 variables	
All-cause rehospitalisation	Unscheduled admission to hospital for any reason, defined as a being admitted for more than 24 hours or past a calendar day.(287, 293)
Cause-specific hospitalisation	Unscheduled hospitalisation due to either cardiovascular or non-cardiovascular causes. • Unscheduled hospitalisation is defined as a being admitted for more than 24 hours or past a calendar day. • **CV causes** include conditions such as heart failure, cardiogenic shock, bioprosthetic or native valve dysfunction, myocardial infarction, stroke, thromboembolism, bleeding, tamponade, vascular complication, arrhythmia or conduction system disturbances, cardiovascular infection (e.g., mediastinitis, endocarditis), or other clear cardiovascular cause. • **Non-cardiovascular cause** includes (but is not limited to) respiratory failure not related to cardiovascular disease (e.g., pneumonia), renal failure, liver failure, infection (e.g., urosepsis), cancer, trauma, and suicide.(287, 293)
Bleeding events	**Type 1:** bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional. **Type 2:** any clinically overt sign of haemorrhage that is actionable but does not meet criteria for type 3, type 4 (coronary artery bypass graft surgery [CABG]-related), or type 5 (fatal bleeding) bleeding. The bleeding must require diagnostic studies, hospitalization, or treatment by a healthcare professional. In particular, the bleeding must meet at least one of the following criteria:

	i) Requires intervention, defined as a healthcare professional–guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug. ii) Bleeding leads to hospitalization or an increased level of care, defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care. iii) The bleeding prompts evaluation, defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging). **Type 3a:** any transfusion with overt bleeding; overt bleeding plus haemoglobin drop ≥ 3 to < 5 g/dL (provided haemoglobin drop is related to bleeding). **Type 3b:** overt bleeding plus haemoglobin drop ≥ 5 g/dL (provided haemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid); bleeding requiring intravenous vasoactive drugs. **Type 3c:** intracranial haemorrhage; subcategories confirmed by autopsy or imaging, or lumbar puncture; intraocular bleed compromising vision. **Type 4:** CABG–related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48-hour period; chest tube output ≥ 2 L within a 24-hour period. **Type 5:** fatal bleeding.(30)
Transient ischaemic attack	Transient ischaemic attack (TIA) is a transient focal neurological signs or symptoms lasting < 24 h presumed to be due to focal brain, spinal cord, or retinal ischaemia, but without evidence of acute infarction by neuroimaging or pathology, or with no imaging performed.(297)
Device implantation	Implantation of any of: • **Transvenous permanent pacemaker** is an electronic device that is implanted in the subcutaneous tissue and gives the heart an electrical stimulation through transvenous wires. • **Leadless pacemaker** is an electronic device that is implanted directly into the right ventricle. • **Transvenous implantable cardioverter defibrillator (ICD)** is a device that is used to correct abnormal heartbeat through transvenous wires. • **Subcutaneous ICD** is an ICD with a presternal lead and is positioned between the latissimus dorsi and serratus muscle within the subcutaneous tissue.

	• **Extravascular ICD** is an ICD with a substernal lead and the device in the subcutaneous tissue of the lateral thorax. • **Cardiac resynchronization therapy (CRT) device and pacemaker (CRT-P)** is defined as a biventricular pacemaker that sends electrical stimulation to both ventricles. • **CRT-D** is a biventricular pacemaker and defibrillator.(70, 298)
ICD therapy delivery	Delivery of either an ICD shock or anti-tachycardia pacing (ATP).(70)
Cardiac arrest	Cardiac arrest is defined as a verified sudden cessation of cardiac mechanical activity causing unresponsiveness, absence of normal breathing and no signs of circulation (excluding syncope or profound vagally-mediated bradycardia) with ventricular fibrillation, rapid ventricular tachycardia or bradycardia resulting in loss of consciousness, pulseless electrical activity, or asystole as the major causes. Return of spontaneous circulation (ROSC) is defined as the resumption of a sustained heart rhythm that perfuses the body after cardiac arrest. Signs include a palpable pulse, measurable blood pressure and/or respiratory effort.(299)
Hospitalised ventricular tachycardia	The patient was hospitalised with ventricular tachycardia, defined as ≥ 3 consecutive beats with a rate > 100 beats per minute originating from the ventricles, independent from atrial and atrioventricular nodal conduction.(294)
Newly diagnosed atrial fibrillation/flutter	Atrial fibrillation (AF) is defined as a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. The minimum duration of an ECG tracing of AF required to establish the diagnosis of clinical AF is at least 30 seconds, or entire 12-lead ECG. Atrial flutter (AFL) is defined as a supraventricular tachyarrhythmia with coordinated but overly rapid atrial electrical activation, usually with some degree of atrioventricular node conduction block. The minimum duration of an ECG tracing of AF required to establish the diagnosis of clinical AFL is at least 30 seconds, or entire 12-lead ECG.(300)
Worsening heart failure	Heart failure (HF) is a clinical syndrome characterised by typical symptoms (e.g., dyspnoea) and/or signs (e.g., ankle swelling), caused by a structural and/or functional cardiac abnormality (e.g., left ventricular hypertrophy or impairment), and associated with elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion from a cardiogenic origin at rest or with exercise. Worsening HF is defined as either an unplanned HF hospitalisation or urgent outpatient visit for HF. Unplanned HF hospitalisation is defined as a patient requiring an unscheduled hospital admission for a *primary diagnosis* of HF with a length of stay that either exceeds 24 h or crosses a calendar day (if hospital admission and discharge times are unavailable). To satisfy the criteria for a worsening HF event, the patient must have an urgent, unscheduled office or emergency visit for HF with signs, symptoms, and diagnostic

	testing results identical to those already described above. The patient must also require treatment for HF such as significant dose increase of oral diuretics, intravenous diuretics or mechanical or surgical intervention for HF. Importantly, clinic visits for scheduled administration of HF therapies or procedures (e.g., intravenous diuretics, intravenous vasoactive agents, or mechanical fluid removal) do not qualify as non-hospitalised HF events.(255, 287, 301)
Cardiogenic shock	Cardiogenic shock is defined as any one of the following: (1) “beginning” cardiogenic shock or compensated shock where a patient may be volume overloaded, tachycardic, and/or hypotensive but no evidence of hypoperfusion on physical exam or laboratory studies. It also includes patients with a (2) “classic” cardiogenic shock with evidence of hypoperfusion on physical exam and laboratory studies “cold and wet.” Invasive haemodynamics (if available) demonstrate the classic depressed cardiac index associated with cardiogenic shock. Cardiogenic shock also includes patients with (3) “deteriorating” and includes above patients plus failure of initial interventions in restoring adequate perfusion in 30 minutes and further escalation is required. Cardiogenic shock also includes (4) “escalation” cardiogenic shock which is an increase in the number or intensity of intravenous therapies to address hypoperfusion, or addition of mechanical circulatory support after the initial 30-minute period of observation and treatment. It can also include patients who are highly unstable, often with circulatory collapse and/or refractory cardiac arrest with ongoing cardiopulmonary resuscitation (CPR). They are being supported by multiple simultaneous acute interventions including extracorporeal membrane oxygenation (ECMO)-facilitated CPR (eCPR).(302)
Mechanical circulatory support	Use of a mechanical circulatory support devices, such as left ventricular assist device.
Heart transplant	Surgery in which a failing, diseased heart is replaced with a donor heart.(303)
Systemic embolism	Systemic embolism is defined as a hospital encounter with a principal diagnosis of an arterial embolism and thrombosis,(304) excluding stroke or transient ischemic attack.
Pulmonary embolism	A condition in which one or more emboli, usually arising from a thrombus formed in the veins, are lodged in and obstruct the pulmonary arterial system, causing severe respiratory dysfunction.(305)
Deep vein thrombosis	Deep vein thrombosis (DVT) is the formation of a thrombus (blood clot) in a deep vein, usually in the legs, but may also include the arms, which partially or completely obstructs blood flow.(306)
Unplanned cardiac surgery	Unplanned cardiac surgery is defined as an unplanned surgical intervention to the heart and the great vessels that requires a sternotomy.(307)
Acute kidney injury	Increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 μmol/L) within 48 hours; or an increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 ml/kg/h for 6 hours.(308)

5.5.4.1 Acute coronary syndrome domain: Level 1 variables

For the ACS outcome measures domain, eight Level 1 variables were agreed: major bleeding event, acute kidney injury requiring renal replacement therapy, target vessel-related MI, unplanned target-vessel PCI, unplanned target-vessel CABG, target lesion stent thrombosis, HF hospitalisation, cardiac arrest.

5.5.4.2 Acute coronary syndrome domain: Level 2 variables

For the ACS outcome measures domain, seven Level 2 variables were agreed: minor bleeding event, vascular access complication, left ventricular EF, CCS angina class, cardiovascular hospitalisation, hospitalisation with unstable angina, attendance at cardiac rehabilitation. The full definitions are provided in **Table 5.2**

Table 5.2. Full list of ACS/PCI outcomes and their definitions.

Acute Coronary Syndrome – Percutaneous Coronary Intervention domain: Level 1 variables	
Major bleeding event	**Type 2:** any clinically overt sign of haemorrhage that is actionable but does not meet criteria for type 3, type 4 (coronary artery bypass graft surgery [CABG]-related), or type 5 (fatal bleeding) bleeding. The bleeding must require diagnostic studies, hospitalization, or treatment by a healthcare professional. In particular, the bleeding must meet at least one of the following criteria: i) Requires intervention, defined as a healthcare professional–guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug. ii) Bleeding leads to hospitalization or an increased level of care, defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care. iii) The bleeding prompts evaluation, defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging). **Type 3a:** any transfusion with overt bleeding; overt bleeding plus haemoglobin drop ≥ 3 to < 5 g/dL (provided haemoglobin drop is related to bleeding). **Type 3b:** overt bleeding plus haemoglobin drop ≥ 5 g/dL (provided haemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid); bleeding requiring intravenous vasoactive drugs. **Type 3c:** intracranial haemorrhage; subcategories confirmed by autopsy or imaging, or lumbar puncture; intraocular bleed compromising vision. **Type 4:** CABG–related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48-hour period; chest tube output ≥ 2 L within a 24-hour period. **Type 5:** fatal bleeding.[22] Note: Major bleeding includes fatal bleeding events, symptomatic bleeding in a critical areas or organs (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or fall in haemoglobin level of ≥ 20 g/L (≥ 2 g/dL) or transfusion of ≥ 2 units of blood. In-hospital major bleeding does not include CABG-related bleeding. Fatal bleeding should be selected when bleeding is believed to be the primary cause of death. Intracranial haemorrhage, of any severity,

	should ideally be confirmed by scanning. Other major bleeding should only be selected if the patient had a major bleeding episode other than those stated above.(290)
Acute kidney injury requiring renal replacement therapy	Renal replacement therapy includes ultrafiltration (haemofiltration), haemodialysis or peritoneal dialysis.(308)
Target vessel related myocardial infarction	Target vessel myocardial infarction is defined as a MI case with evidence of myocardial necrosis in the vascular territory of a previously treated target vessel. As well as direct evidence of invasive angiography, electrocardiographic or other imaging evidence such as echocardiography (e.g., newly developed regional wall motion abnormality or extension of previous abnormality) can be used to adjudicate the involvement of the target vessel territory. The target vessel was defined as the entire major coronary vessel or bypass graft proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. The left main coronary artery and any vessel originating from the left main coronary artery, or its major branches is, defined as target vessel.[295, 309]
Unplanned target-vessel percutaneous coronary intervention	An unplanned percutaneous coronary intervention (PCI) after the index procedure. Repeat target vessel PCI is defined as any repeat PCI of any segment of the target vessel including the target lesion. The target vessel is defined as the entire major coronary vessel or bypass graft proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. The left main coronary artery and any vessel originating from the left main coronary artery, or its major branches is, defined as target vessel. PCI is defined as the placement of an angioplasty guidewire, balloon, or other device (e.g., stent, atherectomy, brachytherapy, or thrombectomy catheter) into a native coronary artery or a graft for the purpose of mechanical coronary revascularisation. The assessment of coronary lesion severity by fluoroscopy, intracoronary imaging (e.g., intravascular ultrasonography) or physiology (e.g., fractional flow reserve) is not considered a PCI procedure.[309, 310]
Unplanned target-vessel coronary artery bypass graft surgery	Repeat revascularisation of the target vessel with unplanned coronary artery bypass grafting (CABG) surgery after the index procedure. Target vessel CABG is defined as any CABG of any segment of the target vessel including the target lesion. The target vessel was defined as the entire major coronary vessel or bypass graft proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. The left main coronary artery and any vessel originating from the left main coronary artery, or its major branches is, defined as target vessel. Coronary artery bypass graft surgery (CABG) is a procedure that involves sternotomy to bypass diseased segment(s) of the coronary tree using blood vessels derived other parts of the body and connected to the aorta.[309, 310]

Target lesion stent thrombosis	Target lesion stent thrombosis is defined as occurring when clinical presentation is consistent with acute coronary syndrome of a previously treated lesion. The categories are defined as follows: **Definite** is defined as angiographic confirmation of stent/scaffold thrombosis, the presence of a thrombus that originates in the stent/scaffold or in the segment 5 mm proximal or distal to the stent/scaffold or in a side branch originating from the stented/scaffolded segment and the presence of at least 1 of the following criteria: • Acute onset of ischemic symptoms at rest • New electrocardiographic changes suggestive of acute ischemia • Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction) • Pathological confirmation of stent/scaffold thrombosis Evidence of recent thrombus within the stent/scaffold determined at autopsy. • Examination of tissue retrieved following thrombectomy (visual/histology) **Probable** is defined, regardless of the time after the index procedure, as any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent/scaffold without angiographic confirmation of stent/scaffold thrombosis and in the absence of any other obvious cause. **Silent** is defined as the incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered stent thrombosis.(309)
Heart failure hospitalisation	Hospital admission primarily due to heart failure. Heart failure is a clinical syndrome characterised by typical symptoms (e.g., dyspnoea) and/or signs (e.g., ankle swelling), caused by a structural and/or functional cardiac abnormality (e.g., left ventricular hypertrophy or impairment), and associated with elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion from a cardiogenic origin at rest or with exercise. Unplanned HF hospitalisation is defined as a patient requiring an unscheduled hospital admission for a *primary diagnosis* of HF with a length of stay that either exceeds 24 h or crosses a calendar day (if hospital admission and discharge times are unavailable). To satisfy the criteria for a HF hospitalisation, the patient must be admitted primarily for HF with signs, symptoms, and diagnostic testing results identical to those already described above. The patient must also require treatment for HF such as significant augmentation of oral diuretics, intravenous diuretics or mechanical or surgical intervention for HF.(255, 287, 293, 301) Please record worsening heart failure under the Level 2 section of the generic outcomes, if available.

Cardiac arrest	Cardiac arrest is defined as a verified sudden cessation of cardiac activity causing unresponsiveness, absence of normal breathing and no signs of circulation (excluding syncope or profound vagally-mediated bradycardia) with ventricular fibrillation, rapid ventricular tachycardia or bradycardia resulting in loss of consciousness, pulseless electrical activity, or asystole as the major causes. Return of spontaneous circulation (ROSC) is defined as the resumption of a sustained heart rhythm that perfuses the body after cardiac arrest. Signs include a palpable pulse, measurable blood pressure and/or respiratory effort.(299)

Acute Coronary Syndrome – Percutaneous Coronary Intervention domain: Level 2 variables

Cardiovascular hospitalisation	Unscheduled hospitalised primarily due to cardiovascular disease. Unscheduled hospitalisation is defined as a being admitted for more than 24 hours or past a calendar day due to primarily a cardiovascular condition. CV causes include conditions such as heart failure, cardiogenic shock, bioprosthetic or native valve dysfunction, myocardial infarction, stroke, thromboembolism, bleeding, tamponade, vascular complication, arrhythmia or conduction system disturbances, cardiovascular infection (e.g., mediastinitis, endocarditis), or other clear cardiovascular cause.(287, 293)
Hospitalisation with unstable angina	Unscheduled admission to hospital with unstable angina as the primary cause. Unstable angina is defined as myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis using high-sensitive (hs)-cardiac troponin (cTn). Unscheduled hospitalisation is defined as a being admitted for more than 24 hours or past a calendar day due to primarily a cardiovascular condition.(287, 293, 311)
Minor bleeding event	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional (Bleeding Academic Research Consortium Type 1).(290)
Vascular access complication	Access site haematoma, arteriovenous fistula, peripheral ischaemia, peripheral nerve injury, pseudoaneurysm or retroperitoneal haemorrhage. **Major** access-related non-vascular events are defined as one of the following:

	• Non-vascular structure, non-cardiac structured perforation, injury, or infection resulting in death, BARC type ≥ 3 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention • Non-vascular access site (e.g., trans-apical left ventricular) perforation, injury, or infection resulting in death, BARC type ≥ 3 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention **Minor** access-related non-vascular events are defined as one of the following: • Non-vascular structure, non-cardiac structured perforation, injury, or infection not resulting in death, BARC type ≥ 3, irreversible nerve injury, or requiring unplanned surgery or percutaneous intervention • Non-vascular access site (e.g., trans-apical left ventricular) perforation, injury, or infection not resulting in death, BARC type ≥ 3 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention.(290, 293) (290)
Left ventricular ejection fraction	Ejection fraction is ideally measured with echocardiography for consistency.
CCS angina class	**CCS grade I:** Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation. **CCS grade II:** Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions. **CCS grade III:** Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace. **CCS grade IV:** Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest.(312)
Attendance at cardiac rehabilitation	Cardiovascular rehabilitation (CR) is a multi-factorial and comprehensive intervention in secondary prevention, supervised and carried out by adequately trained health professionals.(313)

5.5.4.3 Atrial fibrillation domain: Level 1 variables

For the AF outcome measures domain, two Level 1 two variables were agreed: cardiovascular hospitalisation, and catheter ablation.

5.5.4.4 Atrial fibrillation domain: Level 2 variables

For the AF outcome measures domain, six Level 2 variables were agreed: implantable monitoring device, device implantation, recurrence of AF, burden of AF (time spent in AF out of total monitoring period), all-cause hospitalisation, cardioversion. The full definitions are provided in **Table 5.3.**

Table 5.3. Full list of AF outcomes and their definitions.

Atrial fibrillation domain: Level 1 variables	
Cardiovascular hospitalisation	Admission to hospital primarily due to cardiovascular disease. Unscheduled hospitalisation is defined as a being admitted for more than 24 hours or past a calendar day due to primarily a cardiovascular condition. CV causes include conditions such as heart failure, cardiogenic shock, bioprosthetic or native valve dysfunction, myocardial infarction, stroke, thromboembolism, bleeding, tamponade, vascular complication, arrhythmia or conduction system disturbances, cardiovascular infection (e.g., mediastinitis, endocarditis), or other clear cardiovascular cause.(287, 293)
Catheter ablation	Catheter ablation for atrial fibrillation (AF) or atrial flutter (AFL) is defined as a procedure in which catheters are inserted through the veins or arteries to the heart, and energy (e.g., radiofrequency, cryoablation) is delivered to prevent propagation of abnormal AF or AFL. **Atrial fibrillation (AF)** is defined as a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. The minimum duration of an ECG tracing of AF required to establish the diagnosis of clinical AF is at least 30 seconds, or entire 12-lead ECG. **Atrial flutter (AFL)** is defined as a supraventricular tachyarrhythmia with coordinated but overly rapid atrial electrical activation, usually with some degree of atrioventricular (AV) node conduction block. The minimum duration of an ECG tracing of AFL required to establish the diagnosis of clinical AFL is at least 30 seconds, or entire 12-lead ECG.[17]
Atrial fibrillation domain: Level 2 variables	
All-cause hospitalisation	Unscheduled admission to hospital for any reason. Hospitalisation is defined as a being admitted for more than 24 hours or past a calendar day.(287, 293)

Device implantation	Implantation of: • **Transvenous permanent pacemaker** is an electronic device that is implanted in the subcutaneous tissue and gives the heart an electrical stimulation through transvenous wires. • **Leadless pacemaker** is an electronic device that is implanted directly into the right ventricle. • **Transvenous implantable cardioverter defibrillator (ICD)** is a device that is used to correct abnormal heartbeat through transvenous wires. • **Subcutaneous ICD** is an ICD with a presternal lead and is positioned between the latissimus dorsi and serratus muscle within the subcutaneous tissue. • **Extravascular ICD** is an ICD with a substernal lead and the device in the subcutaneous tissue of the lateral thorax. • **Cardiac resynchronization therapy (CRT) device and pacemaker (CRT-P)** is defined as a biventricular pacemaker that sends electrical stimulation to both ventricles. • **CRT-D** is a biventricular pacemaker and defibrillator.(70, 298)
Implantable monitoring device	An implantable device that allows remote rhythm monitoring.(70)
Recurrence of atrial fibrillation	Recurrence of atrial fibrillation/flutter. **Atrial fibrillation (AF)** is defined as a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. The minimum duration of an ECG tracing of AF required to establish the diagnosis of clinical AF is at least 30 seconds, or entire 12-lead ECG. **Atrial flutter (AFL)** is defined as a supraventricular tachyarrhythmia with coordinated but overly rapid atrial electrical activation, usually with some degree of atrioventricular (AV) node conduction block. The minimum duration of an ECG tracing of AFL required to establish the diagnosis of clinical AFL is at least 30 seconds, or entire 12-lead ECG.(306)
Burden of atrial fibrillation (time spent in AF out of total monitoring period)	Burden is defined as the amount of time spent in atrial fibrillation as a proportion of the total monitoring period. Monitoring can be in the form of invasive and non-invasive monitoring devices.

	Duration of the device monitoring period is the fixed monitoring period using ambulatory and between downloads of invasive monitoring devices.(300)
Cardioversion	**Electrical cardioversion** (external or internal) is defined as a procedure in which direct current (DC) is used to restore sinus rhythm. **Pharmacologic cardioversion** is defined as a procedure in which antiarrhythmic medications are used to restore sinus rhythm.(300)

5.5.4.5 Heart failure domain: Level 1 variables

For the HF outcome measures domain, five Level 1 variables were agreed: left ventricular EF, all-cause hospitalisation, HF re-hospitalisation, heart transplantation, and implant of a LVAD.

5.5.4.6 Heart failure domain: Level 2 variables

For the HF outcome measures domain, two Level 2 variables were agreed: resuscitated ventricular arrhythmia, and device implant. The HF Working Group advised that additional parameters would be advantageous for monitoring the chronic disease management aspects of HF, which are discussed in detail in a separate publication.(240) The full definitions for the HF outcomes are provided in **Table 4.3.**

5.5.4.7 Transcatheter aortic valve intervention domain: Level 1 variables

For the TAVI outcome measures domain, four Level 1 variables were agreed: NYHA class, aortic regurgitation, device implantation, re-intervention on the aortic valve.

5.5.4.8 Transcatheter aortic valve intervention domain: Level 2 variables

For the TAVI outcome measures domain, 15 Level 2 variables were agreed: Access-related non-vascular complications, endocarditis, cardiogenic shock, cardiac arrest, serum creatinine, CCS angina class, left ventricular EF, residual aortic stenosis, other transcatheter heart valve procedure, CABG, PCI, all-cause rehospitalisation, new renal replacement therapy, new AF or atrial flutter, sternotomy or thoracotomy due to bleeding. The full definitions are provided in **Table 5.4**.

Table 5.4. Full list of TAVI outcomes and their definitions.

Transcatheter aortic valve intervention – Level 1 variables	
NYHA class	**NYHA class I:** no limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnoea. **NYHA class II:** slight limitation of physical activity. The patient is comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnoea. **NYHA class III:** marked limitation of physical activity. The patient is comfortable at rest. Less than ordinary activity causes fatigue, palpitations, or dyspnoea. **NYHA class IV:** inability to carry on any physical activity without discomfort. Heart failure symptoms are present even at rest or with minimal exertion.(255, 301)
Aortic regurgitation	Presence of aortic regurgitation, and severity (mild/moderate/severe) as determined by echocardiography based on doppler parameters according to the criteria of the Valve Academic Research Consortium (VARC 3) criteria.(293)
Device implantation	Implantation of: • **Transvenous permanent pacemaker** is an electronic device that is implanted in the subcutaneous tissue and gives the heart an electrical stimulation through transvenous wires. • **Leadless pacemaker** is an electronic device that is implanted directly into the right ventricle. • **Transvenous implantable cardioverter defibrillator (ICD)** is a device that is used to correct abnormal heartbeat through transvenous wires. • **Subcutaneous ICD** is an ICD with a presternal lead and is positioned between the latissimus dorsi and serratus muscle within the subcutaneous tissue. • **Extravascular ICD** is an ICD with a substernal lead and the device in the subcutaneous tissue of the lateral thorax. • **Cardiac resynchronization therapy (CRT) device and pacemaker (CRT-P)** is defined as a • biventricular pacemaker that sends electrical stimulation to both ventricles. • **CRT-D** is a biventricular pacemaker and defibrillator.(70, 298)
Re-intervention on the aortic valve:	**Re-do TAVI** is a different procedure to the index TAVI, and a separate registration form should be completed.

	Balloon aortic valvuloplasty is a transcatheter balloon dilatation of the implanted aortic valve after the completion of the index procedure. **Surgical aortic valve replacement** is defined as a deployment of a new (mechanical or bioprosthetic) aortic valve surgically (i.e., procedure involves sternotomy or thoracotomy). **Other aortic valve surgery** is any other surgical intervention on the aortic valve.
Transcatheter aortic valve intervention – Level 2 variables	
All-cause rehospitalisation	Unscheduled hospital admission for any reason. Unscheduled hospitalisation is defined as a being admitted for more than 24 hours or past a calendar day.(287, 293)
Access-related non-vascular complications	**Major** access-related non-vascular events are defined as one of the following: • Non-vascular structure, non-cardiac structured perforation, injury, or infection resulting in death, BARC type ≥ 3 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention. • Non-vascular access site (e.g., trans-apical left ventricular) perforation, injury, or infection resulting in death, BARC type ≥ 3 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention. **Minor** access-related non-vascular events are defined as one of the following: • Non-vascular structure, non-cardiac structured perforation, injury, or infection not resulting in death, BARC type ≥ 3 bleeding, irreversible nerve injury, or requiring unplanned surgery or percutaneous intervention. • Non-vascular access site (e.g., trans-apical left ventricular) perforation, injury, or infection not resulting in death, BARC type ≥ 3 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention.(293)
Endocarditis	Infective endocarditis is diagnosed if at least one of the following criteria is met: (1) Fulfilment of the Duke criteria for endocarditis (2) Evidence of abscess, pus, or vegetation confirmed as secondary to infection by histological or microbiological studies during re-operation; and (3) Evidence of abscess, pus, or vegetation confirmed on autopsy.(293)
Cardiogenic shock	Cardiogenic shock is defined as any one of the following: (1) “beginning” cardiogenic shock or compensated shock where a patient may be volume overloaded, tachycardic, and/or hypotensive but no evidence of

	hypoperfusion on physical exam or laboratory studies. It also includes patients with a (2) “classic” cardiogenic shock with evidence of hypoperfusion on physical exam and laboratory studies “cold and wet.” Invasive haemodynamics (if available) demonstrate the classic depressed cardiac index associated with cardiogenic shock. Cardiogenic shock also includes patients with (3) “deteriorating” and includes above patients plus failure of initial interventions in restoring adequate perfusion in 30 minutes and further escalation is required. Cardiogenic shock also includes (4) “escalation” cardiogenic shock in 11(54) which an increase in the number or intensity of intravenous therapies to address hypoperfusion, or addition of mechanical circulatory support after the initial 30-minute period of observation and treatment. It can also include patients who are highly unstable, often with circulatory collapse and/or refractory cardiac arrest with ongoing cardiopulmonary resuscitation (CPR). They are being supported by multiple simultaneous acute interventions including extracorporeal membrane oxygenation (ECMO)-facilitated CPR (eCPR).(302)
Cardiac arrest	Cardiac arrest is defined as a verified sudden cessation of cardiac activity causing unresponsiveness, absence of normal breathing and no signs of circulation (excluding syncope or profound vagally-mediated bradycardia) with ventricular fibrillation, rapid ventricular tachycardia or bradycardia resulting in loss of consciousness, pulseless electrical activity, or asystole as the major causes. Return of spontaneous circulation (ROSC) is defined as the resumption of a sustained heart rhythm that perfuses the body after cardiac arrest. Signs include a palpable pulse, measurable blood pressure and/or respiratory effort.(299)
Creatinine (µmol/L)	Serum creatinine assay, in µmol/L.
CCS angina status	**CCS grade I:** ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation. **CCS grade II:** slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions. **CCS grade III:** marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace. **CCS grade IV:** inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest.(312)
Left ventricular ejection fraction	Ejection fraction, ideally measured with echocardiography.

Residual aortic stenosis	**Stage 1:** Evidence of structural valve deterioration, non-structural valve dysfunction (other than paravalvular regurgitation or prosthesis-patient mismatch), thrombosis, or endocarditis without significant haemodynamic changes. **Stage 2:** Increase in mean trans valvular gradient > 10mmHg resulting in mean gradient > 20mmHg with concomitant decrease in effective orifice area (EOA) > 0.3cm^2 or > 25% and/or decrease in Doppler velocity index > 0.1 or > 20% compared with echocardiographic assessment performed 1–3 months post-procedure. **Stage 3:** Increase in mean trans valvular gradient > 20mmHg resulting in mean gradient > 30mmHg with concomitant decrease in EOA > 0.6cm^2 or > 50% and/or decrease in Doppler velocity index > 0.2 or > 40% compared with echocardiographic assessment performed 1–3 months post-procedure.(293)
Other transcatheter heart valve procedure	Valve intervention after the index TAVI procedure, excluding repeat aortic valve intervention.
Coronary artery bypass grafting surgery	Coronary artery bypass graft (CABG) surgery after the TAVI procedure. CABG is a procedure that involves sternotomy to bypass diseased segment(s) of the coronary tree using blood vessels derived from other parts of the body and connected to the aorta.(307)
Percutaneous coronary intervention	Percutaneous coronary intervention (PCI) after the TAVI procedure. PCI is the placement of an angioplasty guidewire, balloon, or other device (e.g., stent, atherectomy, brachytherapy, or thrombectomy catheter) into a native coronary artery or a graft for the purpose of mechanical coronary revascularisation. The assessment of the severity of a coronary lesion by fluoroscopy, intracoronary imaging (e.g., intravascular ultrasonography), or intracoronary physiology (e.g., fractional flow reserve) is not considered a PCI procedure.(310)
New renal replacement therapy	The patient developed a new requirement for renal replacement therapy. Renal replacement therapy includes ultrafiltration (haemofiltration), haemodialysis or peritoneal dialysis.(308)
New atrial fibrillation or atrial flutter	A new diagnosis of atrial fibrillation (AF) or flutter.
Sternotomy/thoracotomy due to bleeding	The patient had a sternotomy/thoracotomy due to bleeding.

5.5.4.9 Bleeding

Various classification systems for bleeding are used across the EuroHeart data standards,(167-170) reflecting the relative strengths of each in specific in-patient settings. The preferred bleeding classification for the outcome domain was BARC: of 59 respondents, 25 (42%) selected, 18 (31%) VARC, and 16 (27%) ISTH BARC as first choice.

5.5.4.10 Medical devices

Whenever a medical device featured within the outcomes domain is implanted or used, the associated unique device identification code will be recorded as a Level 1 variable to enable longitudinal device surveillance.

5.6 Discussion

Following an established methodology for data standards development, we have derived and defined a suite of internationally agreed cardiovascular outcome measures. This catalogue spans ACS, AF, HF and TAVI, and includes generic cardiovascular outcome measures that are applicable across a range of cardiovascular diseases. The cardiovascular outcome measures have been evaluated by international experts, and classified hierarchically as Level 1, meaning that collection of the variable is mandatory; or Level 2, where inclusion is optional and is based upon specific study goals. In total, we present 25 Level 1 and 50 Level 2 cardiovascular outcome measures. These may be used in clinical studies and for data alignment and will be integrated into the EuroHeart IT platform to enable standardised measurement and federated research.

The concept of standardised cardiovascular endpoints is not new. Similar work has been published, but is limited to specific cardiovascular diseases,(151, 152, 155) or are specific to RCTs.(287) They also lack a graded structure.(151, 152, 155, 287) Other single pathology outcome sets are yet to be updated such as the ICHOM set on coronary artery disease.(155) Acute MI features as an important outcome to report however its definition has not been updated to align with the international consensus definitions of the different types of MI agreed upon in 2018.(231) This in part may explain the poor uptake of the ICHOM CAD outcome sets in trials published since 2015 (an average of 0.1% increase per month in trials published on ClinicalTrials.gov),(314) which suggests existing barriers exist to implementation. Another limitation includes the heterogenous patient population defined within the coronary artery disease population outcome set published by ICHOM. This encompasses diverse patients with MI, angina, PCI and CABG.(155) Therefore the need for standardising ACS/PCI outcomes, in particular, still persist. The last outcome set published for this group of patients was the ARC recommendations published in 2007. (289)

Similar to ACS/PCI other outcome sets are yet to be updated to suit contemporary HF diagnosis and management in particular EF categorisation(67, 75)(252) These categories were agreed upon through international consensus of leading HF experts and stakeholders in 2021. But

previous outcome sets have not updated the definition of HF in order to capture important HF subtypes such as HFpEF and HFiEF.(146, 239, 255, 315)

Unlike previous frameworks, our cardiovascular outcome measure catalogue is purposefully designed to span many research study designs. Differentiating between Level 1 and Level 2 variables means that centres may participate in data collection of only the ‘essentials’ and select additional optional variables to suit their specific needs. This will maximise the potential for implementation across heterogeneous healthcare environments with differing availability of electronic health records and central infrastructure to support data collection.

The EuroHeart initiative offers a pragmatic and versatile toolset that is likely to enhance the quality and impact of cardiovascular healthcare research and patient care globally.(235) Seemingly small differences in definitions may alter study conclusions, may potentially be misleading, and make comparisons between studies challenging.(316-318) Indeed, regulatory authorities and most major clinical journals prefer prospective identification of a primary outcome measure with a robust statistical approach to multiplicity in outcomes.(319, 320) The alignment of these measures is necessary: the number of RCTs published is increasing year on year, and now exceeds 35,000 annually.(321) In addition, researchers are employing novel methods by which to conduct RCTs and observational studies,(322) including the use of routinely-collected healthcare systems data and registry-based RCTs.(323) Such use of structured data, not purposely designed for the research at hand, compels the use of clinical outcome measures selected from a finite range of variables.(177, 287)

Historically, outcomes such as myocardial infarction have limited specificity and sensitivity in administrative data.(244) The ADAPTABLE trial [NCT02697916] used a common data model as the primary source of end point ascertainment without adjudication, and found that the positive predictive values for hospitalisation for myocardial infarction, stroke, and major bleeding, compared to adjudication were 90%, 72%, and 93% respectively.(245) Adjudication of outcome measures is traditionally considered important to minimise noise and mitigate bias,(246) which may be supplemented (or replaced) by the use of routinely-collected healthcare systems data for clinical outcome measure assessments.(246, 324) Similarly, heart failure re-hospitalisation rates within thirty days vary substantially depending on the methodological approach taken -

between 6.5% and 15% at thirty days according to a recent registry study.(266) There is therefore a need to standardise the cardinal clinical outcome measures and their definitions to maximise the opportunities that are afforded by these important developments to be fully realised.(9) Additionally, in light of the increased use of composite outcomes in clinical trials,(325) a consistent and universally agreed selection of the variables to be included in the design phases is important to minimise the risk of bias in these circumstances.(326)

EuroHeart provides an opportunity for coordinated collection and analysis of cardiovascular data across Europe and beyond. Within the first year of data collection, data were collected using internationally derived data standards for over 40,000 patients with ACS across seven countries.(166, 170)

5.6.1 Strengths

The present work extends and compliments this, using the established and robust methodology,(171) and harnessed the expertise of a wide range of international experts from diverse healthcare settings

5.6.2 Weaknesses

However, we recognise the limitations of this work. In particular, the reliance on a select group of leading experts to define and classify outcome measures can introduce selection bias. The perspectives and experiences of these experts might not fully represent the diverse patient demographics or the full spectrum of clinical realities in different settings. This might limit the universality of the adopted measures. Although the importance of PROMs and PREMs is increasingly recognised,(106) our remit for this project was limited to clinical outcomes. Identifying PROMs for use in EuroHeart will form the next stage of our work.

5.7 Conclusion

We present a suite of internationally developed and agreed outcome measures and their associated definitions for four common cardiovascular conditions. This was derived through an expert-led consensus process based upon contemporary clinical evidence. These will be implemented within the EuroHeart

registry. Their consistent use is strongly encouraged in other registries, healthcare systems data, in RCTs, and observational research.

5.8 Summary

- Existing consensus documents have sought to standardise CVD outcome measures however there are limitations, such as some are mainly tailored for use in trials, some are designed for each specific CVD with no linking with other CVD, not updated and aligned with contemporary diagnosis, classification and management of some conditions such as ACS and HF, lack patient involvement or lack hierarchical specification
- EuroHeart presents a suite of internationally developed and agreed outcome measures and their associated definitions for four common cardiovascular conditions.
- They were derived through an expert-led consensus process based upon contemporary clinical evidence that included 25 Level 1 outcomes (mandatory within EuroHeart), 50 Level 2 outcomes (optional).
- Their consistent use is strongly encouraged in other registries, healthcare systems data, in RCTs, and observational research

Chapter 6

Scoping review of Cardiovascular PROMs that evaluate Health Related Quality of Life

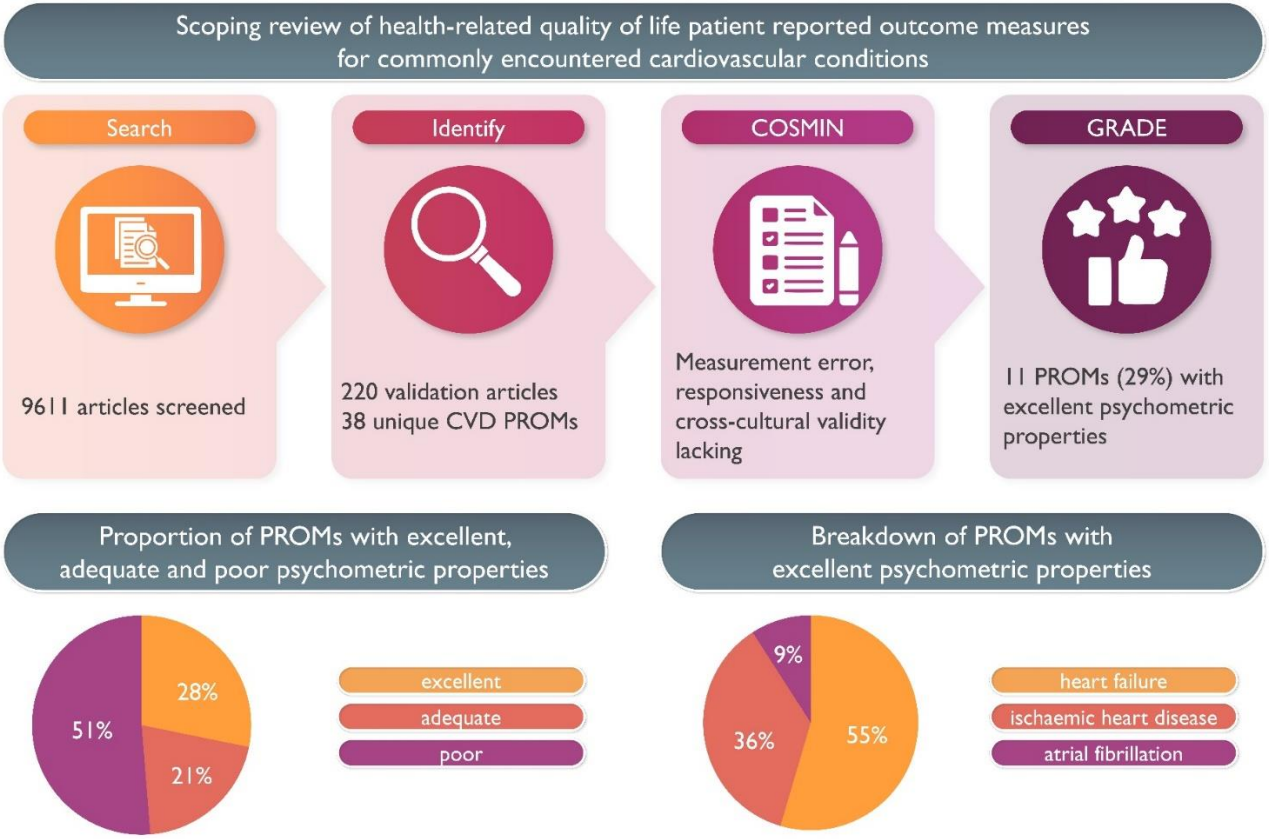
Psychometric properties of health-related quality of life patient reported outcome measures for common cardiovascular conditions: A scoping review and COSMIN analysis

6.1 Contribution

The scoping review, like the systematic review of contemporary cardiovascular outcomes, involved multiple collaborators. My role was to refine and update the search strategy to include articles published from inception to 6th February 2025, review articles derived from the search strategy for inclusion and corroborate the included articles with a targeted search for articles on PubMed and Embase, cleaning data, writing and editing the draft manuscript, and incorporating co-author comments. This was published recently and the details are:

Bhatty A, Smith AB, Scherrenberg M et al. Psychometric properties of health-related quality of life patient reported outcome measures for common cardiovascular conditions: A scoping review and COSMIN analysis. Eur J Cardiovascular Nursing (accepted on 9/11/25, Ref. No.: CNU-D-25-00367R2)

Figure 6.1. Graphical abstract of the scoping review



6.2 Abstract

Aims

HRQoL is an important measure of disease status and represents a holistic approach to delivering patient centred care. We conducted a scoping review of HRQoL PROMs for CVD and evaluated their psychometric properties using the COSMIN guidelines.

Methods and Results

RCTs and observational studies that developed and validated HRQoL PROMs for adults with IHD, aortic stenosis (AS), AF, HF or generic CVD were included that were published from database inception to 8th February 2025 using PubMed, Web of Science, CINAHL and Embase. Two independent reviewers selected and extracted the psychometric properties of each PROM in accordance with the COSMIN checklist: content validity, reliability, internal consistency, structural validity, criterion/convergent, cross-cultural validity, measurement error, hypothesis testing and responsiveness. Each PROM was graded using the GRADE approach.

Of 9430 articles, 220 studies for 38 different PROMs were included (HF n = 17, 45%; AF n = 11, 29%; IHD n = 7, 18%; generic n = 2, 5%; AS n=1, 3%). Eleven PROMs (29%) satisfied all nine COSMIN criteria; the majority (n= 19, 50%) required further validation and 8 were deemed inadequate for clinical use (21%). **Figure 6.1**

Conclusion

This scoping review of HRQoL PROMs in individuals with common CVDs found evidence that many PROMs do not fulfil all nine COSMIN criteria for methodological quality, and for some CVDs there is a limited choice of suitable PROMs for HRQoL measurement. There is an opportunity to improve HRQoL evaluation in CVD.

6.3 Introduction

HRQoL is an important measure of disease status and represents a holistic approach to delivering patient centred care.(13, 58, 280) HRQoL assesses an individual's perception of the impact a condition has on their physical health, psychological and social functioning, and emotional well-being,(327, 328) and is commonly quantified using validated questionnaires or PROMs.(329)

The adoption of HRQoL within routine care and research has broad appeal to patients, trialists and healthcare providers. As mentioned in **section 1.4.3**. evaluating quality of life is increasingly important as over 113 million within Europe were living with chronic CVD in 2019 (48 million of these with IHD(5)). This is driven largely by a combination of an aging population and improvements in CVD mortality due to the implementation of guideline indicated therapy.(5) As more patients are living with CVD for longer, measuring quality of life accurately is increasingly important for healthcare providers as patients subsequently become more prone to experience chronic symptoms that deteriorate over time, which increases healthcare expenditure with inpatient or outpatient hospital visits as well as utilising community services such as general practitioner appointments.(281)

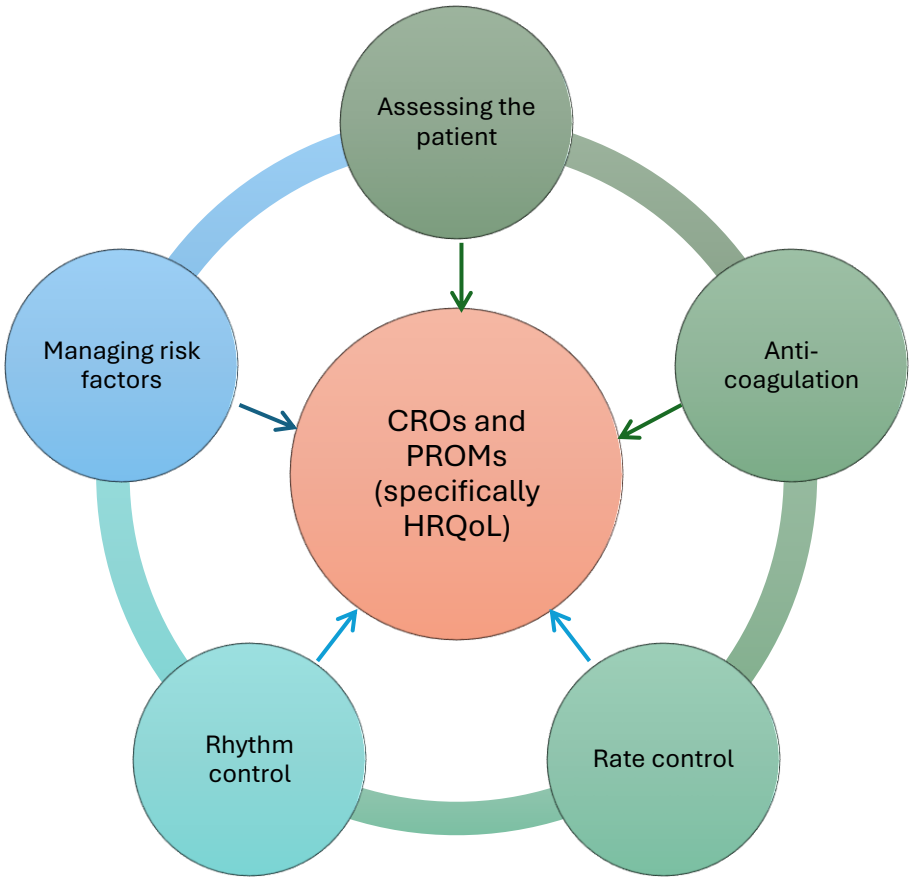
From a patient perspective, employing PROMs has several benefits.(330-332) Of these, employing PROMs within clinical care is associated with increased patient satisfaction with healthcare services.(330-332) Furthermore, patients value improvements in their HRQoL similarly to additional life years gained; and in some instances would trade longevity for better quality of life.(62, 333) In the ‘Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness’ (ESCAPE) trial, 287 hospitalised patients with advanced HF were surveyed on their preferences to trade survival time for better quality of life at baseline and at six months post discharge.(333) At baseline, most patients stated that they would trade a minimum of three months of life for better quality of life whilst in hospital. However, in the post-discharge period most patients stated a preference for survival over quality of life. But those patients with more advanced symptoms, poorer prognosis and reduced functional status were more likely to trade time for improved quality of life.(333) Therefore accurately understanding a patient’s perception regarding their quality of life and prognosis

evolves over time and may influence the treatment goals and therefore a clinician's treatment and truly offer patent centred care.

From a clinical perspective, recent studies in CVD demonstrate that patients directly reporting their symptoms and quality of life is more accurate than a clinician's interpretation of a patient's history as demonstrated in **chapter 1.4.3.2.** (73, 75)A recent meta-analysis of 51 studies demonstrated that poor baseline or deterioration in HRQoL scores is associated with poor clinician derived outcomes such as all-cause mortality and stroke in both the short and long term.(93, 176) Hence measuring HRQoL scores over time may help healthcare providers identify those patients at risk of poor long term outcomes and thus tailor intervention according to clinical need.(93, 176)

Evaluation of HRQoL features in the ESC QIs in some commonly treated CVD conditions including TAVI for AS,(84) HF(85) and AF.(86) As an example, measuring HRQoL at baseline and at follow up features in the ESC QIs for AF, as well as capturing patient reported physical, emotional and psychological symptoms, **Figure 6.2**,(86).

Figure 6.2. The five domains of good quality of care for patients with AF that seeks to optimise the sixth domain, CROs and HRQoL. Adapted from the ESC QIs for AF (86)



Also as mentioned in **chapter 1.4.3.8,** European and American regulators recommend employing PROMs in evaluating pharmaceutical and device labelling claims.(104) This is in response to the growing popularity in employing PROMs as an outcome measure in trials and as demonstrated in **section 3.5,** a PROM was the third most utilised outcome measure within CVD RCTs.(334)

To benefit from measuring HRQoL, however, a comprehensive evaluation of existing questionnaires is required to ensure that generated patient data is accurate, valid in the specific disease and that any longitudinal change in PROM scores reliably reflects a change in disease state.(25, 335) The COSMIN initiative is the most widely employed methodological assessment of questionnaires, providing assessment over 116 items in multiple domains.(336) Previous work has investigated the qualitative assessment of CVD PROMs. However, these studies either did not include contemporary validation studies for some CVD conditions (337-339), restricted to investigating condition specific PROMs that included HRQoL or other PROMs (106, 337-339) or assessed each PROM's adherence to regulatory requirements therefore limiting applicability to trials and clinical practice.(340)

To date, there has been no comprehensive review of the psychometric properties across the common cardiovascular conditions of IHD, AF, HF, AS and generic CVD PROMs for HRQoL. Therefore, we aimed to conduct a scoping review of PROMs that evaluate HRQoL for these conditions and describe their psychometric properties and adherence to the COSMIN framework.

6.4 Methods

The review was reported in accordance to the COSMIN guidelines for literature review (336) and the PRISMA reporting guidelines.(108)

6.4.1 Eligibility criteria

Peer-reviewed RCTs, and prospective and retrospective studies that developed and validated HRQoL PROMs for adults (aged 18 years and older) with IHD (MI and angina included) HF, AF, AS, PCI or generic CVD were included, from

inception to 8th February 2025. Only studies published in English were included and those CVD PROMs that were validated in the original condition. CVD PROMs that were subsequently validated in other CVD were excluded as were review articles, meeting and conference abstracts, secondary analyses and editorials.

6.4.2 Search strategy

PubMed, Web of Science, and Embase was searched using a structured search strategy that followed the population, phenomenon of interest and outcome framework. Pragmatic key words such as ‘cardiovascular disease’ and ‘patient reported outcome measure’ were included but MeSH words were not included (**Appendix D.1**). To minimise publication bias, targeted keyword searches of grey online literature sources were conducted, in conjunction with hand searching of the reference lists of included studies (pearling).

6.4.3 Study selection

6.4.3.1 Screening

Two reviewers (from MS, MH, AB) independently screened titles and abstracts and selected eligible studies after full text assessment using the pre-determined eligibility criteria. At the full-text review, reasons for excluding studies were recorded using the Rayyan software.(195) Disagreements between reviewers were resolved through discussion, and a third reviewer was invited if the disagreement persisted.

6.4.3.2 Data extraction

Key study and PROM characteristics and their psychometric measurement properties were extracted by two independent reviewers (TM, AS). Study characteristics included title, author, year of publication and design. PROMs characteristics included: number of items, domains, response format, administration methods, and each PROM was categorised according to generic

or disease specific CVD type; IHD (encompassing ACS, PCI and angina), AF, HF, TAVI or generic CVD.

6.4.3.3 Evaluation of methodological quality

The methodological quality of each study was assessed using the COSMIN risk of bias checklist (341) across nine domains: content validity, structural validity, internal consistency, cross cultural, measurement error, reliability, criterion/convergent, hypothesis testing and responsiveness.(108)

As per the COSMIN classification, the above terms are defined as the following.(107)

Content validity: The degree to which the PROM's contents are an adequate reflection of the condition to be measured. This term also incorporates another concept called *face validity* which is defined as the degree to which (the items or domains of) a PROM appears as though they are an adequate reflection of the condition to be measured.

Structural validity: The degree to which PROM scores are an adequate reflection of the dimensionality of the condition. Multi-dimensional PROMs such HRQoL must have a relationship with other constructs. For example, HRQoL due to pain must also impact analgesic burden (if assessed in a questionnaire) and mental health.

Internal consistency: The degree of the interrelatedness among the items or domains of a PROM.

Cross cultural validity*:* The degree to which the translated or culturally adapted PROM are an adequate reflection and evaluate the same concepts as the original version of the PROM.

Measurement invariance / error*:* Ensuring that the systematic and random error of a patient's score is not attributed to true changes in the overall score.

Reliability: The proportion of the total difference in measurement scores between different patients is due to 'true' differences. Therefore, it assesses the ability of an instrument to produce the same scores on repeated testing in stable respondents and differentiate between patients.

***Criterion / convergent**:* The degree to which the scores of a PROM are an adequate reflection of a 'gold standard'. This gold standard may be another questionnaire or objective markers such as biomarker / imaging technique.

Hypothesis testing for construct validity: The degree to which PROM scores are consistent with hypotheses (with regard to relationships to scores of other instruments, or differences between relevant groups) based on the assumption that the PROM validly measures the construct to be measured.

***Responsiveness**:* The ability of a PROM to detect change over time in the construct to be measured. (107)

The results were categorised according to a traffic light system; green as excellent, yellow as adequate and red as inadequate. For example, reliability was rated very good if a study provided evidence that patients were stable, time interval was appropriate, test conditions were similar, inter-class correlation (ICC) calculated for continuous scores and kappa for dichotomous /nominal /ordinal data. Adequate was rated for studies where it was assumable that patients were stable, test conditions were similar, and ICC calculated. Doubtful was rated where it was unclear if patients were stable, time interval not stated or unclear if conditions were similar. Studies were rated inadequate where patients were not stable, time interval not appropriate, test conditions not similar and had no ICC or kappa.(336) (**Appendix 9.8D.2**).

6.4.3.4 PROM quality assessment

Thereafter, the psychometric properties of each PROM was assessed and followed the recommended order: content validity, structural validity and internal consistency then cross-cultural validity/measurement invariance, reliability and measurement error, criterion validity (if applicable), hypotheses testing for construct validity, and responsiveness.(336) One reviewer (TM) performed the qualitative assessment of the PROM developmental articles, and a subsequent independent reviewer completed the qualitative assessment of further validation articles (ABS) following COSMIN guidelines.(336) HRQoL were assessed at domain level for where information was available. The psychometric evidence of each PROM measurement property was rated using the updated quality criteria

(108, 342) for health-status questionnaires as sufficient (+), insufficient (−), or indeterminate (?) (**Table 6.1**).

Table 6.1. Criteria for good measurement properties used in this study.

Level	Rating	Criteria
Strong evidence in favour or against	green	Consistent findings in multiple studies of good methodological quality or in one study of excellent methodological quality.
Moderate	yellow	Consistent findings in multiple studies of fair methodological quality or in one study of good methodological quality.
Limited	Red	One study of fair methodological quality.
Conflicting	Red	Conflicting findings.
Unknown	Red	Only studies of poor methodological quality.

6.4.3.5 Quality of evidence

The overall quality of each measurement property and the PROM quality assessment were combined to give an appraisal of the evidence provided by each validation study and where multiple studies evaluated a measurement property of a PROM the results of the studies were summarised to produce an overall rating. The full definitions and criteria of good measurement properties were aligned to contemporary COSMIN guidelines.(336)

The evidence from the quality appraisal was subsequently synthesised for each PROM to determine which would be best for use in clinical practice. Three categories of recommendations based on the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) approach were used for this review:(343)

A - High quality evidence for all relevant measurement properties, most suitable to be recommended for use.

B - High quality evidence for some relevant measurement properties, PROM may have potential to be recommended but more validation is required.

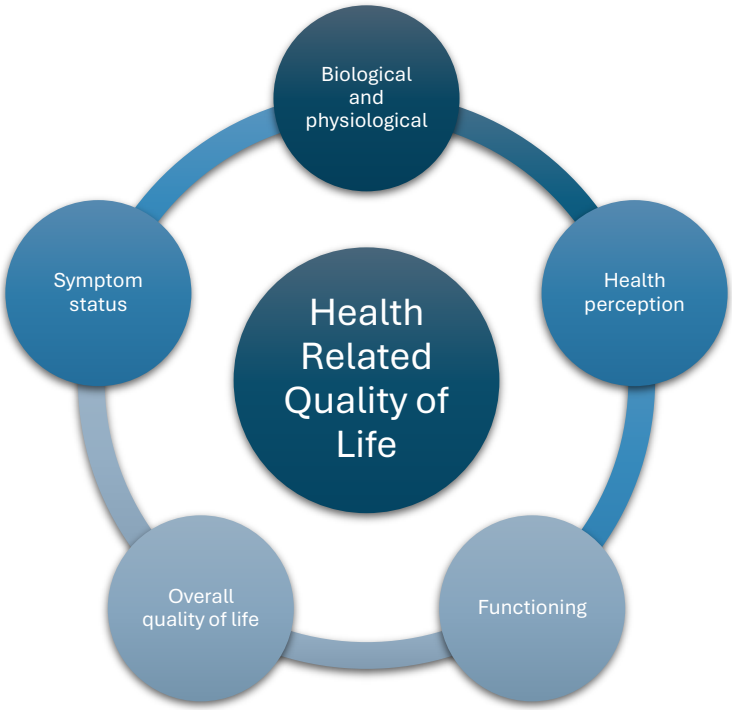
C – PROM with insufficient evidence of measurement properties, no recommendations can be made.

The GRADE approach is a systematic and transparent approach for rating the quality of evidence present in systematic reviews and is used widely in international clinical guidelines such as the ESC.(344)

6.4.4 Data synthesis

The summarised data was described narratively to present the results. Measurement properties of the different PROMs were reported in tables and graphs as appropriate. Additional content validity and comparison of disease specific PROMs was conducted by examining the items of disease specific PROMs, domains and comparing them by mapping onto the Cleary and Wilson conceptual model of health-related quality of life.(343) The model integrates clinical and psychosocial approaches to health care and links the biological and physiological (objective health) variables to the measure of HRQOL or subjective health construct.(345) The five health concepts described in the model are biological and physiological factors, symptoms status, functioning, general health perceptions and overall quality of life. **Figure 6.3**

Figure 6.3. Visual graphic on the Cleary and Wilson conceptual model of health related quality of life.

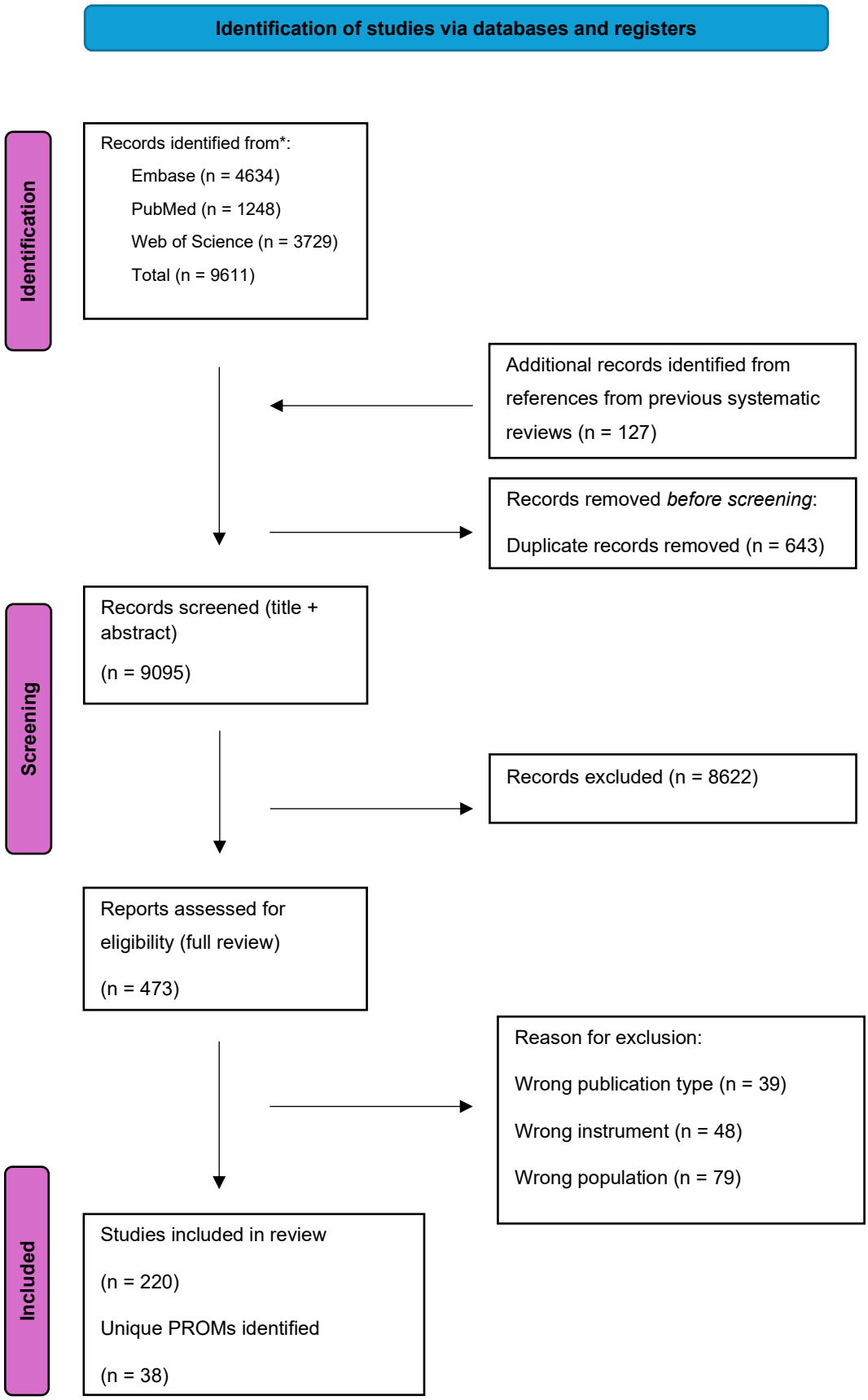


6.5 Results

6.5.1 Study selection

In total, 9430 articles were identified, and 220 studies were included after full text assessment **(Figure 6.4)**. 38 unique PROMs were identified after full text assessment - the rest of the articles were validation studies of PROMs.

Figure 6.4. PRISMA chart of included articles



6.5.2 PROMs characteristics and coverage

Of the included studies, most evaluated HF (116 studies; 52%), then IHD (61 studies, 28%), AF (38 studies; 17%), AS (4 studies; 2%) and generic (2 studies; 1%). Of the included CVD PROMs, most evaluated HF (n = 17; 45%), then AF (n = 11; 29%), IHD (n = 7, 18%), generic (n = 2; 5%) and AS (n = 1; 3%). (See **Appendix D.3** for the full list of included studies)

The content and domains covered by the different PROMs are presented in **Table 6.2.**

Table 6.2. Overview of the cardiovascular-disease specific PROMs identified by the scoping review literature and their characteristics search.

PROM	Measure, items and domains	Response Format	Recall period	Administration method
Minnesota living with heart failure (MLHF)(346)	21 items measuring 2 domains: Physical and emotional. Swelling, shortness of breath, fatigue, poor memory/concentration, and depression. Some items are not included in subscores	Likert scale	4 weeks	Paper, interviewer, self-administered
Chronic heart failure assessment tool (CHAT)(347)	46 items measuring 4 domains: symptoms, activity levels, psychosocial aspects, and emotions	Likert scale	2 weeks	Self-administered
KCCQ short version (348)	20 items measuring 3 domains: Dyspnoea, fatigue, emotional function	Likert scale	2 weeks	Paper, interviewer, self-administered
KCCQ (349)	23 items measuring 7 domains of patients' HF-related health status: Physical Limitation, Symptom Stability, symptom frequency, symptom burden, self-efficacy, quality of life, and social Limitations. Item responses are coded sequentially (1, 2, 3, etc.) from worst to best status. Scores are generated for each domain and scaled from 0 to 100, with 0 denoting the worst and 100 the best possible status.	Likert scale	2 weeks	Paper, self-administered
Quality of life in severe heart failure questionnaire (QLQ-SHF) (350)	26 items, Physical, psychological, symptoms, life satisfaction patients with severe heart failure (EF < 35%).	Likert scale	1 week	Interviewer, Self-administered
	36 item questionnaires for patients with left ventricular dysfunction. Responses are dichotomous (true or false). True responses are summed, and the sum is expressed as	True/false	1 week	Self-administered, telephone

Left ventricular dysfunction questionnaire (LVD-36) (351)	a percentage, so that 100 is the worst possible score and 0 the best possible score.			
Patient reported outcomes measurement information systems Plus HF Profile (PROMIS Plus HF Profile) (352)	Is a library of measures and items; users can select subsets of domains and items and create customized short-form versions based on the clinical need or research question. Contains 86 items across 18 domains consisting of physical, emotional, social, psychological symptoms.	Likert scale	1 week	Paper, self-administered
HF Somatic Perception Scale - 18(353)	Assesses a patient's perception of deteriorating HF symptoms and its effect on quality of life.	5-point Likert scale	1 week	Paper, self-administered
Self-care of HF Index self-care management scale-22(354)	Covers 2 main domains: a patient's self care maintenance (daily weights, daily activity, keeping to appointments) and a patient's self care treatment (symptom recognition, symptom evaluation, quality of life etc)	Likert scale	12 weeks	Paper, REDCAP
Symptom Status Questionnaire-Heart Failure(355)	Covers 7 main items related symptoms: physical and quality of life	4-point Likert scale	4 weeks	Interviewer, Self-administered
Care-Related Quality of Life survey for Chronic Heart Failure (CaReQoL CHF)(356)	20 items and three scales: social and emotional problems, physical limitations, and being in safe hands.	5-point scale	4 weeks	Interviewer, Self-administered
Chronic heart failure health-related quality of life questionnaire (CHFQOLQ-20) (357)	20 items, measuring 4 domains Physical, emotional, psychological, life satisfaction.	5-point Likert scale	4 weeks	Interviewer, Self-administered

Heart Failure-Daily Symptom Diary (358)	HF symptoms cover 3 main domains; physiological symptoms (ankle oedema, shortness of breath etc), physical functioning (walking, climbing stairs, sleeping etc) and psychological symptoms (irritability, fear, and anxiety etc)	Free text	Daily	Interviewer, Self-administered
HeartQoL(359)	Physical, emotional, global QoL. The HeartQoL questionnaire comprises 14-items with 10-item physical and 4-item emotional subscales which are scored from 0 (poor HRQL) to 3 (better HRQL) with a global score if needed.	4 point, 0 to 3 Likert scale	4 weeks	Paper, self-administered
MD Anderson Symptom Inventory Heart Failure (MDASI-HF) (360)	Covers two main domains: physical and psychological. The physiologic symptoms include abdominal bloating, ankle swelling, chest pain, difficulty sleeping with head of bed flat (orthopnea), dizziness, fatigue, loss of appetite, lack of energy, limitation in physical activity, lower extremity swelling, nausea, rapid heartbeat (palpitations), nighttime cough, shortness of breath, sleep problems, thirst, urinary incontinence, headache, waking up at night because of shortness of breath (paroxysmal nocturnal dyspnea), waking up at night to urinate, and sudden weight gain. The psychologic symptoms include anxiety, confusion, depression, fear of disability, fear of sudden death, fear of loss of control, fear of loss of independence, forgetfulness, and mood disturbances. Validated for patients with concurrent cancer and heart failure.	11-point scale	Daily	Interviewer, Self-administered.
Cardiac Health Profile congestive heart failure(361)	The Cardiac Health Profile is made up of three parts: Part I assesses subjectively reported functional ability, part II measures generic QoL for patients with heart disease in general by using a visual analogue scale; and part III measures disease-specific QoL such as specific symptoms in heart failure.	Likert scale	Not stated	Self-administered

HF self-monitoring tool(362)	A self-administered scale comprises 2 domains and covers 38 items. Domain 1 deals with “awareness” and “measurement” of aspects of self-monitoring, domain 2 with “interpretation” of aspects of self-monitoring.	Likert scale	Daily	Self-administered
Multidimensional Index of Life Quality (MILQ) (363)	Physical function, physical health, social, emotional, psychological, mental domains covered.	4-point importance scale and a 7-point satisfaction scale.	Not stated	Telephone, interviewer, self-administered
CCS questionnaires(364)	The CCS grading system employs four grades from I (without limitation of physical activity) to IV (inability to carry out any physical without discomfort) to assess health related quality of life	4 point categories	Not stated	Paper and self administered
Myocardial Infarction dimensional assessment scale(MIDAS) (365)	The MIDAS contains 35 questions measuring seven areas of health status: physical activity, insecurity, emotional reaction, dependency, diet, concerns over medication and side effects.	Likert	1 week	Paper, electronic
Mac New Heart disease health related quality of life (MacNew) (366)	27 items which fall into 3 domains: a 13-item physical limitations domain scale, a 14-item emotional function domain scale, and a 13-item social function domain scale.	Likert	2 weeks	Paper, self-administered
The Quality of Life after Myocardial Infarction Questionnaire (QLMI_v1)(367)	In total 26 items measuring 2 domains: limitations (including symptoms and restrictions) and emotions (including emotional function, confidence and self-esteem)	Likert	12 months	Paper, self-administered

The Quality of Life after Myocardial Infarction Questionnaire (QLMI_2)(368)	18 items measuring, three domains vitality, emotional distress, and sleep.	Likert	6 months	Paper, Self-administered
AF Impact (369)	20 items measuring, Symptoms, treatment concerns, treatment satisfaction, daily activities, overall QoL	Likert	1 week	Self-administered
Toronto Atrial Fibrillation Severity Scale of quality of life (AFSS) (370)	A bedside scale that ranges from class 0 to 4, from no effect on functional quality of life to a severe effect on life quality.	Likert 4 point	4 weeks	Self-administered
Canadian Cardiovascular Society Severity in Atrial Fibrillation scale (CCS-AF)(371)	AF-QoL-7 items deal with the psychological domain while those of the AF-QoL-11 deal with physical activity. The questionnaire comprising the AF-QoL-7, and the AF-QoL-11 domains is identified as AFQoL-18.	Likert 4-point scale	Not stated	Bed side scale
Quality of Life questionnaire for Patients with Atrial Fibrillation (AF-QOL) (372)	4 conceptual domains (Symptoms, Daily Activities, Treatment Concern, and Treatment Satisfaction) from which individual domain and global scores can be calculated.	Likert	4 weeks	Paper, Self-administered
Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) (373)	Covers 5 main domains: symptoms, patient perception of AF, quality of life with the disease, social limitation, and functional health.	Likert	8 weeks	Self-administered
Toronto AF symptoms checklist-16 (SCL) (374)	Covers 6 domains in a short questionnaire: Physical, emotional, psychological, daily activities, fatigue.	Likert, 5-point scale	1 week	Self-administered
AF-6 symptoms scale (375)	Symptoms, global QoL,	Likert, 0 to 10	1 week	Self-administered
Atrial Fibrillation-Specific Measure of Patient-Reported	The QLAF questionnaire consisted of seven domains, 22 numbered questions and 83 items, or simple questions	Yes / No	12 weeks	Self-administered

Health-Related Quality of Life (QLAF) (376)	which made up the domains. Domains were numbered sequentially (I-VII) covering the main clinical manifestations (palpitation, breathlessness, chest pain, and dizziness) and therapeutic interventions (drugs, direct-current cardioversion, and ablation)			
Patient Perception of Arrhythmia Questionnaire (PPAQ) (377)	PPAQ measures frequency and duration of episodes, symptoms, impact on daily activities, and restricted activity days validated in patients with any arrhythmia.	Yes / No	Daily	Interviewer, Self-administered
Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (ASTA) (378)	Covers 9 Symptoms and the effect of symptoms on daily activities validated in patients with any arrhythmia.	4-point Likert scale	12 weeks	Interviewer, self-administered
Atrial Fibrillation Health Literacy Questionnaire (AFHLQ) (379)	47 items measuring health literacy in these dimensions: What is AF, Symptoms of AF, Why do people get AF, Management of AF, What measures can slow or prevent the progression of AF.	(yes, no, don't know)	Not stated	Interviewer, self-administered
CROQ (380)	The CROQ has four versions (CROQ-CABG_Pre, CROQ-PTCA_Pre, CROQ-CABG_Post, CROQ-PTCA_Post) contain 32 core evaluative items and one descriptive item that is not included in scale scores. The post-revascularisation versions of the CROQ (CROQ-CABG_Post 52 items, CROQ-PTCA_Post 47 items) contain these 33 core items plus additional evaluative items about adverse effects and satisfaction with outcome and two descriptive items.	3–6-point Likert	4 weeks	Self-administered
TASQ (381)	The CROQ is scored to produce 6 domains as follows: symptoms (7 items), physical functioning (8 items), psychosocial functioning (14 items), cognitive functioning (3	Likert	4 weeks	Self-administered

	items), satisfaction (6 items), and adverse effects (11 or 6 items).			
Seattle Angina Questionnaire short version (382)	TASQ is a 16-item self-administered questionnaire that assesses AS-specific QoL across five domains: physical symptoms; physical limitations; emotional impact; social limitations, and health expectations.	Likert	4 weeks	Self-administered
Seattle Angina Questionnaire (383)	Physical, Symptoms. 5 domains. Physical limitation, anginal stability, anginal frequency treatment satisfaction and disease perception. Chest pain, chest tightness, and angina.	Likert, 1 to 5/6	4 weeks	Self-administered

6.5.2.1 Heart Failure

The KCCQ was the most frequently evaluated amongst HF PROMs (33 studies; 28%).(348, 349, 384) The HF PROMs included between 7 and 86 items, 2 to 18 domains and all used a Likert scale as a response format for the items. The recall period ranged from one day to one month, and the completion time from 4 to 10 minutes. The domains covered by the HF PROMs domains include the domains in the HRQoL Wilson and Clearly model and life satisfaction (**Figure 6.2).**

6.5.2.2 Ischaemic Heart Disease

The MacNew Heart disease HRQoL questionnaire was the most frequently evaluated amongst the ischaemic heart disease related PROMs (25 studies; 41%).(385) Of the included PROMs, four were MI related (MIDAS,(365) MacNew,(385) QLMI_1,(367) QLMI_2(368)) which included between 26 and 35 items and used a Likert scale as a response format. The MacNew and QLMI cover three domains (physical limitations, emotional function and social function), whereas the MIDAS is more comprehensive by including: physical activity, insecurity, emotional reaction, dependency, diet, concerns over medication and side effects (**Table 6.2**). The two Angina-PROMs were both versions of the Seattle Angina Questionnaire: SAQ-7(382) and SAQ-19(383). SAQ-7 covers 7 items, 5 domains and recall time is up to 4 weeks. The SAQ-19 has 19 items, 5 domains, and completion time is less than 5 minutes.

6.5.2.3 PCI and TAVI

The CROQ questionnaire is the only PROM that evaluates patient outcomes after PCI and / or CABG and has 32 items uses a 3–6-point Likert scale responses, a completion time is 10 minutes and has been evaluated in nine studies.(380) The only PROM originally validated for aortic stenosis and TAVI was the TASQ questionnaire which was evaluated in four studies.(381)

6.5.2.4 Atrial Fibrillation

The ASTA questionnaire is the most frequently evaluated AF PROM (9 studies; 24%).(378) The 11 AF-PROMs (AF impact(369), AFSS, CCS-SAF(371), AFQoL(372), AFEQT(373), Toronto AF symptoms(386), AF-6(387), QLAF(376), PPAQ(377), ASTA(378), AFHLQ(379)) included between 6 and 22 items, used a Likert scale as a response format. The range of domains covered by AF PROMs include physical health, emotional, sleep, vitality, symptoms, treatment concerns, treatment satisfaction, QoL, frequency and severity of symptoms (**Table 6.2**).

6.5.2.5 Generic Cardiovascular Disease

There were two HRQoL PROMs that were originally validated for any cardiovascular disease (MILQ(363) and the Canadian Cardiovascular Society (CCS) questionnaire (312), and included between 5 and 35 items, used a Likert scale as a response format **(Table 6.2**).

6.5.3 Methodological Quality of the studies

6.5.3.1 Content validity

Most PROMs demonstrated strong evidence for content validity (28 PROMs; 74%,**Table 6.3**). The studies that were rated very good provided a clear description of the methodology that was used to access relevance, comprehensibility (i.e. use of skilled trainers, appropriate methods to analyse data, rewording of interviews and verbatim transcription) following COSMIN guidelines.

Table 6.3. Overall levels of evidence per measurement property and PROM.

PROM	Content	Reliability	Internal consistency	Structural	Criterion	Cross cultural	Measurement error	Discrimination	Responsiveness	Grade
MLHF(346)										B
CHAT(347)										B
KCCQ-12 (348)										A
KCCQ-23 (349)										A
QLQ-SHF (350)										B
LVD-36 (351)										A
PROMIS plus HF profile (352)										A

PROM	Content	Reliability	Internal consistency	Structural	Criterion	Cross cultural	Measurement error	Discrimination	Responsiveness	Grade
HF Somatic Perception Scale -18 (353)										B
HF Index self-care score (354)										A
Symptom Status Questionnaire (355)										B
CaReQoL CHF (356)										B
CHFQOLQ-20 (357)										B
Heart Failure-Daily Symptom Diary (358)										C
HeartQoL (359)										A
MDASI-HF(360)										B

PROM	Content	Reliability	Internal consistency	Structural	Criterion	Cross cultural	Measurement error	Discrimination	Responsiveness	Grade
CHPchf (361)										B
HF self-monitoring tool (362)										B
MILQ(363)										C
CCS questionnaires (364)										C
MIDAS (365)										B
MacNew (366)										A
QLMI_v1(367)										B
QLMI_v2 (368)										C

PROM	Content	Reliability	Internal consistency	Structural	Criterion	Cross cultural	Measurement error	Discrimination	Responsiveness	Grade
AF Impact (369)										B
AFSS (370)										C
CCS-AF (371)										C
AFQoL (372)										B
AFEQT (373)										B
Toronto AF symptom checklist (374)										B
AF-6 symptoms scale (375)										B
QLAF (376)										B
PPAQ (377)										B
ASTA(378)										A
AFHLQ(379)										C

PROM	Content	Reliability	Internal consistency	Structural	Criterion	Cross cultural	Measurement error	Discrimination	Responsiveness	Grade
CROQ(380)										A
TASQ(381)										C
SAQ-7(382)										A
SAQ-19(383)										A

Abbreviations: MLHF: Minnesota Living with Heart Failure; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVD: Left Ventricular Dysfunction questionnaire; PROMIS: Patient Reported Outcome Measurement Information Systems Plus Heart Failure; CHFQOLQ-20: Chronic heart failure health-related quality of life questionnaire; CHAT: Chronic heart failure assessment tool; MDASI-HF: MD Anderson Symptom Inventory-Heart Failure; CaReQoL CHF: Care-Related Quality of Life survey for Chronic Heart Failure; CHPchf: Cardiac Health Profile congestive heart failure; QLQ-SHF :Quality of life questionnaire in severe heart failure; MILQ: Multidimensional Index of Life Quality; CCS: Canadian Cardiovascular Society; MIDAS: Myocardial infarction dimensional assessment scale; MacNew: MacNew Heart disease health related quality of life questionnaire; QLMI: Quality of Life after Myocardial Infarction Questionnaire; AF: Atrial Fibrillation; AFSS: Atrial Fibrillation Severity Scale of quality of life-20; AFQoL-18: Quality of Life questionnaire for Patients with Atrial Fibrillation; AFEQT: Atrial Fibrillation Effect on QualiTy-of-life; ASTA: Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; PPAQ: Patient Perception of Arrhythmia Questionnaire; AFHLQ: Atrial Fibrillation Health Literacy Questionnaire; QLAF: AF specific health related quality of life; CROQ: Coronary Revascularisation Outcome Questionnaire; SAQ: Seattle Angina Questionnaire; TASQ: Toronto aortic stenosis quality of life questionnaire.

Level of evidence rating: Green: Good; Yellow: Adequate; Red: Doubtful or Inadequate

COSMIN recommendation category: A- Most suitable to be recommended, B -may have potential to be recommended but further validation studies are required, C - Not suitable to be recommend

6.5.3.2 Structural /Construct validity

Most CVD PROMs demonstrated strong evidence for structural validity (27 PROMs; 71%). The methodological quality for structural validity of the included studies ranged from very good to inadequate **(Table 6.3)** and was evaluated using exploratory factor analysis (EFA), confirmatory factor analysis (CFA) or item response theory models (IRT). EFA is statistical method of revealing latent (or unobserved) relationships between connected variables and is commonly used in psychometric studies to investigate complex datasets.(388) CFA is another statistic method used in psychometrics that tests whether observed variables accurately reflect the latent constructs that researchers originally developed them to describe.(389) IRT is an umbrella term that incorporates multiple mathematical models that describe how patients respond to set questionnaires, and in particular evaluates the relationship between the characteristics of a questionnaire and the patient's abilities such as comprehension. This allows researchers to understand both the questionnaire and patient respondents in more depth.(390)

Item response theory models were less common with only two studies (4%) using these models. Overall, the quality for structural validity of 19 studies (37%) were rated as very good because they used classical test theory (CTT) model or IRT models, 10 adequate (19%), and 7 as inadequate (13%) due to small sample sizes or use of inappropriate methods to evaluate structural validity **(Table 6.3)**. CTT is a mathematical model that assumes a patient's total PROM score is the sum of their 'true' score and any measurement error and is sometimes referred to as the true score model.(391)

6.5.3.3 Internal consistency

Most PROMs provided strong evidence for internal consistency (30 PROM, 79%). Methods to assess this include the Cronbach alpha which is a statistical technique developed to describe how closely related a set of items are within a questionnaire and their reliability and internal consistency.(392) Among the PROMs that fulfilled the prerequisite of one-dimensionality, with limited evidence provided for internal consistency was demonstrated for 8 PROMs (21%).

6.5.3.4 Cross-cultural validity and measurement invariance

Half of included CVD PROMS provided evidence for cross-cultural validity of very good/adequate methodological quality (19 PROMs; 50%, **Table 6.3**).

6.5.3.5 Reliability and measurement error

Most PROMs evaluated provided adequate evidence for reliability (27 PROMs; 71%). The main method used to assess test-retest reliability was intra-cluster correlation coefficient a few studies used Pearson or Spearman correlation coefficients. Test-retest reliability refers to a questionnaire's ability to reproduce the same scores for a patient over time, assuming the patient's health status hasn't changed. This indicates that the measurement is stable.(107) The intra-cluster correlation coefficient describes the extent to which items within and between each cluster may be similar and is important in calculating power and sample sizes in cluster randomised trials.(393) Both Pearson and Spearman correlation coefficients measure the linear relationship between two sets of data with Spearman correlation coefficients used primarily for ordinal data and Pearson for nominal data. (394)

Measurement error was one of the COSMIN domains least evaluated by CVD PROMs with only 10 PROMs demonstrating adequate evidence on evaluation (26%, **Table 6.3**).

6.5.3.6 Hypothesis testing for construct validity (Convergent and Divergent validity)

Most PROMs provided evidence for convergent/criterion validity (32 PROMs; 84%) by comparing the correlations of the PROM with a gold standard biomarker or other questionnaire such as the SF-36.(395) The main method used was comparing the PROMs with other measurement scales that measure similar constructs. The main statistical methods used include correlations using Pearson and Spearman correlation coefficient and multi-trait multimethod analysis. After applying the criteria for good measurement properties, strong

positive evidence was found for most PROMs (**Table 6.3**).

6.5.3.7 Hypothesis testing for construct validity (Known Group, Discrimination)

The majority of PROMs provided evidence for hypothesis testing for construct validity/ discrimination / known group validity (22 PROMs; 58%) by comparing the correlations of the PROM with a gold standard biomarker or other questionnaire such as the Short Form 36.(395) The main methods for demonstrating discriminant or known group validity include using analysis of variance comparing scores of known groups and multi trait–multimethod analysis or predictive models using regression analysis. The known severity groups were categorized using mostly the NYHA and compared severity PROM scores across the four NYHA severity groups.(75) Other studies determined the predictive validity of the PROM using logistic regression or Cox proportional hazards models and reported the area under the curve.

6.5.3.8 Responsiveness

Most PROMs did not have adequate evidence of responsiveness in their validation studies (20 PROMs; 53%). The main methods for demonstrating responsiveness were based on hypothesis testing comparing changes on the PROM and a gold standard, or change scores of pre and post treatments, baseline and follow up, standardized response mean, effect sizes, or a clinically important change/difference. Cohen effect size criteria of c >0.80 large, 0.2 poor and 0.5 moderate effect size were used.

6.5.4 Recommendations

Of all the 38 PROMs that were reviewed in this study, 11 (29%) were given an overall rating score of A. These were; the KCCQ questionnaires,(348, 349) HeartQOL,(359, 396) LVD-36,(351) PROMIS HF profile,(352) Self care for HF Index,(397) MacNew,(366) CROQ,(380) SAQ questionnaires (382, 383) and the ASTA questionnaire.(378) Most evaluated HF (six PROMs), two PROMs

evaluated ischaemic heart disease and one evaluated AF. An overall rating of B was given to 19 PROMs (50%) and a C rating was given to 8 PROMs (21%, **Table 6.3**).

6.6 Discussion

This scoping review and COSMIN analysis of 38 PROMs from 220 studies for the evaluation of HRQoL in individuals across a range of CVD found that 11 instruments (29%) had excellent psychometric properties across all nine COSMIN criteria with most PROMs (50%) requiring further validation prior to recommending their routine use within cardiology. The psychometric properties that were prioritised were content validity, reliability, internal consistency, discrimination, and structural validity due to its clinical implications. The quality of patient data generated from such instruments, therefore, is reduced potentially limiting its ability to inform clinical care and the generalisability of trial results.

Similar to previous reviews,(339, 340) we found that the majority of HRQoL CVD PROMs (71%) available did not satisfy all nine domains of the COSMIN checklist for robust psychometric properties.(341) One reason may be that some PROMs were developed and validated before the COSMIN guidelines were developed. For systematic reviews with COSMIN analysis for disease-specific instruments such as AF (339) most instruments were rated as good, in line with our findings, with a specific focus on cross cultural validity, measurement error and responsiveness for further validation. Similar to other reviews we found that most heart failure questionnaires were still advised to undergo further metric validation.(338)

However, there were differences between our analysis and others. We placed emphasis on a comprehensive psychometric evaluation using the COSMIN analysis whereas others used the Evaluating the Measurement of Patient-Reported Outcomes (EMPRO) tool which places more emphasis on administrative burden as well as psychometric properties of questionnaires over COSMIN.(338) The EMPRO tool spans eight domains containing a total of 39 items. These domains are reliability (eight items), conceptual and measurement

model and administrative burden (seven items each), validity (six items), responsiveness, interpretability and cross-cultural validity (three items each) and alternative modes of administration (two items) and therefore the EMPRO tool provides a broader perspective on the questionnaire outside of its psychometric analysis.(338) As mentioned in **section 1.4.4,** the COSMIN analysis focuses on evaluating psychometric properties alone by examining over 100 items spanning nine domains.(336) Utilising differing tools could therefore cause the results to differ.(398) Other studies focussed on disease specific PROMs(337-339) whereas we placed more emphasis on all the common cardiovascular conditions with one evaluation(337) occurring before the development and validation of the TASQ questionnaire(381) for AS and TAVI. Finally, one review analysed the adherence of a broad range cardiovascular conditions, including congenital heart disease, to FDA regulatory criteria for PROM development.(399) Only two PROMs fulfilled all the COSMIN criteria according to the previous review (KCCQ-23(349) and MacNew(385)) whereas ours identified others which were well validated (352). The COSMIN analysis does contain an element of subjectivity and previously demonstrated a low inter-rater reliability which could explain the difference in the analyses. This demonstrates the need for additional training for experts and an independent reviewer to ratify results.(400)

We graded 19 (50%) PROMs as a B and recommended that they may be used in research and clinical practice but require further validation on cross cultural validity/measurement invariance and measurement error. For example, limited evidence of cross-cultural invariance was provided in under half of HRQoL CVD PROMs (16 PROMs, 42%) whereas most questionnaires presented limited evidence for measurement invariance (28 PROMs, 74%). A notable exception was the PROMIS Plus HF questionnaire which was shown to be measurement invariant by sex, age, and education level.(352)

The CVD specific PROMs that adhered to all nine COSMIN criteria were: the 12 and 23 item KCCQ,(348, 349), HeartQOL,(359, 396) LVD-36,(351) PROMIS HF profile,(352) Self-care for HF Index self-care management score,(397) MacNew,(366) CROQ,(380) SAQ questionnaires(382, 383) and the ASTA questionnaire.(378) These findings are in broad agreement with other studies (339, 340) which rated these PROMs adequate using the COSMIN criteria.

The commonly used methods for evaluating the structural validity domain of the PROMs were exploratory factor analysis and confirmatory analysis, and only two studies used IRT models. IRT models are defined for use in the COSMIN structural validity domain and provide more insight into cross-cultural validity/measurement invariance, which there was no evidence found for most PROMs in this review. The commonly used methods for assessing responsiveness were Cohen's effect size or effect sizes as standardized mean difference between baseline and follow up but the minimal important change that mattered to patients was not established hence there is no known threshold of improvement that is clinically relevant.

6.6.1 Clinical and research implications

Whilst there are many PROMS available for the measurement of HRQoL in common CVDs their psychometric properties vary within and across the disease states. There are few with cross cultural validity, with the majority providing limited evidence for measurement error. Good practice dictates that an instrument should be translated and culturally sensitive to the target population(401) as the results from a poorly understood questionnaire are less reliable and valid.(108) Measurement error refers to a change in score from an instrument that is not due to random error(341) and is especially important given the subjective nature of PROMs. This can obscure the effect of an intervention due to noise which contributes to type II errors.(402) This is further exacerbated by some instrument's inadequate rating for content validity, reliability and internal consistency.(403) A recent review found that over half of HF randomised control trials published in highly cited journals utilised a PROM, hence weaknesses in a PROM's measurement error, for example, may obscure the safety and efficacy of evaluated treatments.(92) Patient outcomes generated from inadequately validated questionnaires may directly impact patient care as major organisations, such as the ESC, have advocated for their increased uptake within routine care for AF,(86) HF(85) and TAVI.(84, 404) Understandably this has repercussion for the use of PROMs in clinical care and research especially.

We found only one disease specific HRQoL instrument for AS. TAVI is expanding to wider populations given recent safety and efficacy data,(405) and

using PROMs during assessments of TAVI has become a marker of good clinical care.(84) However the TASQ was ranked as having inadequate psychometric properties therefore its patient reported data should be interpreted with caution. A generic PROM may be used until further validation studies have been performed.

As a minimum, the PROMs rated B in our study require further validation in cross cultural /measurement invariance, measurement error, responsiveness, and a minimum clinically important difference. We propose that the PROMs that were rated C require validation work before these are used in research or clinical practice.

6.6.2 Strengths and limitations

A strength of this study is that methodological quality of the PROMs was assessed in validation studies from database inception to February 2025 using the COSMIN checklist. This scoping review combined our search strategy with hand searching of relevant terms to ensure all relevant HRQoL PROM articles and their validation studies were included to provide a more comprehensive evaluation. Assessing all validation articles from inception to the present day also allows for a contemporary appraisal of each PROM and their psychometric testing that was lacking in some of the other review articles on this topic. The analysis was adapted to provide a more visual representation of PROMs (traffic light system) that allows non experts in PROMs methodology to better understand the relevant strengths and weakness of each PROM. A consistent implementation barrier for PROMs has been poor clinician understanding of the merits of PROMs(126) and displaying visual analogues to PROMS has previously demonstrated better comprehension rates.(406)

There are limitations of the present study that should be noted. First, only PROMs measuring health related quality of life were assessed but no other forms of PROMs such as utility tools or PROMs that asses functional and mental health. PROMs have broad applicability and utility in assessing multiple patient centred concepts and restricting our analysis to HRQoL PROMs provides only a narrow view of the patient's health status. However patients prefer HRQoL over other aspects of patient health status and therefore our

analysis is patient centred and relevant.(407) Also, only PROMs available in English were included, hence we may have missed PROMs validated and published in other languages which could alter the results of the psychometric testing. However, most articles published in other languages would affect cross cultural validity aspect of the COSMIN analysis and would be unlikely to affect the other eight domains. Furthermore, we did not evaluate if a PROM that was originally validated for one CVD could be validated for another CVD. There are some PROMs, such as the HeartQOL, that have been validated for other CVD such as AF and coronary and valvular artery disease.(396, 408, 409) As such the choice of available PROMs for TAVI, for example, may broaden with multiple analyses for PROMs that evaluated more than one CVD. However, there is only a small number of PROMs that evaluate more than one CVD and the inclusion of multiple indications for a PROM is unlikely to have changed the overall conclusions of our analysis.

6.7 Conclusion

In this scoping review and analysis of the psychometric properties of 38 PROMs for the evaluation of HRQOL in individuals with common CVDs, I demonstrated that only 11 PROMs met all nine requirements of the COSMIN criteria for robust psychometric properties. The main deficient areas were lack of evidence on cross cultural validity/measurement invariance, measurement error, and information on responsiveness. I have shown that caution should be drawn to the implementation of most PROMS for the measurement of HRQoL in individuals with CVDs. As a minimum, available PROMs required additional validation work, and for some CVDs there is a limited selection of suitable PROMs for HRQoL measurement.

6.8 Summary

- Fewer than a third of HRQoL PROM met all of the COSMIN criteria and would be suitable to recommend for routine clinical care (11 PROMs; 29%).

- Half of existing HRQoL PROMs for common CVDs require further validation work in cross cultural validity, measurement error and responsiveness prior to routine use within clinical care and research.

- I found only one PROM specifically designed to assess HRQoL for aortic stenosis and transcatheter aortic valve intervention, and it did not meet all nine COSMIN criteria.

- PROMs that evaluate HRQoL and are validated for common CVD vary in their psychometric properties; most require further validation studies prior to use, particularly for cross-cultural validity, measurement error and responsiveness.

- The quality of patient reported outcome data generated from such instruments may have limitations in informing clinical care and the generalisability of trial results.

- Most of the HRQoL CVD PROMs that met all nine COSMIN criteria were validated for heart failure (6 instruments, 55%), then ischaemic heart disease (4 instruments, 36%), and a minority were validated for atrial fibrillation (1 instrument, 9%).

Chapter 7
Ranking existing Health Related Quality of Life PROMs for CVD

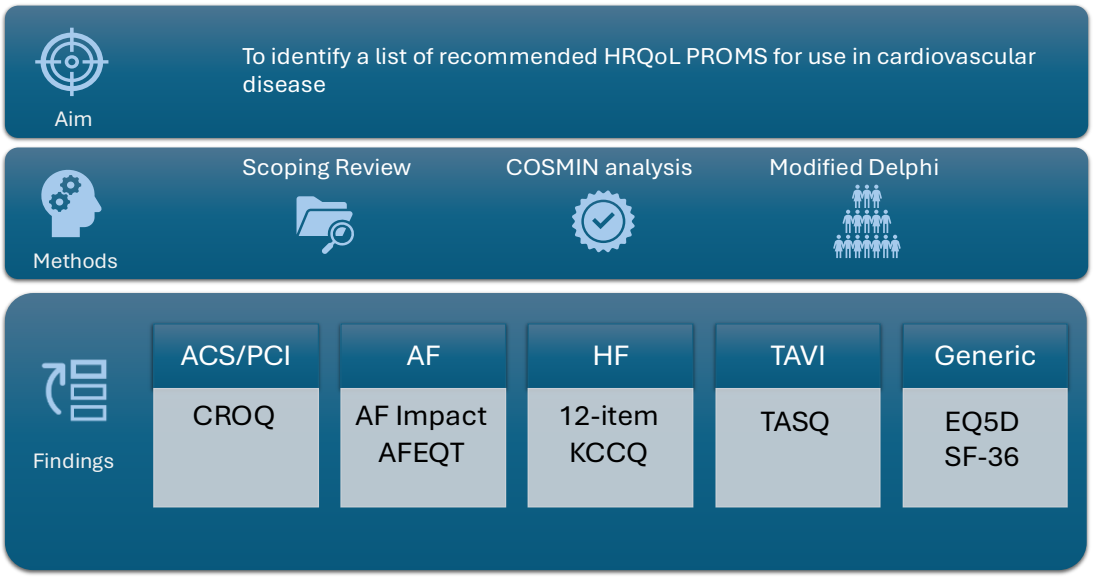
Patient Reported Outcome Measures for cardiovascular diseases: the European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart) in collaboration with the European Society Cardiology (ESC) Patient Forum

Below is a summary of highest ranked HRQoL PROM listed for the commonly occurring conditions; ACS/PCI, AF, HF, TAVI and generic CVD. This ranking is based on a consensus amongst healthcare providers, patients and PROMs methodologists ranking available HRQoL PROMs across the common CVD using the findings from **Chapter 6**. The project enlisted the help of numerous collaborators.

7.1 Contribution

I led this project. I approached the Global Cardiovascular Outcomes Consortium (modified Delphi members from **Chapter 4 and Chapter 5**), identified and recruited patients with CVD from international organisations such as the ESC Patient Forum and PROMs methodologists to participate in the modified Delphi process, prepared a synthesis of the findings from **Chapter 6** alongside key PROM characteristics and provided this to participants in an information pack via email. I then conducted the introductory, explanatory and results meetings with all invited participants, compiled the voting results, wrote the first draft and final manuscript incorporating feedback from the Working Group. An overview of the project is provided in **Figure 7.1.**

Figure 7.1. Graphical abstract for the project



7.2 Abstract

Background and Aims

HRQoL in CVD is a PROM that directly measures an individual's health status. We aimed to identify a list of recommended HRQoL PROMS for use in CVDs.

Methods and results

We followed the EuroHeart methodology for data standards development. We conducted a scoping review to identify 41 CVD PROMs across ACS / PCI, AF, HF, TAVI and generic CVDs. Identified PROMS underwent a contemporary qualitative assessment. Results were then used in a modified Delphi method to reach consensus on a final set of recommended PROMs. The modified Delphi panel comprised of 94 multi-disciplinary experts [patients (n=24), PROMs methodologists (n=3) and healthcare professionals (n=67)] from the Global Cardiovascular Outcomes Consortium that ranked each PROM using a Likert scale (0-5).

The highest ranking PROMS across the domains were: CROQ with 3.9 out of 5.0 for the ACS/PCI domain, 12-item KCCQ with 4.5 points for HF, TASQ with 3.0 points for TAVI, AFImpact and AFEQT with 3.9 points for AF and the five-dimension EuroQoL and 36 item SF-36 with 3.5 points for the generic domain.

Conclusion

I have presented a suite of internationally derived and agreed HRQoL PROMs for CVD that may be employed in registries, randomised clinical trials, regulatory frameworks, and routine care.

7.3 Introduction

PROMs for cardiovascular disease CVD complement clinical markers of disease and wellbeing, and provide a direct and reliable measure of an individual's health status.(280) The importance of PROMs in CVD to patients, healthcare professionals, trialists and regulators have been elucidated in **sections 1.4.3.1, 1.4.3.4, 1.4.3.7, 1.4.3.8 and 1.4.3.9.** PROMs as mentioned earlier are standardised questionnaires that report patient-centred concepts such as the impact of the health condition on daily functioning and HRQoL, as well as symptom burden.(97).

An interesting example that supports the routine use of PROMs to patients was a prospective study of 28 oncologists and 286 oncology patients.(331) Patients were randomly assigned to one of three arms; the intervention group in which patients regularly completed validated HRQoL questionnaires before a clinic visit with the results relayed to the clinicians, the 'attention' group that completed the questionnaires before a clinical encounter but the results were not relayed to the clinicians and the control group which did not complete any questionnaires prior to an encounter. (331) The pre-specified primary outcomes were serial HRQoL scores, physician – clinician communication and clinical management. Both the intervention and attention group demonstrated better, clinically meaningful HRQoL scores that reached statistical significance (p =.006 and p =.01, respectively) compared to the control group. Improvements in HRQoL scores were utilized to discuss non-specific symptoms of significance to patients (p=0.03), pain, and physical function without increasing clinic timings in the intervention group (p = 0.016).(331) The authors concluded that routinely assessing HRQoL with validated questionnaires improves patient-clinician communication, influences clinicians to discuss symptoms that patients care about, and improves HRQoL in some patients without increasing clinic times.(331) These benefits are transferable for cardiovascular clinical practice once PROMs are embedded into clinical care with similar results being demonstrated in an angina clinic.(410)

The ESC and the AHA advocate the routine use of PROMs in clinical practice.(89, 106) Indeed, HRQoL PROMs have been incorporated into recent guidelines (252, 404) and quality indicators for a range of CVDs,(84-86) and they are likely to play an increasing role in reporting and comparing quality of

care across Europe. Moreover, there is variation in the psychometric properties of PROMs used in CVD,(25, 338-340) and qualitative assessment of PROM instruments is needed to ensure that the data generated are reliable, validated for the target condition and population and therefore meaningful.(335) This impacts cardiovascular research as contemporary cardiovascular studies are increasingly employing PROMs as primary outcome measures.(92, 334)

The results from the systematic review into cardiovascular outcomes (in **Chapter 3**) showed that PROMs are the third most common primary outcome measure reported in RCTs published in highly cited journals.(334) This corroborates the findings of another systematic review into the inclusion of PROMs within HF RCTs.(92) Between 2000 and 2020, 417 RCTs were included in the search strategy and over half of studies employed a PROM as an outcome measure (n = 226 studies; 54.2%; 95% CI, 49.3%–59.1%). The quality of PROM reporting was assessing using the CONSORT-PRO tool(411) and RCTs reported a median of 4 items (IQR, 3–6) out of 11 suggesting the quality of reporting PROMs (when included) was modest. The CONSORT PRO tool is an extension of previous guidance on the reporting of outcome measures within RCTs with the extension aiming to improve PROM reporting in particular.(411, 412) A key feature of the recommendation is demonstrating the evidence of the validity, reliability and reproducibility of the PROM in question to ensure the trial results are meaningful, reliable and generalizable to the target population especially as PROMs are increasingly used in CVD studies.(411) Utilising the COSMIN tool (336) from a recent scoping review, allows for a contemporary appraisal of existing HRQoL PROMs within CVD (from **Chapter 6**).

Standardised outcome sets that include PROMS for CVD have been published previously.(150, 152, 413) However, these lack a comprehensive, up-to-date qualitative assessment using tools such as the COSMIN,(336) have recommended multiple PROMs within each domain that may increase administrative burden,(152) and lacked focus on PROMs that specifically evaluate HRQoL (which, arguably, is preferred by patients).(413)

EuroHeart is an ESC project that previously published a catalogue of internationally derived standardised data standards(167-170) and clinical outcomes(240, 414) using an established methodology(171) across common

CVD domains. To provide a comprehensive platform for the evaluation of care and outcomes for patients with CVD, we aimed to evaluate existing HRQoL PROMs using the COSMIN guidelines. This was undertaking in collaboration with the Global Cardiovascular Outcomes Consortium and ESC patient forum.

7.4 Methods

We categorised PROMs as either generic or disease specific. Generic PROMs evaluate health outcomes and are validated across CVD states.(415) This allows comparison of overall HRQoL between various diseases. Disease specific PROMs evaluate concepts that are specific to cardiovascular conditions, and in this project: ACS / PCI, AF, HF, and TAVI. (167-170, 240, 241)

7.4.1 Internal group

The internal group comprised the project chair (CPG), clinical experts (CW, AB), a project manager (CR) and a data manager (SC) and well as experts PROMs methodology (TM, ABS, JS) and two patient representatives (JD and MR) from the ESC Patient Forum.

7.4.2 EuroHeart Methodology

We followed the EuroHeart methodology in developing and achieving consensus for cardiovascular data standards.(171) Briefly, this began with a scoping review to provide a ‘candidate’ list of CVD PROMs that evaluate HRQoL followed by its selection, qualitative assessment using the COSMIN analysis and ranking of existing PROMs by domain experts in the WG using a Modified Delphi method with feedback and comments from the WG.

7.4.3 Scoping review

The results of a scoping review of HRQoL PROMs for CVD were adapted and used for the modified Delphi,(416) to allow for more PROMs that evaluate generic CVD which was reported in accordance to the COSMIN guidelines.(108) In brief, Embase, Web of Science, CINAHL and PubMed was searched for studies that originally developed a HRQoL PROM across the common cardiovascular conditions and interventions and their subsequent

validation papers in adults from database inception to 6th June 2024 were included, which was the basis of the first round of voting. The search was updated on 8th February 2025 which changed the COSMIN analysis of some HF and AF PROMs that was the basis of a second round of voting. Databases were searched using a strategy that followed the population, phenomenon of interest, comparison and outcomes framework.(417) Only studies published in English were included. Any study that validated an existing CVD PROM for another condition was excluded as well as review articles, meeting and conference abstracts, secondary analyses, and editorials. The results of the scoping review were also corroborated with other reviews of CVD PROMs and existing registries to ensure adequate coverage. (106, 167-170)

7.4.3.1 Qualitative assessment of PROMs and overall grading

All included PROMs were comprehensively evaluated using the COSMIN analysis (336) by two independent PROMs methodologists with expertise in psychometric analysis of questionnaires (TM and ABS), in line with guidance on the implementation of PROMs in trials and clinical practice.(335, 418) The quality of each COSMIN domain was categorised according to a traffic light system; green as excellent, yellow as adequate and red as doubtful, or inadequate (**Table 6.1**). This was done to improve patient and clinician understanding as visual analogues of PROMs has previously demonstrated better comprehension.(406)

Furthermore, expert recommendations were given that appraised the evidence of each measurement property and overall quality of each PROM and its suitability for routine clinical practice as per the COSMIN guidelines.(336) The overall recommendations were categorised using the GRADE approach.(343) The GRADE approach is a systematic and transparent approach for rating the quality of evidence present in systematic reviews and is used widely in international clinical guidelines such as the ESC.(344)

A score of A represented high quality evidence and therefore most suitable to be recommended for use. A score of B represented high quality evidence for some relevant measurement properties and may have potential to be recommended but more validation studies are required. A score of C

represented insufficient evidence of measurement properties and therefore no recommendations could be made yet.(343)

The summary of this assessment was provided to the WG to inform voting. Additional baseline characteristics such as target population, sample questions, estimated completion time of each PROM were provided to add further context.

7.4.4 Working Group

The Global Cardiovascular Outcomes Consortium were approached to participate in the modified Delphi process. This included representatives from all of the ESC WGs and Associations that had previously contributed to the CDOs for the common cardiovascular conditions.(414) Additional international healthcare professionals, PROMs methodologists and patients were approached to provide specific expertise on PROMs as well as patients from external organisations. Five WGs were convened: one for the generic CVD domain and one for each of the four disease domains. In total the Global Cardiovascular Outcomes Consortium consisted of 73 healthcare professionals, 3 PROMs methodologists and 22 patients. The following organisations each provided at least one expert to participate in the voting:

Global Cardiovascular Outcomes Consortium and in collaboration with the ESC, Association of Cardiovascular Nursing and Allied Health Professionals, Acute Cardiovascular Care, European Association of Cardiovascular Imaging, European Association of Preventative Cardiology, European Association of Percutaneous Coronary Intervention, European Heart Rhythm Association, ESC Committee for Young CV Professionals, ESC Registry Committee, HFA, ESC Patient Forum and the ESC WGs: Aorta and Peripheral Vascular Diseases, Atherosclerosis and Vascular Biology, Cardiac Cellular Electrophysiology, Cardiovascular Pharmacotherapy, Cardiovascular Regenerative and Restorative Medicine, Cardiovascular Surgery, Coronary Pathophysiology and Microcirculation, Cellular Biology of the Heart, e-Cardiology, Myocardial Function, Pulmonary Circulation and Right Ventricular Function and Thrombosis.

7.4.5 Variable recommendations

Members of the WG were invited to participate in a modified Delphi process to rank each PROM on a Likert scale of 0 to 5 in terms of recommendation: a zero

score indicated they did not feel confident to vote, a one score indicated they did not recommend the PROM in question while five indicated they strongly recommended an instrument. For the ACS/PCI, TAVI and generic domains WG members were asked three additional context specific questions regarding certain PROMs. The first question regarded the CROQ(380) and whether it should be included as a standalone PCI PROM. To date, it is the only PROM that is validated for ACS as well as following PCI and CABG, therefore extending its potential use to patients with stable angina who have been revascularized by either techniques.(419) The second example concerned the EQ5D questionnaire within the generic domain,(420) given its additional use in converting HRQoL scores into QALYs. This provides a metric for economic evaluation that international regulators use routinely prior to implementing proposed treatments.(421-423) By including the EQ5D as a stand-alone generic PROM may broaden the potential for registry based trials or pharmaceutical or device surveillance studies across EuroHeart participating countries in collaboration with EMA that may not be possible if the EQ5D is not voted as the preferred generic PROM. The final question concerned the TAVI domain. Only one disease specific PROM originally validated for patients with severe aortic stenosis was identified; the TASQ.(381) Consequently the TAVI working group were asked whether generic PROMs could be considered as an alternative, similar to the other standardised sets such as ICHOM set on valvular heart disease.(424)

All voting was conducted via an online poll. The PROM with the highest average Likert score was identified. The threshold for the additional questions was a participant voting to include of at least 75% or above.(425) The threshold for exclusion was less than 75% of participants voting to include the variable in line with previous EuroHeart projects.

7.4.6 Confirmation of the recommendations

The results of the Delphi voting were presented in two online meetings on 13th and 20th November 2024 where the average Likert score of each PROM was presented and discussed. Participants were invited to provide comments and feedback during the online meetings. This resulted in the ratification of the list of

recommended PROMs for each domain and whether additional variables met the threshold for inclusion or exclusion.

7.4.7 Patient and public involvement

The ESC Patient Forum and representatives from the Voice platform (n=5) and Heart Hive (n=6) were involved throughout the project. Two patient representatives from the ESC Forum (J.D. and M.R.) provided feedback about the design, development and delivery of the project by means of several online meetings from June 2024 to August 2024. Feedback at the design stage was that COSMIN analyses were challenging to comprehend; therefore separate meetings were conducted with patients to discuss the scoring system in November 2024. The inclusion of “I do not know” was requested if patients did not feel confident to vote, which was incorporated in the Likert scale.

7.5 Results

7.5.1 Scoping review

After 9430 articles were screened, 221 validation studies of 41 HRQoL CVD PROMs were included after full text review. Of these, 17 (41%) evaluated heart failure, 10 (24%) atrial fibrillation, 5 (12%) ACS/PCI, 1 (2%) TAVI, and 8 (20%) generic CVD. The full list of included PROMs and their validation studies are listed in **Appendix D.3**

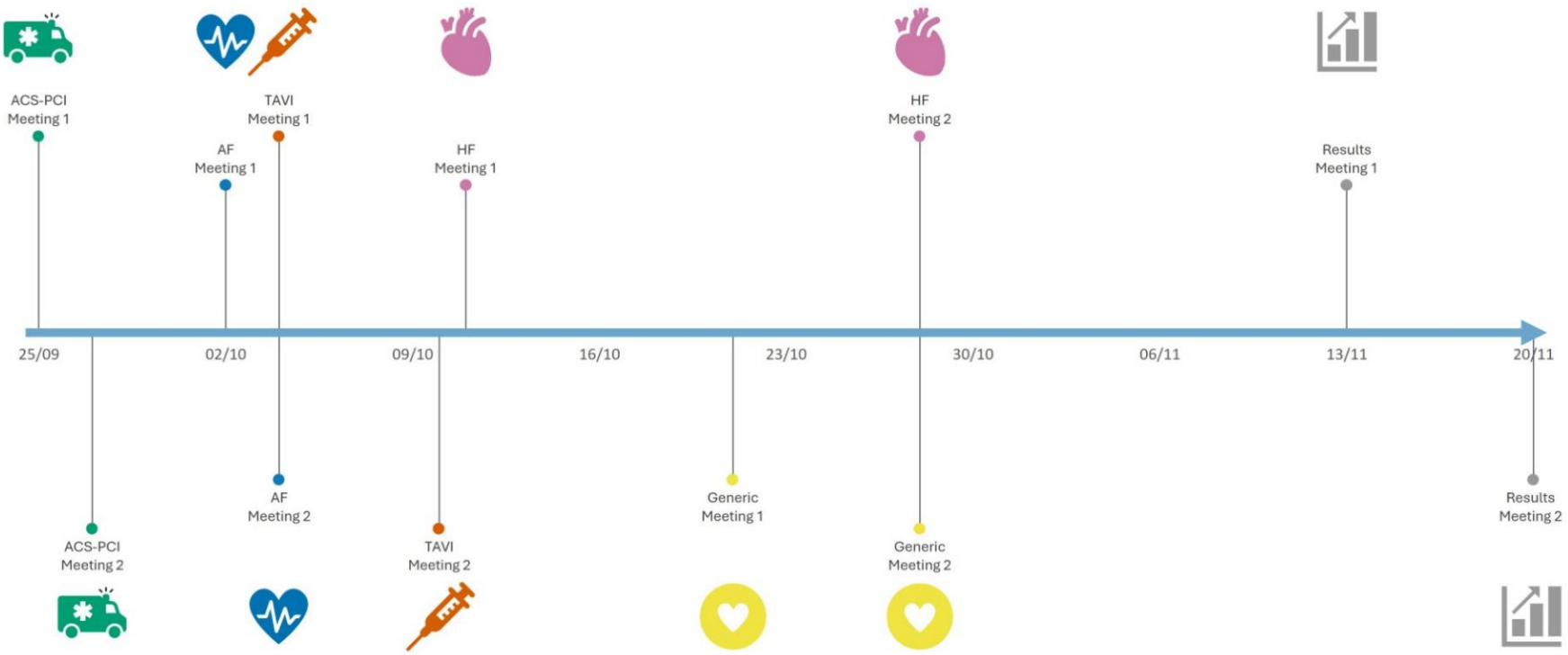
7.5.1.1 COSMIN Analysis and Recommendations

Nine aspects (COSMIN) of the methodological evidence of a PROM were assessed: content validity, reliability, internal consistency, structural validity, criterion / convergent, measurement error, cross cultural validity, hypothesis testing and responsiveness alongside the overall recommendation by the independent expert. Of the 41 included PROMs, 9 (22%) were recommended for use in clinical practice, 22 (54%) required further validation studies and 10 (24%) were not recommended for clinical practice. The full COSMIN breakdown is given in **Appendix D.2.**

7.5.2 Working Group Process

The PROMs and their qualitative assessment were presented to each WG in twelve meetings ranging from 25th September 2024 – 20th November 2024 and voting ranged from September 2024 to December 2024 (**Figure 7.2**). A second round of voting was convened in May 2025 for the HF and AF domains only, as the updated search produced further validation articles in these domains only that subsequently altered their COSMIN scores.

Figure 7.2. Timeline of all the virtual meetings with the cardivoascular outcome domain working groups from 2024-2025.



A total of 90 domain experts voted across all domains. The response rate for the disease specific domains ranged from 78% – 82%, and 56% responded to the generic questions; the breakdown is provided in **Table 7.1**.

There were five ACS/PCI PROMs that 38 experts reviewed, voted on and responded to whether the CROQ(380) be included as a separate PCI only PROM. In the TAVI domain, 28 experts reviewed the only disease specific PROM originally developed for TAVI and answered whether generic PROMs be included as an additional question. In the generic domain 43 experts reviewed eight PROMs and answered if EQ5D-5L(420) should be included as a standalone generic PROM given its additional role in health economic evaluations.(421) A further 32 experts reviewed the ten AF PROMs, and 33 experts reviewed 17 HF PROMs.

Table 7.1. Response rates across (a) each domain and (b) according to each voting group.

A)

Domain	Invited (n)	Voted (n)	%
ACS/PCI	45	37	82
AF	40	33	83
TAVI	35	28	80
HF	54	42	78
Generic	77	43	56
Average	-	-	76

Abbreviations: *Acute coronary syndrome / Percutaneous coronary intervention (ACS/PCI); Atrial fibrillation (AF); Transcatheter aortic valve intervention (TAVI); Heart failure (HF)*

B)

	Healthcare Professionals			PROMs Methodologists			Patients		
Domain	**Invited (n)**	**Voted (n)**	**%**	**Invited (n)**	**Voted (n)**	**%**	**Invited (n)**	**Voted (n)**	**%**
ACS/PCI	31	26	84	3	2	67	11	9	82
AF	28	24	86	3	2	67	9	7	78
TAVI	24	21	88	3	2	67	8	5	63
HF	40	33	83	3	2	67	11	7	64
Generic	61	33	54	3	2	67	13	8	62
Average	-	-	79	-	-	67	-	-	69

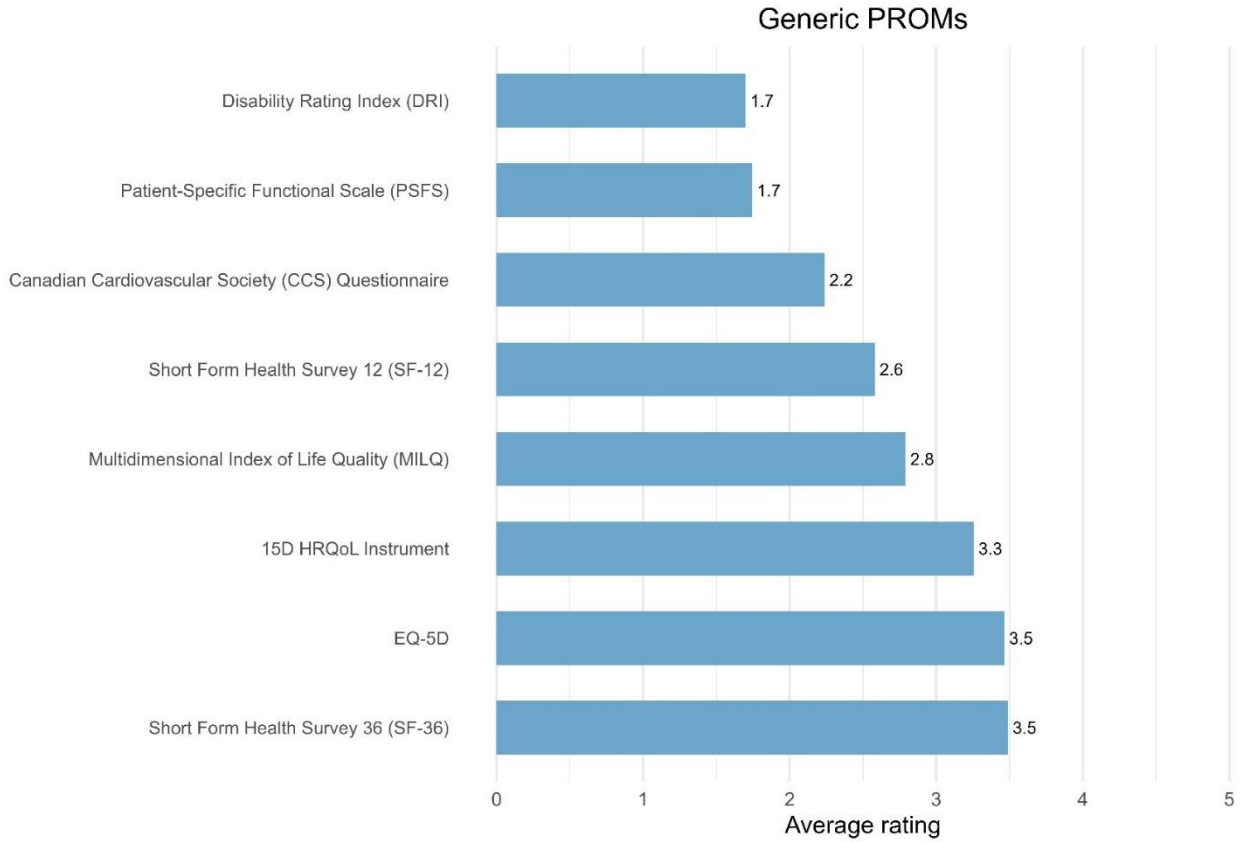
Abbreviations: *Acute coronary syndrome / Percutaneous coronary intervention (ACS/PCI); Atrial fibrillation (AF); Transcatheter aortic valve intervention (TAVI); Heart failure (HF)*

7.5.2.1 Generic cardiovascular domain recommendations

For the generic CVD domain, both the EQ5D-5L(420) and the Short Form 36 (SF-36)(426) had the highest average Likert rating of 3.5 each (**Figure 7.3**). Patients tended to prefer the SF-36 because it comprehensive covered all aspect of quality of life, had broad applicability across the range of CVD and comprehensible despite its length. Whereas healthcare professionals preferred the EQ5D-5L because it combined questions with the visual analogue scale, was quicker to complete and is well known amongst clinicians. However, including EQ5D-5L as a standalone generic outcome measure did not reach the overall 75% threshold for inclusion because some felt it was routinely collected in some countries and would likely increase administrative burden (**Figure 7.4**).

Figure 7.3. Average voting results for each PROM within the generic cardiovascular disease domain. A) overall average rating for each condition, B) voting according to each voting group.

A)



B)

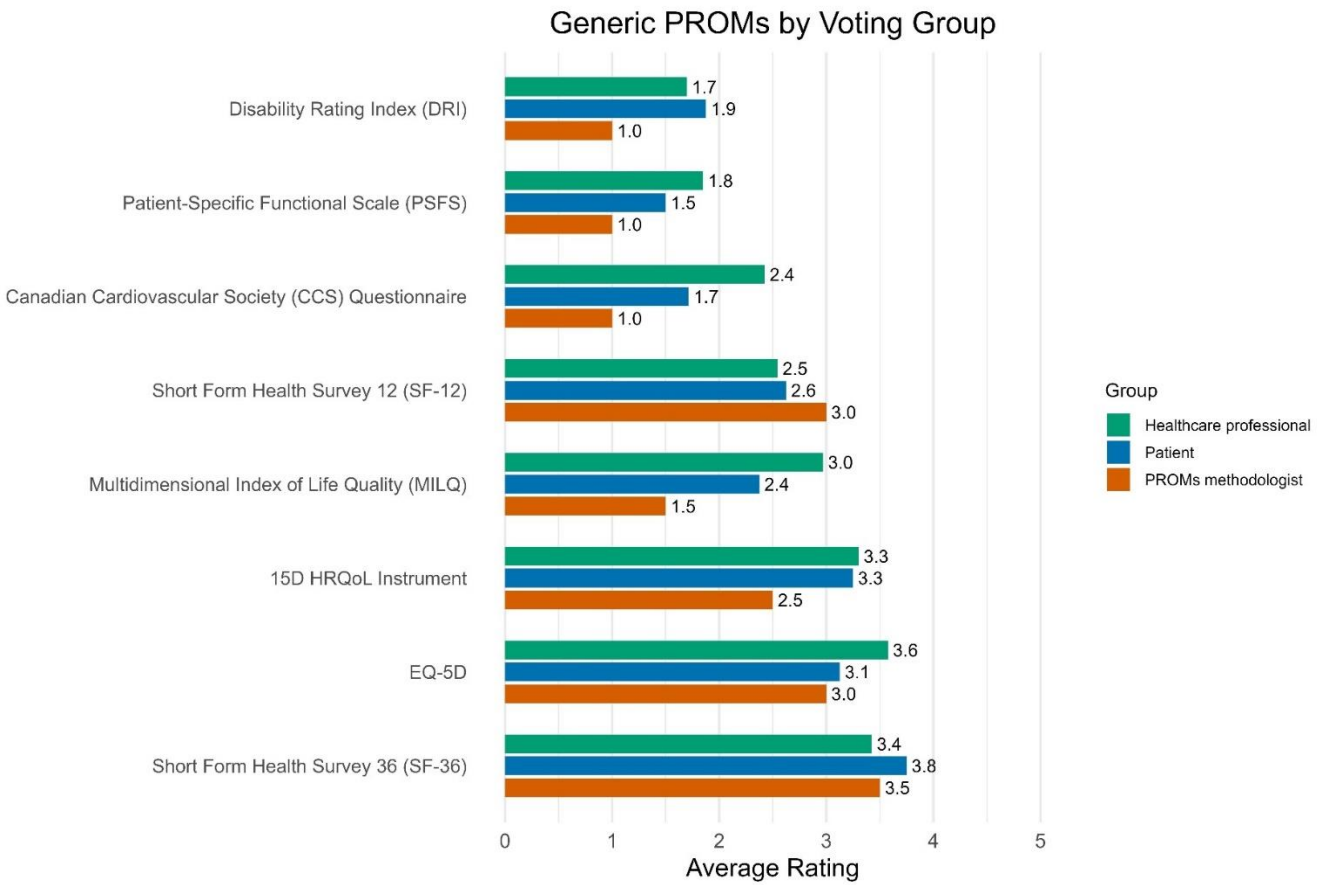
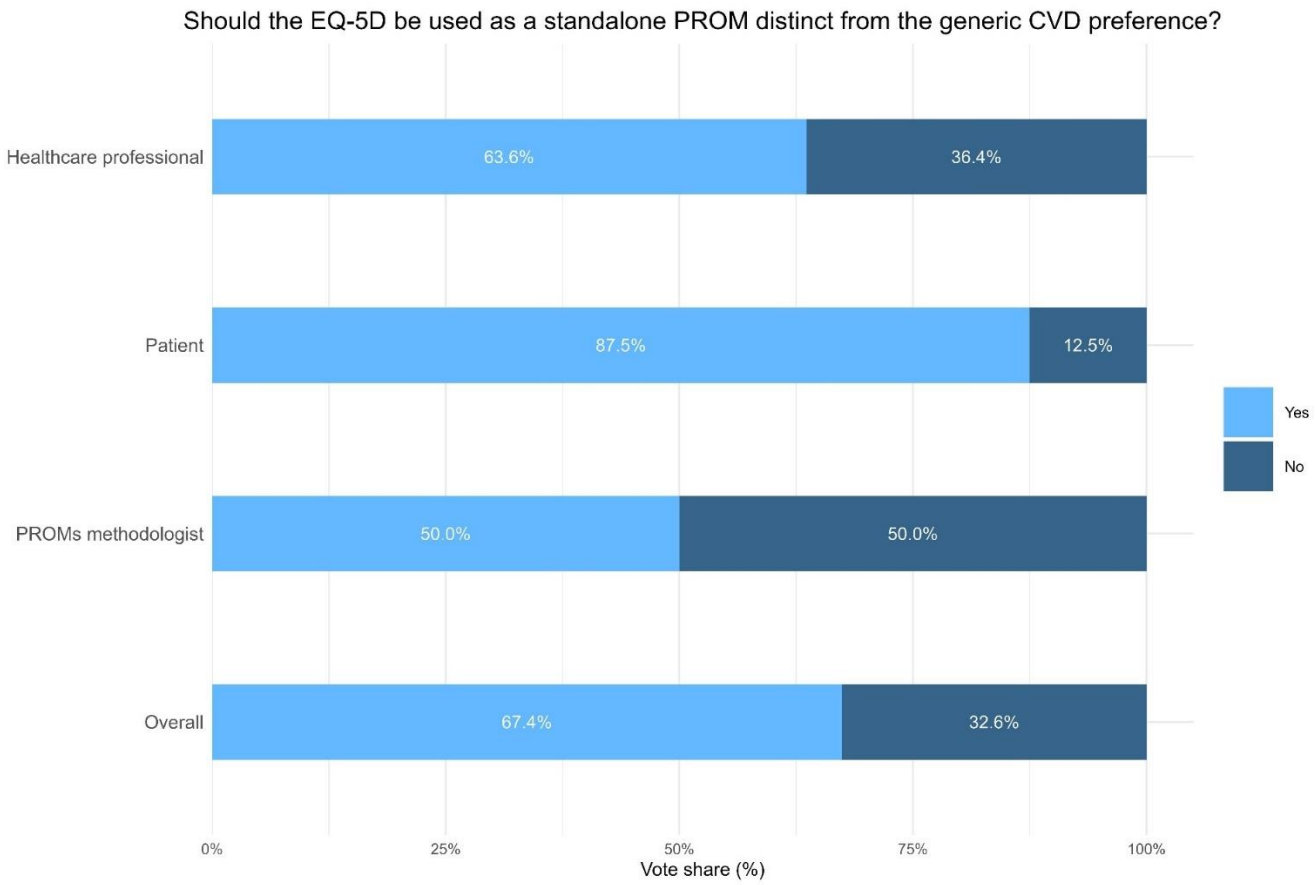

Generic PROMs by Voting Group
Disability Rating Index (DRI)
1.7
1.9
1.0
Patient-Specific Functional Scale (PSFS)
1.8
1.5
1.0
Canadian Cardiovascular Society (CCS) Questionnaire
2.4
1.7
1.0
Short Form Health Survey 12 (SF-12)
2.5
2.6
3.0
Multidimensional Index of Life Quality (MILQ)
3.0
2.4
1.5
15D HRQoL Instrument
3.3
3.3
2.5
EQ-5D
3.6
3.1
3.0
Short Form Health Survey 36 (SF-36)
3.4
3.8
3.5
0
1
2
3
4
5
Average Rating
Group
Healthcare professional
Patient
PROMs methodologist

Figure 7.4. Average voting results on including EQ5D as a standalone generic PROM.

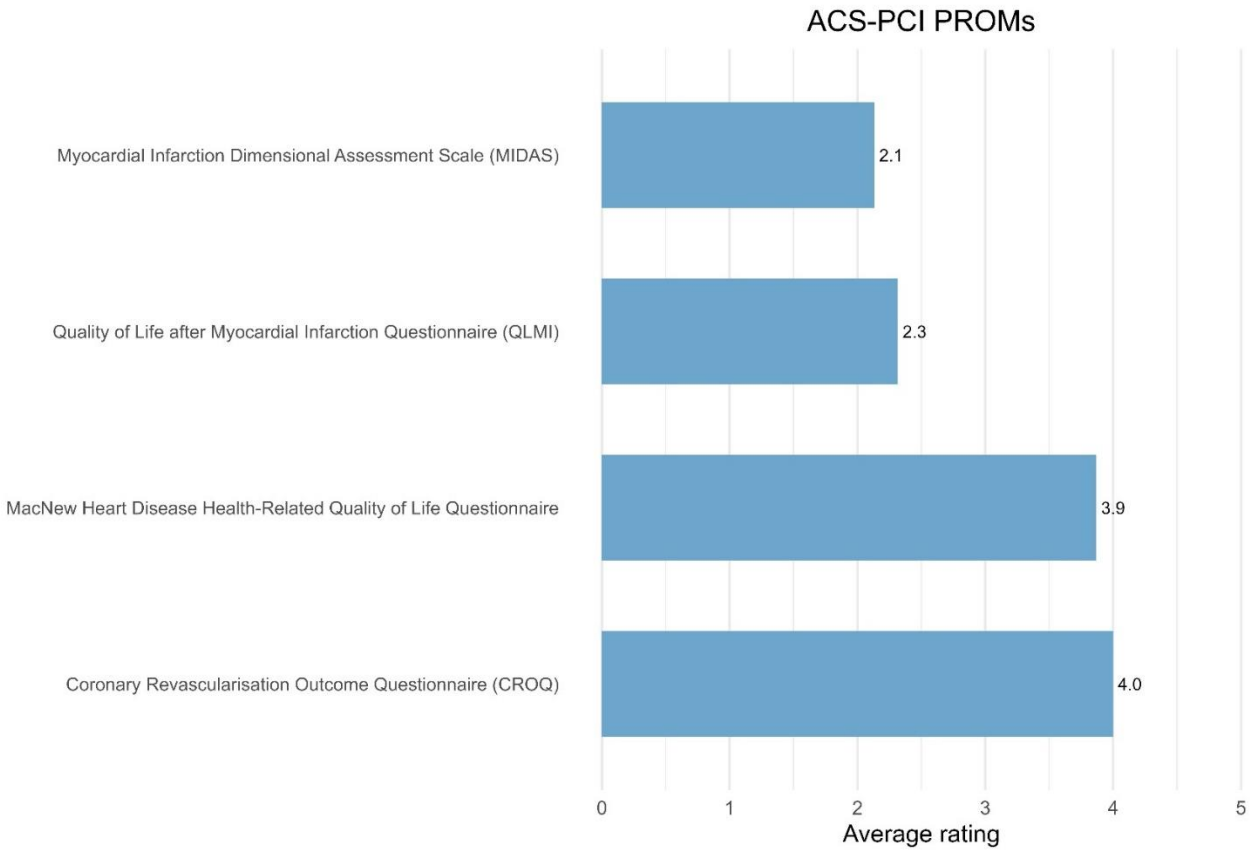


7.5.2.2 Acute coronary syndrome / percutaneous coronary intervention recommendations

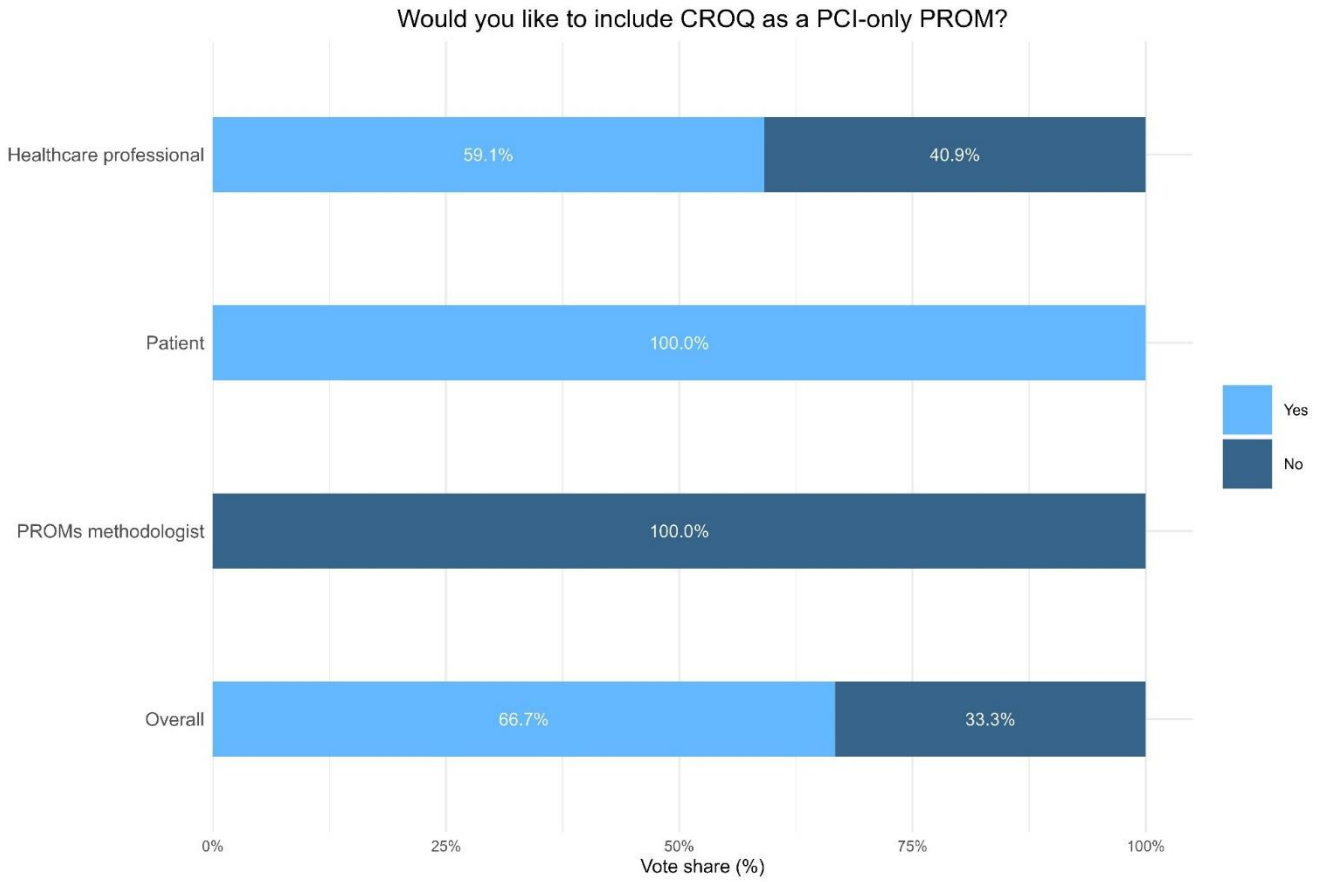
For the ACS/PCI domain, the CROQ questionnaire(380) was preferred with the highest average Likert rating of 4.0, with general agreement across categories of voter followed by the MacNew questionnaire with an average Likert rating of 3.9(366) (**Figure 7.5**). Although all patient representatives voted in favour of adopting the CROQ as a standalone PROM specifically for PCI due its simple, comprehensible questions, it did not reach the predefined 75% consensus threshold required for recommendation. This was because some healthcare professionals felt it would take too long to complete in busy PCI centres with high turnover.

Figure 7.5. Average voting results for each PROM within the ACS/PCI domain. A) overall average rating for each ACS/PCI PROM, B) on including CROQ as a standalone PCI PROM.

A)



B)

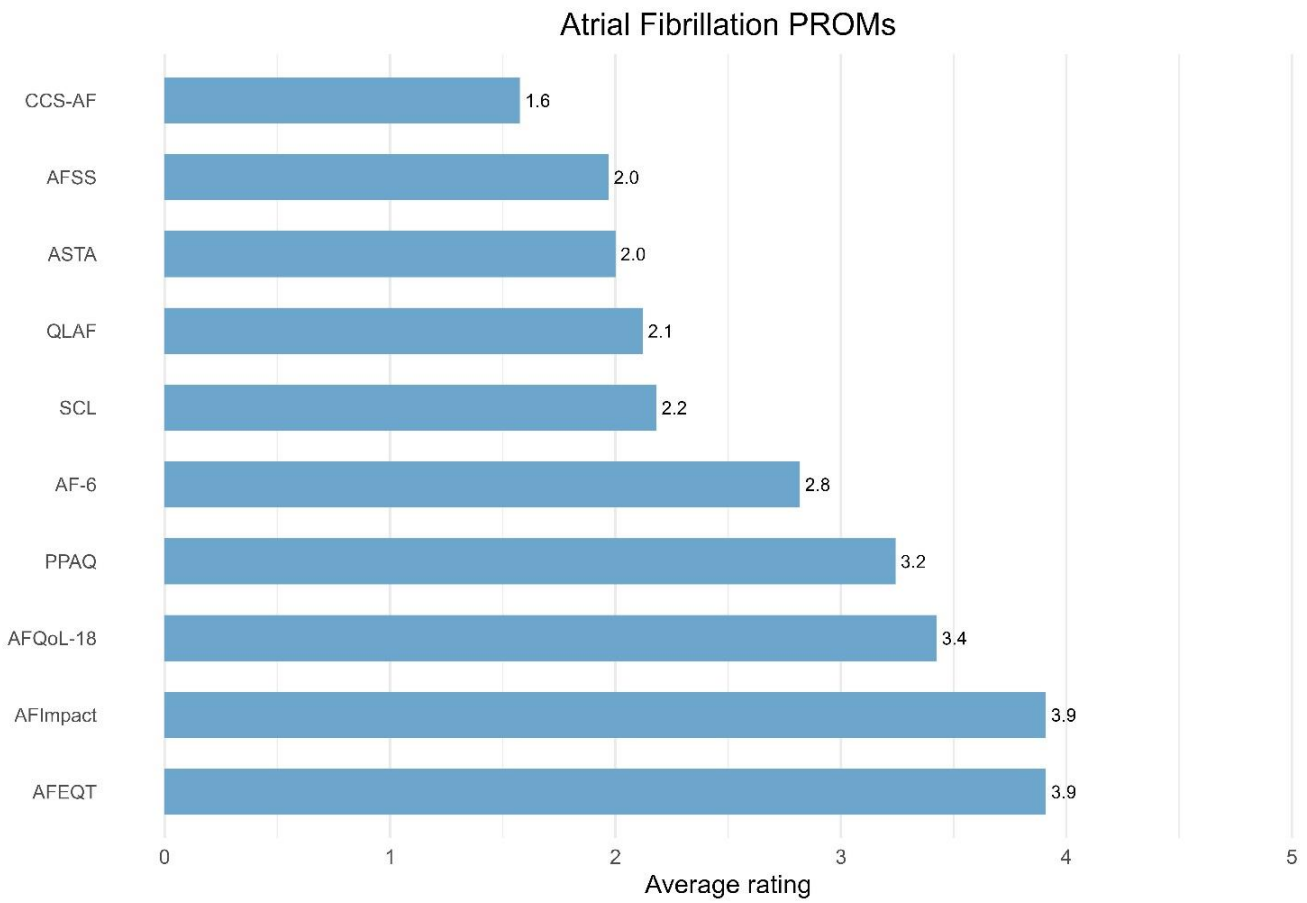

Would you like to include CROQ as a PCI-only PROM?
Healthcare professional
59.1%
40.9%
Patient
100.0%
PROMs methodologist
100.0%
Overall
66.7%
33.3%
0%
25%
50%
75%
100%
Vote share (%)
Yes
No

7.5.2.3 Atrial fibrillation recommendations

For the AF domain, both AF Impact(369) and the AFEQT(373) were ranked highest with an average Likert score of 3.9. There was general agreement across each voter group who felt that the questionnaires explored all patient relevant domains such as the psychosocial impact of AF and overall quality of life coupled with evidence of robust psychometric properties (**Figure 7.6**).

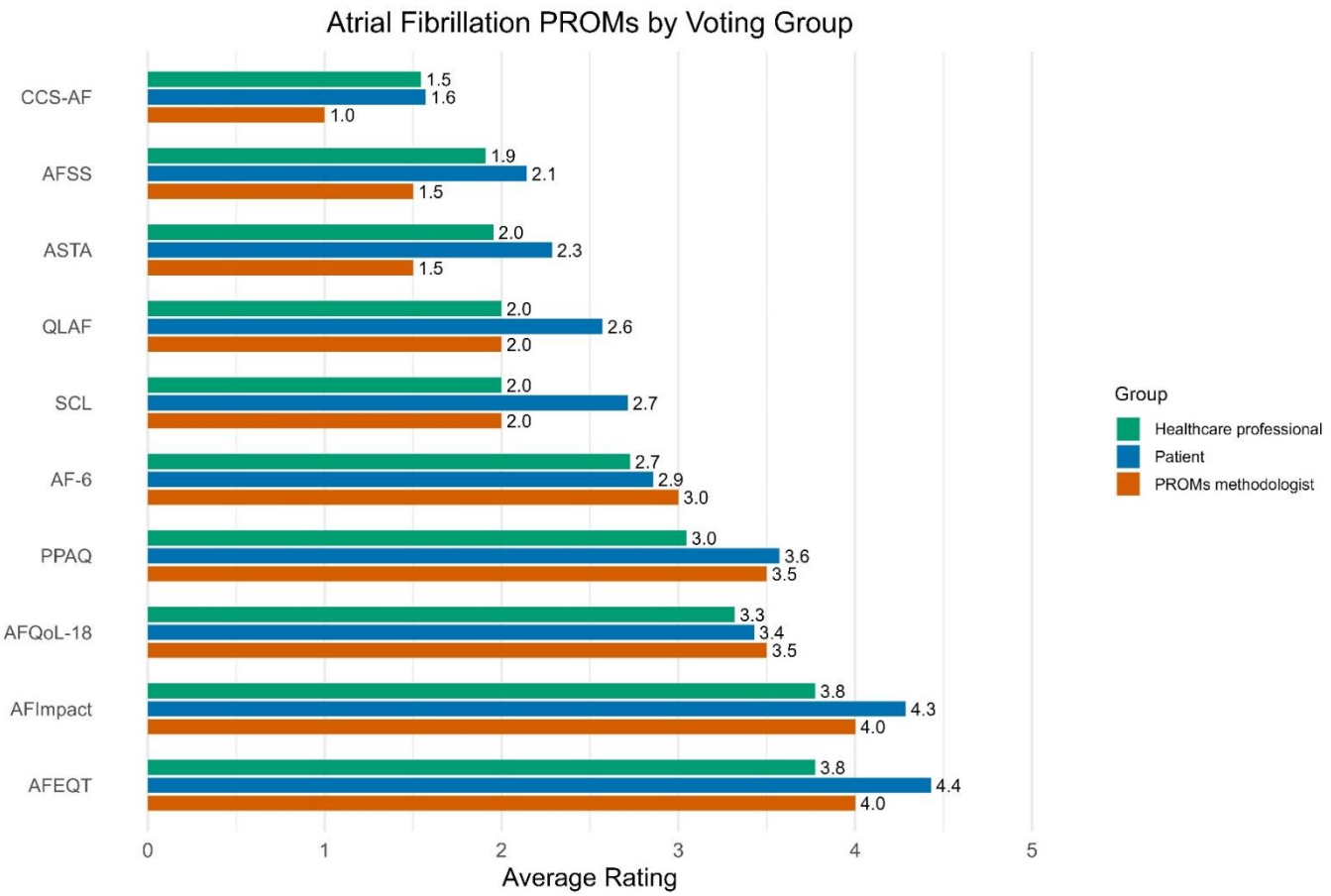
Figure 7.6. Average voting results for each PROM within the AF domain. A) Overall average rating for each AF PROM, B) voting results according to each voting group.

A)



Abbreviations: CCS-AF: Canadian Cardiovascular Society – Atrial Fibrillation; AFSS: Atrial Fibrillation Severity Scale of quality of life-20; ASTA: Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; QLAF: AF specific health related quality of life; SCL: Toronto AF Symptom Checklist; PPAQ: Patient Perception of Arrhythmia Questionnaire; AFQoL-18: Quality of Life questionnaire for Patients with Atrial Fibrillation; AFEQT: Atrial Fibrillation Effect on QualiTy-of-life;

B)



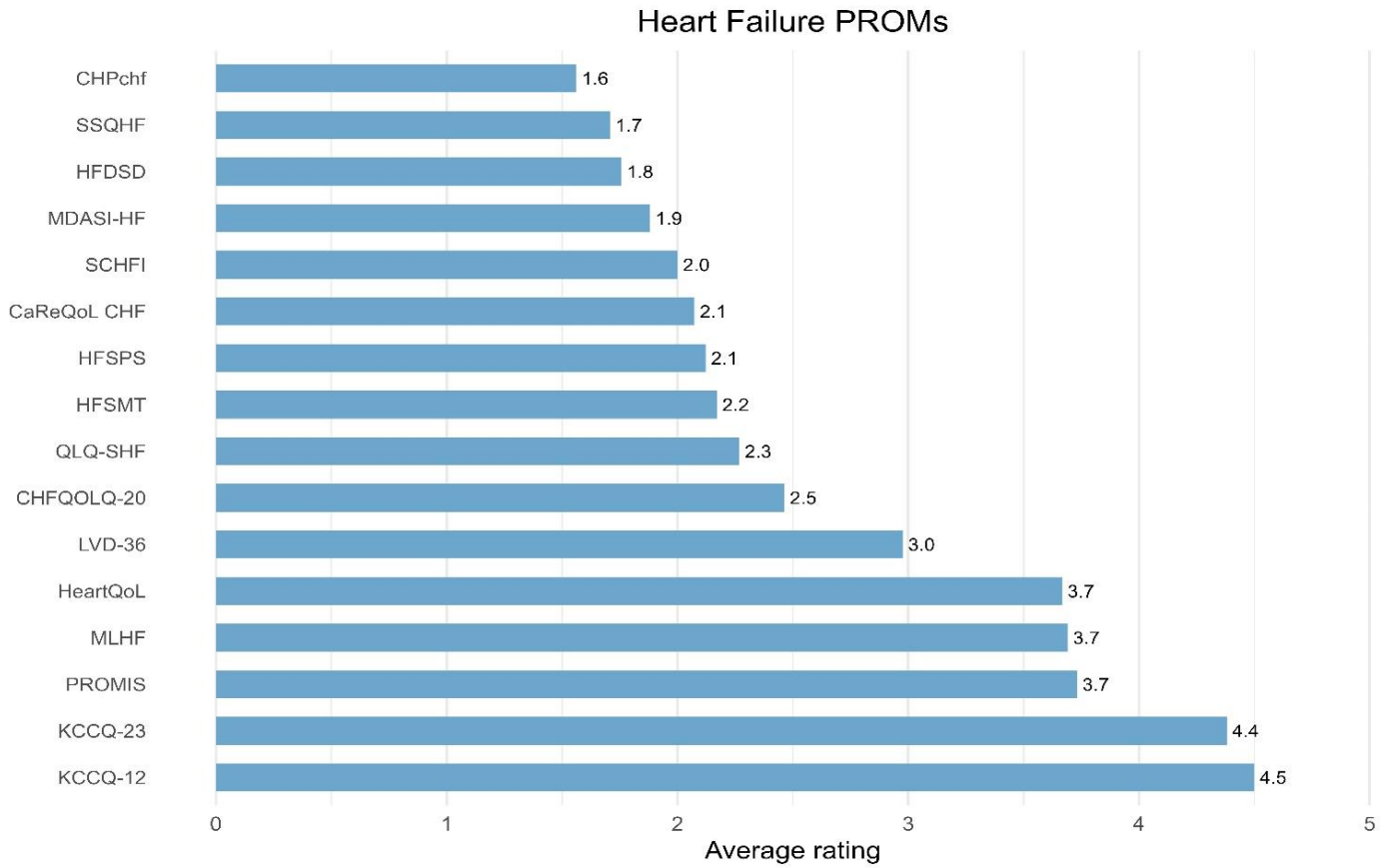
Abbreviations: CCS-AF: Canadian Cardiovascular Society – Atrial Fibrillation; AFSS: Atrial Fibrillation Severity Scale of quality of life-20; ASTA: Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; QLAF: AF specific health related quality of life; SCL: Toronto AF Symptom Checklist; PPAQ: Patient Perception of Arrhythmia Questionnaire; AFQoL-18: Quality of Life questionnaire for Patients with Atrial Fibrillation; AFEQT: Atrial Fibrillation Effect on QualiTy-of-life;

7.5.2.4 Heart failure recommendations

For the HF domain, both versions of the KCCQ(348, 349) were ranked highly with the short 12-item KCCQ highest with an overall average Likert score of 4.5. There was however heterogeneity between voter groups notably with PROMs methodologists equally preferring the PROMIS plus HF profile,(352) HeartQOL,(359) LVD-36(351) and both versions of the KCCQ. Whereas patients ranked HeartQOL and PROMIS plus HF profile highest (**Figure 7.7**). The PROMs methodologists found it difficult to choose between the 7 PROMs as they all were well validated, whereas the healthcare professionals gave preference to those well validated questionnaires that were shorter to complete and used frequently in heart failure trials.

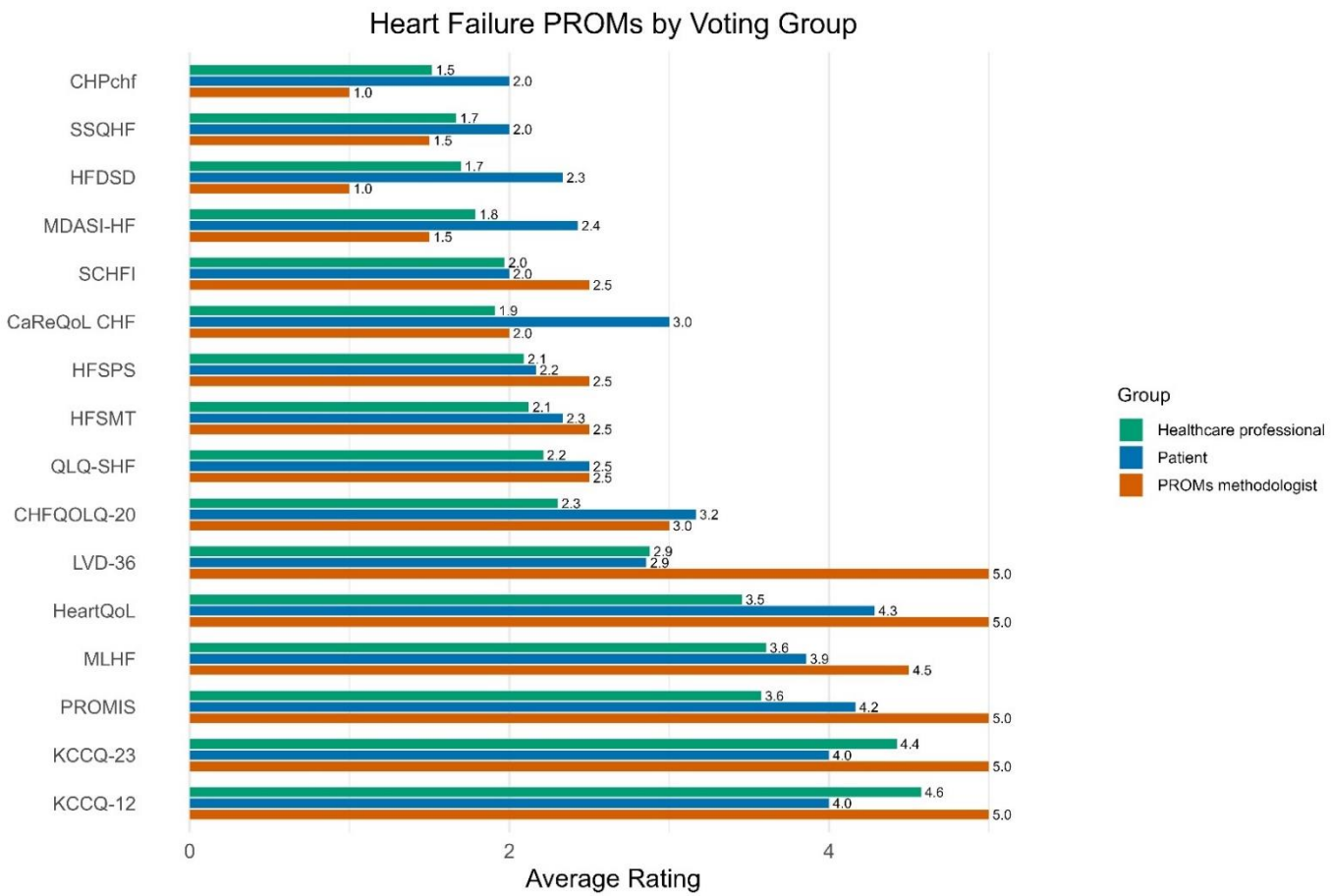
Figure 7.7. Average voting results for each PROM within the HF domain. A) Overall average rating for each HF PROM, B) voting results according to each voting group.

A)



Abbreviations: CHPchf: Cardiac Health Profile congestive heart failure; SSQHF: Symptom Status Questionnaire Heart Failure; HFDSD: Heart Failure Daily Symptom Diary; MDASI-HF: MD Anderson Symptom Inventory-Heart Failure; SCHFI: Self Care Heart Failure Index; CaReQoL CHF: Care-Related Quality of Life survey for Chronic Heart Failure**;** HFSPS: Heart Failure Somatic Perception Scale; HFSMT: Heart Failure Self Monitoring Tool; SHF-QLQ: Quality of life questionnaire in severe heart failure**;** CHFQOLQ-20: Chronic heart failure health-related quality of life questionnaire; LVD-36: Left Ventricular Dysfunction questionnaire; MLHF: Minnesota Living with Heart Failure; PROMIS: Patient Reported Outcome Measurement Information Systems Plus Heart Failure; KCCQ: Kansas City Cardiomyopathy Questionnaire;

B)



Abbreviations: CHPchf: Cardiac Health Profile congestive heart failure; SSQHF: Symptom Status Questionnaire Heart Failure; HFDSD: Heart Failure Daily Symptom Diary; MDASI-HF: MD Anderson Symptom Inventory-Heart Failure; SCHFI: Self Care Heart Failure Index; CaReQoL CHF: Care-Related Quality of Life survey for Chronic Heart Failure**;** HFSPS: Heart Failure Somatic Perception Scale; HFSMT: Heart Failure Self Monitoring Tool; SHF-QLQ: Quality of life questionnaire in severe heart failure**;** CHFQOLQ-20: Chronic heart failure health-related quality of life questionnaire; LVD-36: Left Ventricular Dysfunction questionnaire; MLHF: Minnesota Living with Heart Failure; PROMIS: Patient Reported Outcome Measurement Information Systems Plus Heart Failure; KCCQ: Kansas City Cardiomyopathy Questionnaire

7.5.2.5 Transcatheter aortic valve intervention recommendations

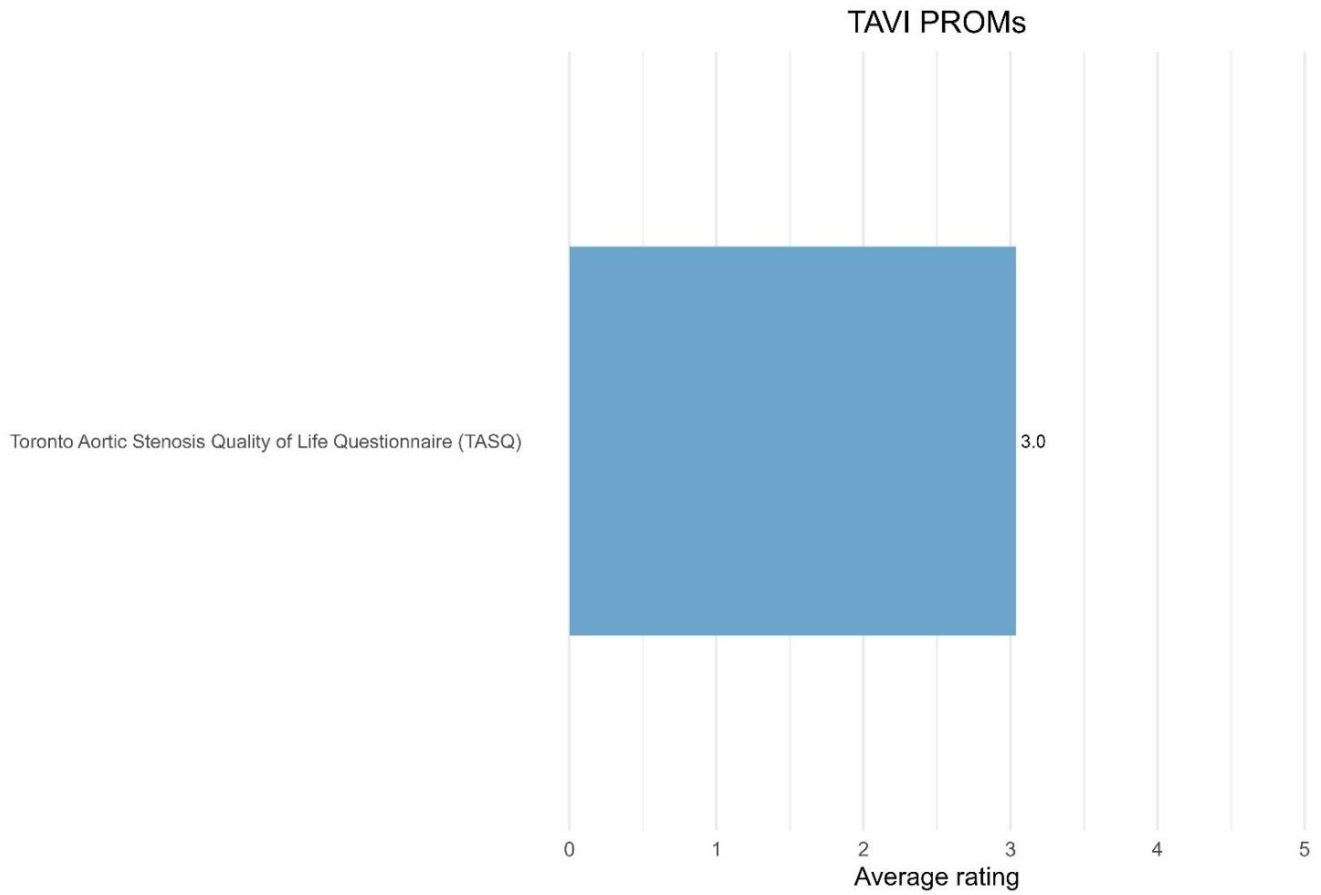
For the TAVI domain the TASQ was the only PROM to score and had a mean Likert score of 3.0 (**Figure 7.8**). Including the generic PROMs within the TAVI domain did not meet the 75% threshold and was not included despite patients voting in favour as TASQ is not well validated whereas healthcare professionals felt that a generic PROM may not capture nuances specific to TAVI and aortic stenosis.

7.5.2.6 Overall comments

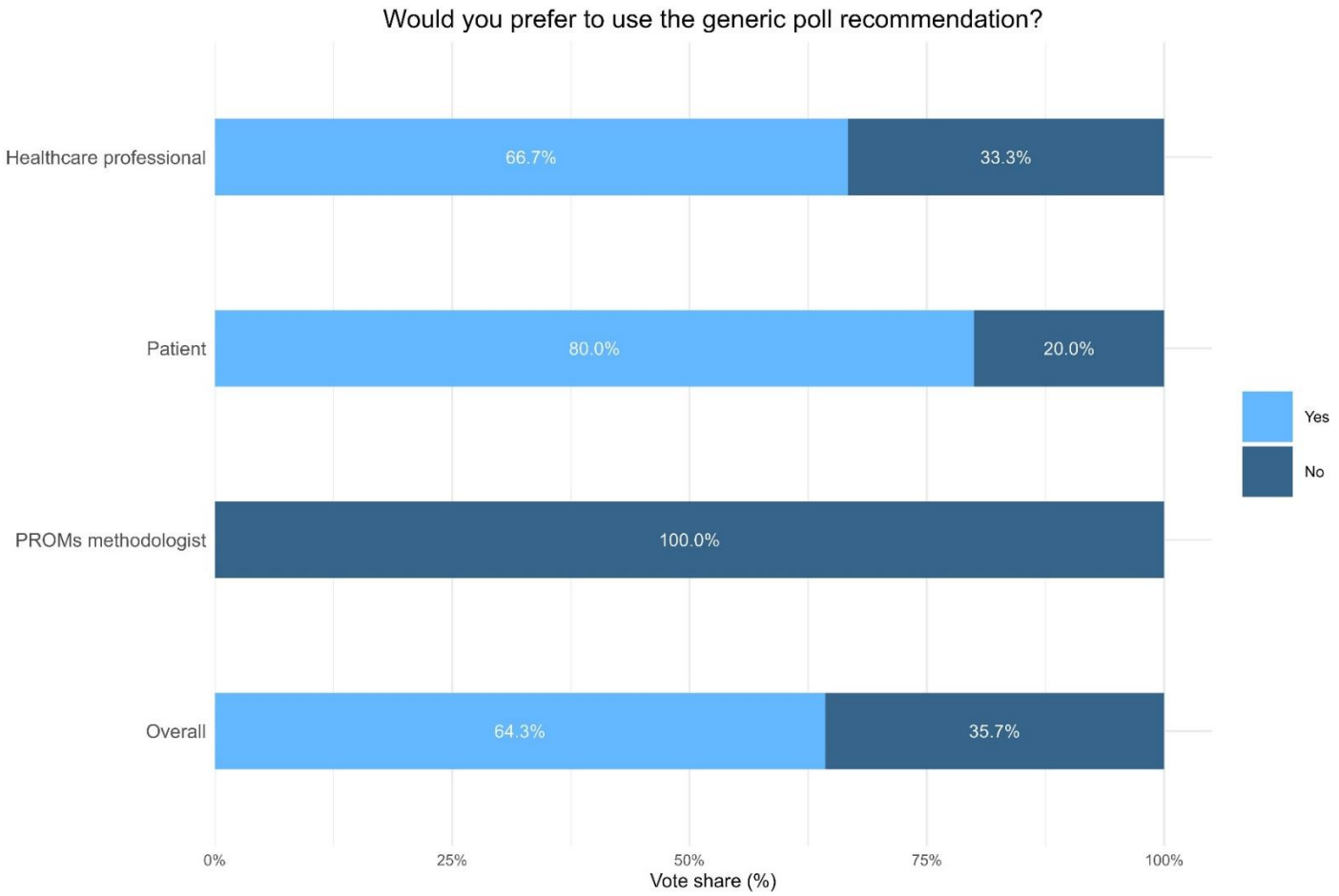
There was a consistent theme that emerged from eliciting the WG's feedback on each PROM that was true for each domain that centred on the feasibility of implementing PROMs within clinical care and research. Some experts felt that selecting a PROM may depend on what each organisation would try to achieve with its implementation (i.e. its goal; clinical care, registries, or research), duration to complete the questionnaire, the ability of a PROM to be implemented electronically and its associated costs. One solution offered would be to select different PROMs for different settings and therefore not excluding any PROM from the overall ranking would be beneficial.

Figure 7.8. Average voting results for the TAVI PROM within the TAVI domain. A) Overall average rating for TASQ, B) on incuding generic PROMs into the voting.

A)



B)


Would you prefer to use the generic poll recommendation?
Healthcare professional
66.7%
33.3%
Patient
80.0%
20.0%
PROMs methodologist
100.0%
Overall
64.3%
35.7%
Yes
No
0%
25%
50%
75%
100%
Vote share (%)

7.6 Discussion

Following the Modified Delphi process including healthcare professionals, PROMs experts and patients, we present a suite of internationally derived and agreed validated HRQoL PROMs for CVD. These include four common CVD domains, as well as generic CVD to allow wide scope for their application for evaluating an individual's HRQoL. We propose that the highest ranked HRQoL PROMs are preferentially employed in registries, randomised clinical trials, regulatory frameworks, and routine care.

Interest in collecting PROMs within cardiology is steadily increasing, supported by position statements from major international organisations advocating for their integration within clinical trials,(105) registries(106) and routine clinical care.(89) Like EuroHeart, the ICHOM have published outcome sets that incorporate PROMs across the common cardiovascular disease conditions.(150, 152, 413) Similar to EuroHeart, the ICHOM sets recommend KCCQ-12(348) for use within HF(152) and include AFEQT(373) in their recommendations for AF (**Table 7.2**) (413)

Table 7.2. Table comparing the recommended PROMs in both ICHOM and EuroHeart outcome sets.

Outcome sets	ACS /PCI	Heart Failure	AF	TAVI	Generic
ICHOM	SAQ-7, Rose dyspnoea, PHQ-2	KCCQ-12, NYHA, PHQ-2 PROMIS physical function	AFEQT, SF-12, AFSS, PROMIS Global Health and Cognitive Function, WPAI	EQ5D, HVD, NYHA CCS	None
EuroHeart	CROQ	KCCQ-12	AFEQT, AFimpact	TASQ	EQ5D, SF-36

Abbreviations: **SAQ**: Seattle Angina Questionnaire; **KCCQ**: Kansas City Cardiomyopathy Questionnaire; **NYHA**: New York Heart Association; **PHQ**: Patient Health Questionnaire; **PROMIS**: Patient Reported Outcome Measurement Information System; **AFEQT**: Atrial Fibrillation Effect on Quality of Life; **SF**: Short Form; **AFSS**: Atrial Fibrillation Severity Scale; **WPAI**: Work, Productivity, Activity Impairment; **EQ5D**: EuroQOL 5 Dimension; **HVD**: Heart Valve Disease; **CCS**: Canadian Cardiovascular Score; **CROQ**: Coronary Revascularisation Outcome Questionnaire; **TASQ**: Toronto Aortic Stenosis Questionnaire

Yet, there are important differences. For example in previous sets,(152) the EMPRO tool(398) was used to appraise the psychometric qualities of HF PROMs whereas EuroHeart employed the COSMIN criteria(336) for all domains as COSMIN provides more in-depth information of the measurement properties of a questionnaire which may in part explain the difference in preferred PROMs within HF between ICHOM and EuroHeart. In contrast to ICHOM,(413) we specifically focussed on domain specific HRQoL PROMs because these evaluate the impact of health status on a patient's quality of life and encompass physical, emotional and mental wellbeing,(97) factors that are strongly aligned with the priorities of both European regulators and patient advocacy groups.(104, 407) Therefore, we placed emphasis on presenting all available HRQoL CVD PROMs and their psychometric analysis from a contemporary review(416) to our Working Groups, in contrast to ICHOM,(413) to ensure that the rankings reflected a contemporary appraisal of evidence and that all PROMs were considered. For example, within the HF domain, the ICHOM working group members were only presented three HF HRQoL PROMs, KCCQ,(59) MLHF (346) and PROMIS to choose from(152, 352) as these questionnaires were considered robust from a comprehensive review completed in 2009. (427) Indeed other PROMs with more recent validation studies such as HeartQOL may have been excluded from voting prematurely which may explain the differences between the two sets.(396) Furthermore, we voted to not include generic CVD PROMs within specific domains, such as TAVI, by our Working Group members as they wanted to included disease specific PROMs evaluate concepts that are specific to each cardiovascular condition of ACS/ PCI, AF, HF, and TAVI. (167-170, 240, 241)

This emphasis on disease specific HRQoL may also explain why both patient representatives and healthcare professionals unanimously supported CROQ as a PROM for ACS/PCI, given its patient-centred design and focus on psychosocial dimensions of recovery whereas it was not included for voting in the ICHOM set.(150, 380) However the EuroHeart and ICHOM ranking for ACS/ PCI may not be comparable as the intended scope was different between the two sets.(155) EuroHeart focused on HRQoL PROMs that evaluated ACS/PCI whereas ICHOM broadened their scope to include any patient with coronary artery disease which includes angina and therefore included PROMs that

evaluate symptoms of coronary artery disease such as the SAQ and the Rose Dyspnoea Scale. (150, 383, 428) Similarly, the TASQ questionnaire also was not considered for voting within the ICHOM recommended set for heart valve disease partly because their scope included all types of valvular heart disease that TASQ is not validated for, whereas the EuroHeart recommended set specified PROMs validated only for TAVI.(381, 424)

Administrative and patient respondent burden are recognised as important barriers to overcome in routine PROM implementation.(126, 140, 429) EuroHeart aimed to reduce this by highlighting the preferred PROM to use in each domain whereas previous sets recommended multiple PROMs as shown in **Table 7.2**.(150, 413, 424) Also, the use of a hierarchical ranking is a hallmark EuroHeart feature on outcomes(240, 414) and is lacking in previous outcome sets.(150, 152, 413) This affords flexibility for institutions looking to collect PROM data routinely that may not be able to implement one or more specific PROM due to feasibility issues,(126) such as cost of obtaining a PROM,(141) lack of an appropriate translation(401) or regulatory requirements for pharmaceutical labelling claims,(399) which may in part explain the variable uptake of PROMs within cardiology clinical care. This was vocalised by our WG members, who felt that some PROMs may be preferred over others across the multiple geographies that EuroHeart spans.

In clinical practice the assessment of a patient's health, such as symptom burden or quality of life, is interpreted by clinicians and together with objective markers of disease and informs a treatment strategy.(89, 280) For example, the impact of symptomatic, paroxysmal AF, alongside objective markers, may lead to a recommendation for invasive catheter ablation in accordance with ESC guidelines.(71) However, there can be significant discrepancies between clinician interpretation and PROs such as functional health.(11) The use of standardised PROMs improves the accuracy of reporting a patient's symptoms and HRQoL, and may enhance healthcare provider-patient communication and patient satisfaction.(430) The employment of PROMs as an outcome measure within CVD research has steadily increased,(92, 334, 431) and important patient centred metrics such as HRQoL are independent predictors cardiovascular events and cost of health care.(93, 432, 433) As such, some international regulatory bodies have specified drug approval for HF may be

attained on the basis of improving patient outcomes alone(98) and others have specified multidimensional PROMs such as HRQoL may be an acceptable trial primary outcome as an alternative to more traditional outcomes such as hospitalisation, confirming the expanding role of PROMs within research and regulatory affairs.(96)

However, implementation of PROMs within cardiology clinical practice and registries is variable ranging from individual centres(93) to international registries collecting and reporting PROMs scores.(434) There is an opportunity to promote the international adoption of PROMs for common CVD. Examples of successfully implementing validated PROMs is the Australian Cardiac Outcomes Registry in TAVI(435) and the Asian Sudden Cardiac Death in Heart Failure registry (ASIAN-HF).(434) ASIAN-HF prospectively records patients with symptomatic HF or HF with reduced EF across 11 countries that collects important patient baseline characteristics and their validated HRQoL PROM scores at baseline and regular follow up.(434) Recently, they have demonstrated that serial poor HRQoL scores are significant predictors of HF hospitalisation and death that is consistent across sex, socioeconomic and ethnic groups.(436) Therefore, this shows that it is possible to implement PROMs in clinical registries that span multiple geographies and different healthcare systems. There is a need for the widespread implementation of valid, reproducible, standardised tools such as PROMs in clinical care and randomised control trials across the common CVD from a European context.

7.7 Strengths

We present an international expert consensus to guide HRQoL PROM selection in each of the common cardiovascular conditions, which complements our previous work on clinician derived cardiovascular outcomes,(240, 414) and follows a robust methodology.(425) The modified Delphi is a structured and systematic method in attaining consensus amongst experts.(437) It differs from a standalone Delphi method as it involves structuring questions and guiding the discussion to achieve consensus on a particular topic and is considered to be superior.(437) Therefore it is imperative to include many experts that had expertise in using PROMs in a variety of settings. As a consequence, we consulted with a broad range of international multidisciplinary experts and

patients from within ESC affiliated working groups and associations but also PROMs methodologists and healthcare providers outside the ESC. Furthermore the consensus was supported by evaluating the comprehensive qualitative assessment of each PROM using the COSMIN criteria and relaying this information to the experts.(336)

7.8 Weaknesses

There are limitations to our work. Importantly, selection bias could have been introduced as we relied on a group of experts. Furthermore, we included a limited number of patients to classify the PROMs. As mentioned in **section 1.4.5.1.,** patients of different socioeconomic demographics, gender and nationality may differ in what they consider to be good HRQoL.(117, 118) This may translate into which PROMs they considered to be meaningful. We were not able to include similar number of patients from each EuroHeart participating country and most of our patients from lower socio-economic positions were not well represented. Incorporating more patients, and from a wider variety of socioeconomic backgrounds and cultures, would provide a more complete representation of patients' views and offer parity with the opinions of healthcare professionals. The lack of representation may introduces selection bias into our results as the opinions of a select few patients were only included.

We acknowledge that there could also have been familiarity bias in voting preference whereby those PROMs that were well known to voters were ranked highly. Some WG members vocalised that they preferred well known PROMs such as the KCCQ as it had featured in many notable trials. Finally, the Global Cardiovascular Outcomes Consortium were not provided with a full feasibility assessment, such as cost and licensing agreements of each PROM, which may represent barriers to the implementation of these measures. This was consistent feedback from our working group members and will form the main basis for **Chapter 8**. Nonetheless, this expert consensus has the potential to facilitate the systematic integration of HRQoL PROMs into cardiovascular research, regulatory frameworks, and clinical practice, thereby advancing a more holistic and patient-centred evaluation of health outcomes.

7.9 Conclusion

We present a catalogue of internationally recommended PROMs for use across the common cardiovascular conditions. We followed the Modified Delphi process using a scoping review and contemporary comprehensive qualitative assessment followed by expert-led ranking of each PROM. The routine use of PROMs in clinical care, registries and trials can improve quality of care and outcomes and increase patient satisfaction.

7.10 Summary

- According to a consensus of 94 experts, patients and PROMs methodologists from the ESC Patient Forum and the Global Cardiovascular Outcomes Consortium, seven HRQoL PROMs were ranked highest for use in registries, observational studies and randomised clinical trials.

- These were HRQoL PROMs were CROQ for ACS/PCI, KCCQ-12 for HF, AFEQT and AFimpact for AF, TASQ for TAVI and EQ5D and SF-36 for generic CVD.

- The adoption of internationally derived and agreed HRQoL PROMs for cardiovascular disease provide a direct and reliable measure of an individual's health status that places the patient's voice within observational studies, randomised clinical trials, regulatory frameworks, and routine care.

Chapter 8
Evaluating the feasibility of Patient Reported Outcomes Measures

A FeAsibility items Checklist for assessing implementation characTeristics of patient reported Outcome measures in Research, Regulation and Routine clinical care (FACTOR3): development and evaluation

The following chapter details the progress made on my last project during the MD which is to develop a checklist that evaluates how feasible it is to implement a PROM in clinical practice, research and regulatory affairs which had been highlighted by some WG Members in the **Chapter 7**. To achieve this, I conducted a modified Delphi with participants with PROM expertise in a clinical, trial and research context.

8.1 Contribution

I conducted the scoping review to inform the consensus building process, identified, approached and recruited experts from a broad array of disciplines to participate in both rounds of voting, gave a short presentation to the multi-disciplinary experts during video conference calls, organised the voting poll and collected and displayed the results to international regulators. I then identified three independent reviewers to trial the checklist on six well known PROMs across multiple disciplines and calculated the intra class correlation between their scores. I drafted the original manuscript and then incorporated co-author suggestions.

8.2 Abstract

Introduction

PROMs provide valuable data to inform regulatory decision making, health technology assessment and routine clinical care. We aimed to develop a

feasibility item checklist for PROMs and their selection, beyond their psychometric properties (FACTOR3).

Method

We followed a five-stage method to select parameters for PROM evaluation. 1) A scoping literature review identified candidate items for consideration; 2) round 1 modified Delphi was used to select items for inclusion or exclusion, conducted by the design group (n=14); 3) feedback on the checklist was provided by representatives from the EMA and NICE; 4) round 2 modified Delphi was used to finalise item selection, conducted by the clinical domains group (n=21) and 5) evaluation of the feasibility item checklist using a selection of PROMS (EQ5D-5L, HeartQOL, the Oxford Hip Score, The EORTC Core Questionnaire QLQ-C30, Re-QOL-10 and NEI-VFQ-25).

Results

The scoping review identified 13 items relating to the intrinsic feasibility of using PROMs which were considered in the modified Delphi. The final FACTOR3 checklist included eight unique candidate items: price; licensing, comprehensibility, duration, coverage, translations, electronic device compatibility; and minimal important difference. Of the six PROMS evaluated, the intraclass correlation coefficient was 0.81 suggesting good reliability.

Conclusion

FACTOR3 is a feasibility item checklist to assess the implementation characteristics of PROMs in research, regulation and routine clinical care. It may be used in conjunction with existing psychometric evaluation and user guides for PROMS to facilitate their use in health care.

8.3 Introduction

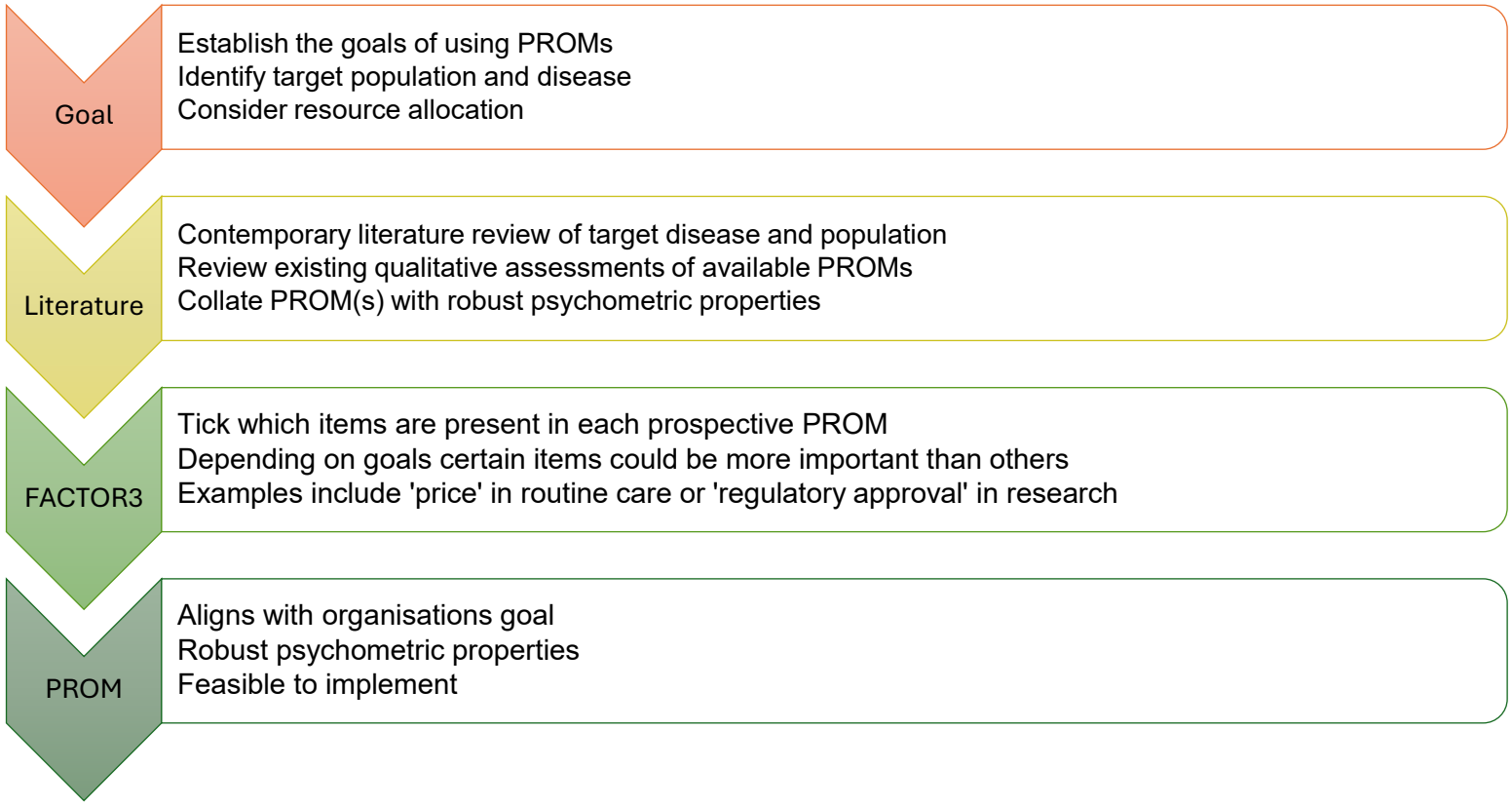
The importance of PROMs has been discussed in **section 1.4.3.**

The EMA and the US FDA recommend the use of validated PROMs for medical device or drug evaluation in the target population and disease and for the results to be appropriately communicated to healthcare providers and patients when supporting pharmaceutical labelling claims.(104, 438) In the UK NHS, PROMs are routinely used to evaluate the outcomes of elective hip and knee surgery, with results informing an assessment of healthcare provider performance as well as supporting clinical decision making(82) as well as benchmarking quality of care.(58, 280, 439)

There are over 7,000 validated PROMs spanning the range of medical diseases and interventions,(136) but limited guidance exists in formally assessing their intrinsic feasibility of implementation. The PROTEUS consortium recommends a qualitative assessment of the reliability and validity of a PROM prior to its selection,(335) such as COSMIN evaluation.(336) Assessment of some feasibility items is recommended such as the cost of using a PROM, licencing (126, 140, 141) and the ability of a PROM to be understood by the user (125). However, there are additional factors such as operational costs including searching for more information on a PROM through subscription websites,(136) regulatory approval for the use of a PROM in a randomised clinical trial (142, 143) and metrics that interpret change in PROMs scores over time such as the MID that determines the ability of a PROM to be used in research, regulatory affairs and routine clinical,(144, 145) but are not included in recommended assessment guides.

We aimed to develop a feasibility item checklist for assessing the implementation characteristics of PROMs in research, regulatory affairs and routine clinical care, and evaluate it against commonly used PROMs. This could complement user guides and address an implementation gap (**Figure 8.1**).

Figure 8.1. Visual graphic on how the FACTOR3 checklist may fit into the PROM selection process.



8.4 Methods

The development of the FACTOR3 checklist consisted of five stages: 1) scoping review to identify candidate items for consideration, conducted by the steering committee; 2) first stage modified Delphi to include or exclude items, conducted by the design group; 3) feedback on the checklist by the regulator group; 4) second stage modified Delphi to provide feedback on items, conducted by the clinical domain group; and 5) evaluation of the feasibility item checklist using a selection of PROMS.

8.4.1 Steering committee

The steering committee comprised clinical experts (A.B., C.W., C.P.G), a PROMs methodologist (A.B.S.) and a data manager (S.C.). They designed the study, formulated a list of candidate variables from the scoping review, identified and invited individuals to the other three working groups (design, clinical domain and regulator group), and collated and presented the results of the polls to the groups.

8.4.2 Scoping review

A scoping review was performed by the steering committee to identify potential factors in the published literature and existing user guides. All prospective and retrospective articles and grey literature (335, 411, 418) relating to feasibility of implementation of PROMs in adults from inception to 6th March 2024 in English was included. PubMed was searched using a pre-defined search strategy (**Appendix E.1**) and was conducted by A.B. These were assimilated and formed the basis of the questions for voting.

8.4.3 Modified Delphi

The steering committee identified potential members for each of the working groups by selecting co-authors of PROMs research manuscripts, those holding senior positions in regulatory affairs, health care professionals with experience of PROMs, and from personal references and recommendations by other Delphi

participants. The aim was to achieve wide representation across multiple geographies (Europe, North America, and Oceania) and clinical and academic disciplines. We therefore contacted PROMs methodologists, developers of PROMs, health economists, biostatisticians, patients, patient representatives, and multidisciplinary healthcare providers. No minimum sample size was placed on the number of working group members and Delphi participation. Each working group member's expertise was confirmed by the steering committee (apart from patients and patient representatives) before being invited to participate via email. Once accepted, the steering committee allocated each panellist either the design or clinical domain group detailed below, sent them an information pack via email and invited them to attend a virtual presentation about the project.

The first stage of modified Delphi meetings consisted of 14 experts as part of the design group who voted in the online survey. Participants were invited to provide feedback via free text, during voting and discussion was encouraged around the rationale for including / excluding items distilled from the scoping review and the scope of the checklist. Feedback to provide additional items was welcomed.

Once the list of variables and their definitions for the checklist were agreed, they were reviewed by the regulators for their feedback and agreement. The group comprised of representatives from the EMA and NICE that were either PROMs methodologists, patient representatives or trialists. They did not participate in the voting process.

The second stage of modified Delphi meetings consisted of 21 experts as part of the clinical domain group who voted in the online survey from the results garnered from the first stage Delphi. Participants were encouraged to include / exclude items distilled from the design group. Members of the design group and steering committee only voted once in the first stage to prevent unequal weighting of votes.

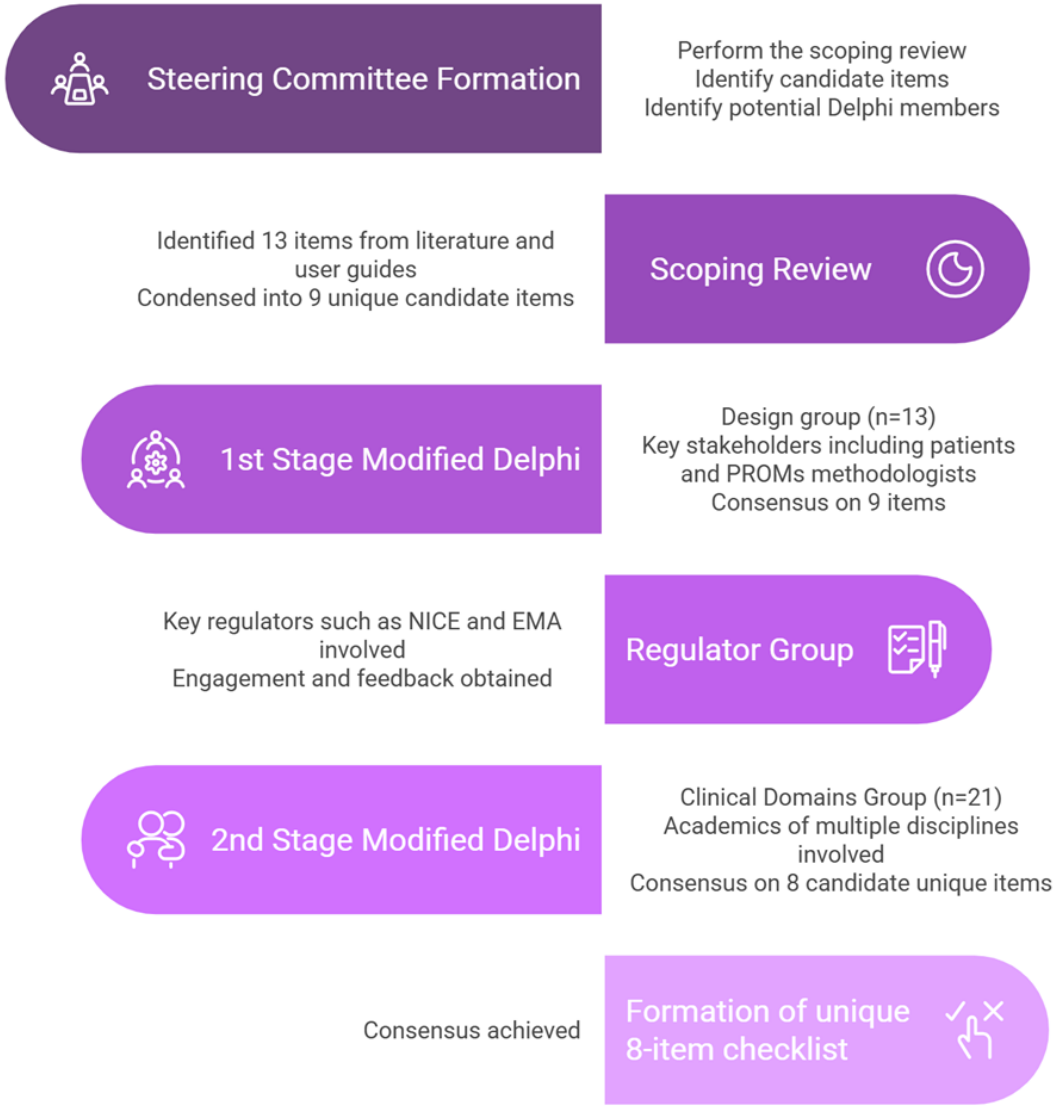
The virtual presentation was delivered and chaired by A.B. and supported by C.W. and C.P.G. and sought to summarise the current PROM selection process as per user guides, highlight aspects of feasibility that are not addressed in the literature, and the candidate feasibility items extracted from the scoping review

for discussion. Following the presentation, panellists were emailed an online survey. All panellists received the same presentation and options for voting.

The survey was in English using the ‘Jisc’ platform (https://www.jisc.ac.uk/). Participants were asked to provide their name and email address to protect against duplicate voting. As part of the survey, participants were asked to review the candidate feasibility item checklist variables that had been generated from the scoping review and to vote to “include” or “exclude” each variable. Judgement was based upon the panellist’s perception of the feasibility and applicability of each variable. Written comments were invited for each item, which were collated and thematically categorised by the steering committee.

The threshold for inclusion of a candidate feasibility item checklist variable was at least 75% of panellists voting on an item to include and was decided *a priori*. (257, 425) The threshold for exclusion was at least 75% of participants selecting for the variable to be excluded or achieving less than 75% to include. No financial or in-kind incentive was offered to panellists for completing their survey or virtual meeting. The overall process is shown in **Figure 8.2**. The full list of the participants is included in **Appendix E.2**

Figure 8.2. Formation of the FACTOR3 checklist



8.4.4 Evaluation of checklist

Three clinician reviewers who were independent of the modified Delphi method for the development of the feasibility item checklist, were invited to evaluate six PROMs against the final checklist. Specific PROMs (EQ5D-5L, HeartQOL, the Oxford Hip Score, The European Organisation for Research and Treatment of Cancer [EORTC] Core Questionnaire Quality of Life Questionnaire [QLQ-C30], Recovering Quality of Life [Re-QOL-10] and the National Eye Institute [NEI] Visual Function Questionnaire-25) were selected because they were routinely used in clinical practice (for example within the NHS of England), derived by

international organisations, widely cited in the literature and to cover different clinical specialities. Each reviewer was given a sample of the questionnaires and URL links to each organisation's website as some checklist items may be difficult to answer on a questionnaire alone. For example, licensing and cost information will not be available by reviewing the questions in a PROM.

The presence of each item of the feasibility item checklist was assigned a score of 1 and the overall score was recorded. A PROM that scored highly against the feasibility item checklist was deemed feasible or easy to implement, with feasibility being defined as the intrinsic characteristics of a PROM that allows ease of implementation. This differs to alternative definitions of feasibility that assess the extent to which a PROM may be successfully used or carried out within a particular setting.(440) The ICC was performed to evaluate reviewers' inter-rater reliability which was collated and stored in MS Excel.

8.4.5 Patient and public involvement

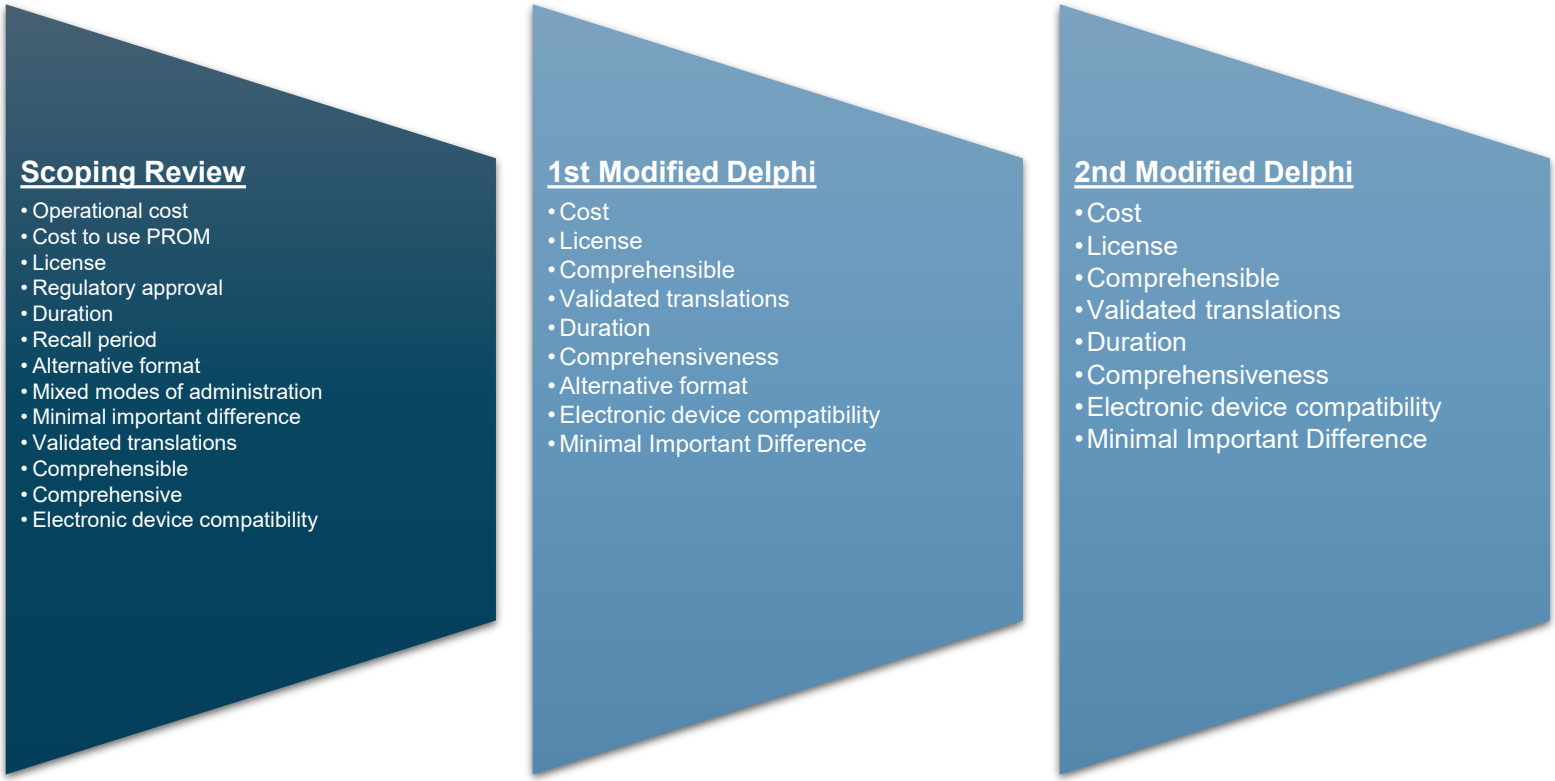
Two patient representatives from the ESC Patient Forum (J.D. and M.R.) were involved in the first stage modified Delphi meetings and one patient representative (T.W.) was involved in the second stage modified Delphi meetings. They provided feedback on all candidate items extracted from the steering committee and scoping review and emphasised the inclusion of patient comprehension and comprehensiveness of a PROM into the checklist. These two items achieved consensus.

8.5 Results

8.5.1 Steering committee

Following the scoping review, an initial list of 13 items was drafted by A.B (**Figure 8.3).** The steering group reviewed these and merged some items together to form a list of nine unique candidate. This list was used in the modified Delphi exercise.

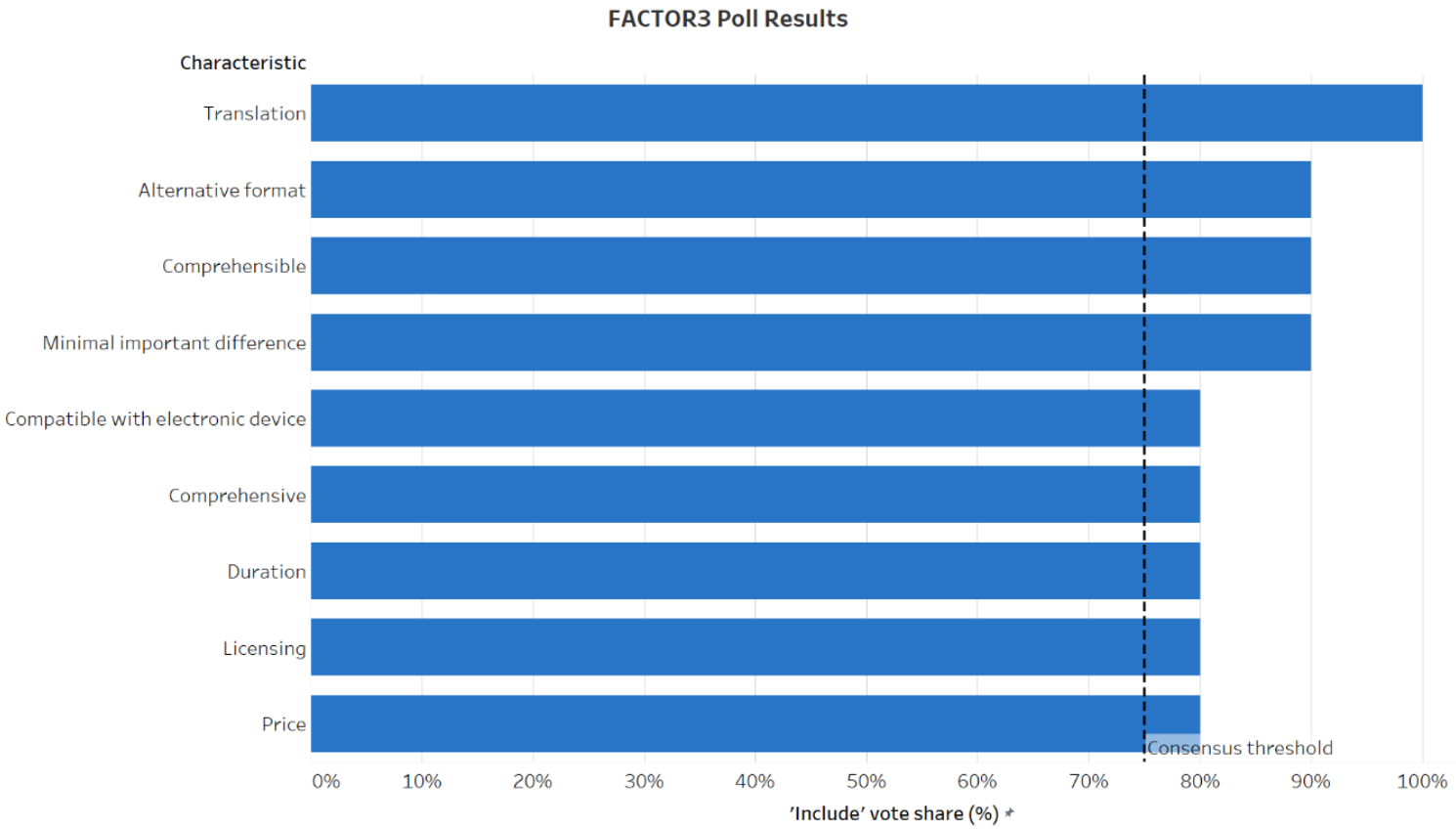
Figure 8.3. Evolution of FACTOR3 items



8.5.2 Design group

This consisted of five PROMs methodologists, one biostatistician, two health economists, four healthcare providers, and two patient representatives. All participants were from Europe (n=14, mostly the UK), and there were nine men and five women. A series of engagement and feedback meetings was held between 7th June 2024 and 10th June 2024, with subsequent voting on the nine items. The results were then presented and discussed among the design group during an online meeting held on 17th June 2024, and the design group voted to include all nine items. The distribution of votes is shown in **Figure 8.3.** There was detailed discussion about the ideal scope of the checklist, whether additional variables were required and whether there should be weighting of items to give more importance to some items over others.

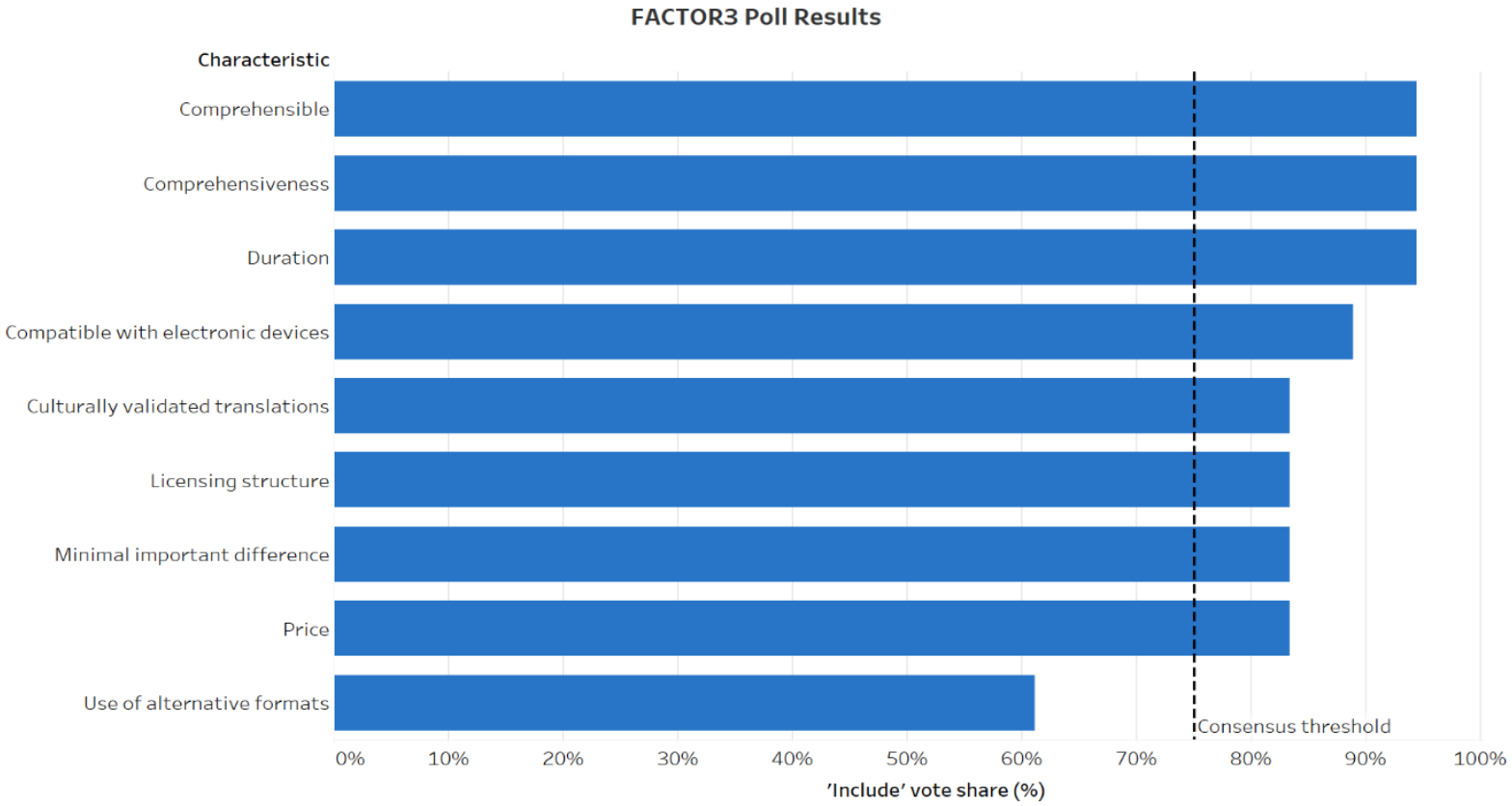
Figure 8.4. Voting distribution of 1st stage modified Delphi with the design group



8.5.3 Clinical domain group

The group included individuals with expertise in cardiology (n=4), ophthalmology (n=3), dermatology (n=3), orthopaedics and rheumatology (n=3), medical oncology (n=2), mental health (n=1), neurology (n=1), clinical epidemiology (n=1), urology (n=1), medical device regulatory affairs (n=1), and a patient representative (n=1). The experts were from Europe (n=12), North America (n=7) and Oceania (n=2) and comprised of fourteen men and seven women. Sequential meetings were held between 17th December 2024 and 6th February 2025 amongst the 21 experts from the clinical domain group. From the nine-candidate list of items derived from the scoping review and design group consensus, eight items were voted on to include into the FACTOR3 checklist. The distribution of votes is shown in **Figure 8.4.** There was consistent feedback over the scope of the checklist, refinement of the names of items and how to utilise the checklist in both trials and clinical practice which is reported below.

Figure 8.5. Voting distribution of 2nd stage modified Delphi with clinical domains group.



8.5.4 FACTOR3 checklist

The final feasibility items checklist (FACTOR3) includes eight items and are to be used in addition to the psychometric evaluation of a PROM. The checklist is provided in **Table 8.1.**

Table 8.1. FACTOR3 checklist table.

1. Is it free to use according to the intended context?
2. Is a license required?
3. Are the questions easily understood?
4. Does the duration of PROM align with the goal?
5. Does the PROM cover all necessary aspects of the disease (or regulatory approval for trials only)?
6. Are there culturally validated translations of the PROM in the desired language(s)?
7. Is the PROM compatible with electronic devices?
8. Does the PROM contain minimal important difference?

Yes answers equate to a score of 1 and No equates to 0.

8.5.4.1 Licensing structure that aligns with the goal

Often validated PROMs are subject to licensing arrangements that may vary according to intended use, such as routine clinical care, clinical registry use and industry and non-industry funded trials. Obtaining appropriate permissions to respect copyright, therefore, may be time consuming and possibly subject to prohibitive terms and conditions involving access to confidential patient data as highlighted by one of the panellists. Other panellists felt that the licensing structures alone was an important considerations that could influence the choice of PROM during the selection process.(126). Some panellists also cautioned against the use of unlicensed PROMs because it raised uncertainty over the origin of a questionnaire and the validity of the results. Unlicensed

PROMs are usually modified versions of existing PROMs to generate patient outcome data from conditions that lack any validated questionnaire. An advantage to adapting an existing PROM is it is a cheaper alternative for trialists compared with developing and validating a new PROM and therefore less burdensome.(438) However, any alterations need to be explicitly stated in the trial protocol and the questionnaire may require further validity testing to ensure any trial patient data generated is reliable.

8.5.4.2 Cost

This domain refers to both using a PROM and its operational cost. Linked to the licensing structure of a PROM is the cost of administering and managing it, in a variety of settings, which may impede its routine use. The cost of using the same PROM in different settings such as clinical registries or industry funded trial could differ significantly as mentioned by some of our panel members.

Operational costs that may be incurred involve implementing an electronic PROM into existing software of electronic health records. Also, obtaining a valid and culturally appropriate translation could incur costs and the panellists felt this may be a barrier for some organisations and therefore be considered when selecting a PROM.(401, 441)

Our panellists felt that the total cost of operationalising a PROM has a significant impact on selecting some PROMs over others and must feature in the FACTOR3 checklist.

8.5.4.3 Comprehensibility

Results from PROM data may be unreliable if patients refuse to complete the questionnaires because they do not understand the questions (leading to increased missingness of data) or, worse, answer whilst not fully comprehending the question. (442) Missingness of data refers to the proportion of patients that either do not complete the questionnaire or the healthcare providers do not collect the PROM results.(443) Missing data is related to the burden of completing the questionnaire (patient burden) and the burden of collecting and reporting the completed questionnaires (administrative burden). Interpreting overall PROM scores with significant amounts of missing data may be challenging as it may obscure the overall safety and efficacy of an

intervention and increase uncertainty over a hospital provider performance when used in clinical registries.(443, 444)

There are currently four mechanisms which explain missing data(445):

1) Missing completely at random – the probability of a missing data point that is unrelated to an observed and unobserved variable and occurs randomly.
2) Missing at random – the probability of a missing data point due to an observed variable after accounting for all known variables.
3) Not missing at random - the probability that a data point is missing depends on the value of the variable itself or of another unmeasured variable.(445)
4) Missing by design – the probability that the data point is missing due to the design of the study. This may involve randomly assigning participants to have missing items or measurement occasions in order to reduce participant burden and the cost of data collection. (446)

The problem of missing data is compounded if the PROM was developed with no or limited patient involvement to ensure patients of all backgrounds could understand the carefully crafted questions.(447) As mentioned in **section 1.4.5.1**. a significant proportion of PROMs were developed with limited or no patient input, therefore our panellists felt this was a prescient problem for trialists and healthcare providers alike.(447) Allowing the content of a PROM to be at a grade six (age 10 years) reading level can help ensure patient comprehension as literacy levels vary across the population, and this increases the likelihood of patients completing the questionnaire.(401) This is in line with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) consensus guidance on the principles of good practice for the translation and cultural adaptation of PROMs in 2005.(401) Although comprehension overlaps with content validity, and therefore assessed in qualitative assessments,(336) our patient representatives emphasised its inclusion over others. Similar to other items, our panellists recommended engaging with a patient group to review the comprehensibility of potential PROMs prior to their implementation.

8.5.4.4 Translated, validated and culturally adapted into the language of choice

Another way that PROM data could be unreliable is if there is no validated translation that are culturally adapted to provide equivalent meaning to the original PROM.(401) Ensuring PRO data is of high quality is a major concern for healthcare providers in major metropolitan cities that contain a culturally diverse patient population, for organisations that span multiple geographies such as EuroHeart or for trialists recruiting for large multinational trials.

The previously mentioned ISPOR guidance agreed that all proposed PROMs require cultural translations appropriate for the target population.(401, 448)

8.5.4.5 Duration

Longer PROMs are associated with low respondent rates in comparison to shorter ones, especially for patients who are ill, fatigue easily or have cognitive impairment.(143) A recent trial investigated the burden of completing questionnaires on patients and its predictors, and recruited 275 patients from a surgical clinic to complete a bespoke lengthy HRQoL PROM and interviews with the trialists evaluating response burden using the a different questionnaire.(449) Response rates were generally high but those patients with a reported low cognitive function were more likely to report a higher response burden (β = -0.20; t(270) = -3.38; P = 0.01; model-adjusted R^2 = 0.04), despite 31.6% of all patients indicated that additional questions should have been asked.(449) Importantly, other clinical and demographic characteristics were not predictors of a higher response burden and therefore missing data.

However, PROMS that are long and or take longer to complete can be important depending on the target population and objective of data collection objectives. Participants may be willing to complete lengthier measures if they understand why the data are being collected and how they will be used.(450) The panellists agreed that the choice of PROM should be considered against the duration of time it takes for completion as well as the organisation’s goal in using the PROM. Some panellists advised for a local patient and public group to be involved early in a project to determine if the PROM has a high respondent burden or not.

Another aspect of duration highlighted by some panel members was the recall period. The recall period refers to the time between the first questionnaire (usually at baseline before treatment) and the second (after treatment) and may influence respondent burden.(127, 450, 451) Having shorter recall periods may increase patient burden and not allow enough time for the intervention to make a noticeable change in health status.(127) Conversely, longer recall periods may improve respondent burden but patients may under or overestimate the intervention effect on their health status due to response shift as highlighted in **section 1.4.5.2**.(451) Patients require enough time to accurately recall changes in their health status without further strain and therefore decisions on the recall period depend on the target population characteristics.(451) Therefore our panellists felt it was an important consideration during the selection process of a PROM.

8.5.4.6 Comprehensiveness

This item had two considerations. The first was whether the PROM had regulatory approval to be used as an outcome measure in the targeted area of research. The panellists felt that regulatory approval was equally as important as having robust psychometric properties when conducting trials.

The second consideration was how well the PROM encapsulates the elements of the target disease according to the patients. Striking the balance between shorter questionnaires and adequate coverage that doesn't contribute to respondent burden was also raised. Comprehensive PROM coverage improves the reliability of responses by ensuring PROM data reflects the patient perspective entirely. (452) The experts stressed its inclusion despite some overlap with a questionnaires content validity (341) and therefore psychometric evaluation. The experts emphasised that the PROM should be validated in the target population.

8.5.4.7 Electronic device compatibility

Many healthcare organisations use electronic health records, and the ability to incorporate a PROM with its software or complete it by smartphone use is clearly advantageous. This increases response rates and allows questionnaires to be completed beyond the hospital visit.(453) Subsequent interpretation and

analysis of data is less burdensome than using paper records. The ability to implement an electronic questionnaire streamlined with existing healthcare systems that is appropriate and acceptable to licensed owners of the PROM was also a consideration. Some panellists felt that in some circumstances a PROM may be compatible with a smartphone app but not incorporated with healthcare records which may conversely increase administrative burden.

8.5.4.8 Minimal important difference

The MID provides a clinical context to the results of a PROM and is therefore meaningful to clinicians. It provides a measure of the smallest change in the PROM of interest that patients perceive as important, either beneficial or harmful, and that may potentially warrant a change in management.(144). A barrier to PROM implementation is negative clinician perspectives,(429) and the panellists felt that providing appropriate context to PROM results was, therefore, important.

8.5.5 Factors not included in the final checklist

One item that did not meet the voting threshold for inclusion in the final checklist was the availability of the PROM to be provided in an alternative format. Alternative PROM formats give a method of improving the reliability of responses. These include visual analogue scales of PROMs to improve comprehension and reduce respondent burden.(406) A recent trial investigated the comprehension of 40 hospitalised patients of the longitudinal PORMs scores using text only information, visual analogues and graphical representation of data. (406) Comprehension was the primary outcome and assessed by the International Organization for Standardization protocol. Overall understanding significantly improved with the visual analogues, then graphical representation and finally the text only information (83%, 70%, 63% respectively, [p = 0.05]).(406) Therefore visual analogue scales may be an alternative PROM format to improve patient comprehension and reduce respondent burden however it did not reach consensus.

Furthermore, a concern from focus group members was to ensure adequate support for all patient populations to complete an assessment such as, but not

limited to, patients with visual or hearing impairment and neurodivergent patients. This ensures underserved groups are appropriately represented in trials and registries and can avoid health disparities.(454)

8.5.6 Checklist evaluation

The agreed checklist was used by clinicians to evaluate a variety of PROMs. The results of each reviewer's assessment of the PROMs are in **Table 8.2**. The calculated ICC was 0.81 suggesting the checklist has good inter-rater reliability.

Table 8.2. Each reviewer's score for each PROM.

PROM	Reviewer 1	Reviewer 2	Reviewer 3
EQ5D-5L	8	8	8
Oxford Hip Score	8	8	8
Re-QOL-10	7	6	6
EORTC-QLQ-30	5	3	4
HeartQOL	5	5	5
NEI VFQ-25	7	4	5

8.5.7 How to use the FACTOR3 checklist

The FACTOR3 checklist evaluates the intrinsic feasibility characteristics of a questionnaire and can streamline the PROM selection process prior to implementation in research, regulatory affairs and routine clinical care. The PROTEUS guide remains an important document to consult that elaborates the current selection process; identifying all available questionnaires on a disease domain and evaluating their psychometric properties.(335, 418) We recommend

completing the FACTOR3 checklist early in the PROM selection process such as after the psychometric evaluation stage. This ensures that all important feasibility concerns are comprehensively addressed prior to implementation that aligns with the organisation’s goals.

These goals could differ depending on available resources, target population characteristics and context of care. For example, in research, comprehensiveness in terms of regulatory approval could matter more to an organisation than other items and help to decide which PROM to choose further on top of its qualitative assessment. Whereas other items such as price and licensing structure of a questionnaire for routine clinical care in a publicly funded institution may be paramount. Therefore, the Delphi panellists voted against weighting each item which allows the checklist to be flexible with any context.

8.6 Discussion

Using a modified Delphi approach that was inclusive of a scoping review, expert opinion and stakeholder involvement, we developed and evaluated the FACTOR3 feasibility item checklist for assessing the intrinsic implementation characteristics of PROMs in research, regulation and routine clinical care. FACTOR3 may be used in conjunction with existing psychometric evaluation,(336) regulatory guidance,(97, 104) ethical,(455) and protocol guidance,(418) PROTEUS trials and practice resources (335, 411, 456) and other user guides for PROMs – providing a comprehensive and complementary selection process for the contemporary selection of PROMs. FACTOR3 has eight components - price, licensing, comprehensibility, duration, translation, coverage, electronic device compatibility and minimal important difference that were informed by the literature and international experts and stakeholders in PROMs. Our evaluation of six PROMs (frequently employed in research and or clinical settings) against FACTOR3 criteria by three independent assessors found that the feasibility item checklist provided consistency in results.

The PROTEUS guide is a comprehensive manual that provide guidance on implementing PROMs in trials and clinical practice.(335) Given the proliferation of available validated PROMs (136), it recommends selecting an instrument that has robust psychometric properties that aligns with the organisation's goals,(335) informed by the COSMIN analysis (341). However, there are practical considerations for the efficient use of PROMs beyond an instrument's psychometric evaluation.(106) As such both the checklist and the PROTEUS guide highlight licensing and price as an important factor to consider after a psychometric evaluation has been completed. For example, the HeartQOL PROM was developed by the European Association of Preventative Cardiology that has robust psychometric properties and is validated in multiple languages across a range of cardiovascular diseases.(359) A license is required prior to use but there is considerable variation in price depending on its intended use and can amount to a significant amount for industry funded projects which can be prohibitive to some institutions.(457) When applying for research grants, an inclusive, proactive approach should be considered and costed appropriately.

Generating high quality patient-reported outcome data informs clinical care and the generalisability of trial results yet is affected by respondent burden of the target population. (125, 127, 143, 458) High levels of missing data or unreliable responses due to poor comprehension can lead to misinterpretation of results.(418) This can deepen health inequalities in poorly served populations partially due to feasibility concerns.(454) The lack of available valid translations and poor comprehension and digital literacy impacts underserved communities that are traditionally underrepresented in research and trials the most.(127, 459) Therefore the Delphi panellists felt that addressing respondent burden in more depth in a feasibility checklist was needed (which differs to the PROTEUS guide).(450) Maximising the response rates and its reliability needs to be catered to the diverse patient population that differs by socioeconomic status and literacy. (127, 460) PROMs that are available in electronic formats as well as the availability of pen and paper options may suit patients with poorer digital literacy who do not own an electronic device.(461) However, the use of electronic health records is widespread and the ability of a PROM to align with existing software may improve compliance, (453) provides a source for data collection and storage (462) and is some patients' preferred mode of completing questionnaires.(127) All these factors could be implemented without bias as a meta-analysis into mixed modes of administration of PROMs has shown.(463)

In clinical trials, PROMs scores alone can be challenging to interpret. With large enough sample sizes, differences in PROMs scores may be statistically significant but not meaningful to patients and therefore clinicians. (112). In contrast to the PROTEUS guide this checklist includes the MID, which is defined as the smallest change of interest that patients perceive as important, either beneficial or harmful, and that can guide clinical management.(144) The mean change in scores in each arm of a trial can be compared against the MID that informs whether the change in score is significant or not (145) and can particularly aid in the assessment of an intervention's safety and efficacy.(144)

To our knowledge, this checklist is the first to evaluate the intrinsic feasibility of implementing a PROM with broad applicability for clinical practice and trials. It provides a practical supplement to existing psychometric and quality assessments in the evaluation of prospective PROMs depending on the organisation's goals that is in line with regulatory requirements.(97, 104) We

identified a list of intrinsic feasibility items necessary for consideration prior to the selection and adoption of PROMs distilled from expert opinion using the Modified Delphi method. However, we recognise limitations of this work. We used a focused definition of feasibility whereas other more broad definitions exist such that evaluate the extent to which a PROM may be successfully carried out within a particular healthcare or research setting.(440) Furthermore to ascertain some aspects of feasibility (such as licensing and cost) require users to explore a diverse range of materials to clarify which may increase administrative burden initially.(126) Although the items were filtered from a scoping review, the final checklist was agreed upon by consensus of experts and is therefore subject to potential selection bias. Furthermore, the group of experts and stakeholders were chosen to be a representative sample but the sample size was small and completed in English only. However, the experts had broad expertise in PROMs use in clinical practice and trials and the stakeholder group consisted of major European regulators and patient representatives that shaped the discussion and provided further strength to our findings.

8.7 Conclusion

Informed by scoping review, and modified Delphi methods including PROMs methodologists, clinicians, patients and regulators, we have developed a checklist of implementation feasibility items that should be considered when selecting a PROM. We anticipate that the keys users and beneficiaries of FACTOR3 will be researchers conducting studies and writing papers, the health care sector when considering a PROM for routine use and assessment of clinical practice, and regulators for the evaluation the success of clinical outcomes in regulatory decision making. The checklist could have broad applicability and serves to act as a decision-making tool, in conjunction with existing psychometric assessments and user guides, for the selection of a PROM.

8.8 Summary

- There are additional feasibility factors intrinsic to a PROM beyond its psychometric properties that impede its routine use, but limited guidance exists in formally assessing these prior to implementation.
- Eight unique items were included in the FACTOR3 checklist through consensus of interdisciplinary international stakeholders including patients, PROMs methodologists, health economists, biostatisticians, trialists, PROM developers and clinicians. This was reviewed and agreed upon by the EMA and NICE.
- The FACTOR3 checklist is the first to formally evaluate the intrinsic feasibility characteristics of a PROM with broad applicability for clinical practice and trials.
- It may be used in conjunction with existing psychometric evaluation and user guides for PROMs – providing a comprehensive and complementary selection process for contemporary use of PROMs in routine care, regulatory affairs and research.

Chapter 9
Discussion

9.1 Introduction

Recent advances in interventional and medical CVD therapy and their integration into routine clinical care have resulted in large reductions in the age-standardised mortality rates across Europe since the 1980s.(5, 464) Despite the success of guideline indicated therapy, the prevalence of CVD continues to rise across Europe (1, 5) and it remains the leading cause of death in Europe accounting for over 4 million deaths each year.(5) The healthcare burden of CVD places a significant strain on healthcare expenditure amounting to over €280 billion lost each year,(15) and is forecasted to increase due to an aging population as mentioned in **section 1.1**.(5, 6) Recent surveys have demonstrated that recurrence rates for atherosclerotic cardiovascular disease, for example, is high and may account for up to 15% of admissions within the first year of an MI across select European countries,(465) suggesting that either existing therapies may not be fully implemented into clinical care or that chronic CVD still significantly impacts the HRQoL of patients.(465)

There is, therefore, a need to develop safe and effective therapies that aims to improve the morbidity, mortality and quality of life for patients impacted by their condition and that existing evidence-based therapies are fully integrated into clinical care across Europe. This is predicated on two fundamental aspects:

1) The appropriate selection of clearly defined standardised outcome measures that balances clinical relevance and importance to both healthcare providers and patients.
2) Integrating selected outcome measures within an existing international unified registry that allows for continuous feedback and therefore quality improvement across Europe.(8, 9)

The overarching aim of my MD thesis was to achieve such standardisation of both CROs and PROMs, termed the totality of outcomes, in patients with common CVD conditions within the EuroHeart project.(10)

Standardising CROs ensures that healthcare providers are more confident in the efficacy and safety of interventions from trials,(9) their conclusions are

easily understood and generalisable to other similar trials,(31) improve the reliability of meta-analyses and allow for the conduct of more pragmatic trial designs such as R-RCTs that span multiple geographies.(8) This has been mentioned in **section 1.3.**

However, tackling the healthcare burden of CVD is not limited to improving outcomes of value to trialists and healthcare providers alone but also includes outcomes important to patients such as quality of life, symptom burden and functional and mental wellbeing.(58, 281) Due to the aging population and improving mortality for common CVD, more patients are living with CVD in Europe and are therefore likely to experience more symptoms and decompensated episodes from CVD, **section 1.4.3**.(1, 5, 465) PROMs represent a more accurate and reliable tool to appraise quality of life, symptoms and functional health compared with clinician interpretation (12, 25, 73) and is advocated for use by patients, professional cardiology societies and regulators, **section 1.4.3.10**.(24, 25, 64, 76, 100) Standardising patient outcomes involves a contemporary qualitative assessment of all relevant PROMs that guarantees its validity in the target population, reliably detecting meaningful changes in health status and is an accurate representation of patients concerns.(58, 99, 107)

To achieve my overarching goal of standardisation, I employed the five-step EuroHeart approach to standardising CVD clinical data.(171) This is an established and methodological approach to harmonising multiple existing data definitions that is in continuity with previous EuroHeart projects in standardising in hospital clinical variables for the common CVD conditions.(167-170) **Figure 9.1**.

Figure 9.1 The circle of standardisation.

To facilitate this, I conducted a systematic review of CROs that CVD trials have employed over the past 11 years that were published in highly cited journals.(334) The systematic review into CROs, to my knowledge, is the first to be completed across the common CVD. The results have informed a modified Delphi exercise between international cardiology experts to select and define relevant CROs to include in a new outcome set for the common CVD and formally endorsed by patient representative groups such as the ESC Patient Forum and international clinical working groups and associations.(241) This differs to previous outcome sets as it is contemporary, involved patients in the design and endorsement of outcomes, and is designed to use in both trials and registries. This will ensure its smooth integration into clinical care. (148)

I have also completed a scoping review of all HRQoL PROMs in the common CVD that had a contemporary, comprehensive qualitative assessment using the COSMIN analysis. These results formed the basis of another modified Delphi exercise between trialists, healthcare providers, patients and PROMs experts to hierarchically rank each PROM according to their preference across the common CVD. This ranking is different to other CVD outcome sets that include PROMs as it uses a contemporary review to inform its process, include all HRQoL PROMs, offers one PROM to use for one condition thereby reducing

the administrative and patient burden and is endorsed by multiple international patient and clinical organisations. (151-153, 155)

A major barrier to integrating PROMs into trials, routine care and regulatory frameworks identified during this exercise was evaluating its feasibility. I then completed a scoping review into the feasibility of using PROMs with the results informing a modified Delphi exercise involving PROMs experts, healthcare providers, patients, PROMs developers and regulators. The subsequent consensus was an eight-item checklist, termed the FACTOR3 checklist, which evaluates the feasibility of integrating prospective PROMs into care during the selection process. To my knowledge, the FACTOR3 checklist is the first to formally assess a PROMs feasibility.

In the subsequent sections, I will present how my MD thesis addresses gaps in the literature, summarise the findings of each component of my MD and contextualise the results within the wider literature. I will then present the strengths and limitations of each project and then critically appraise the whole work. I will then suggest future directions for research before providing a conclusion.

9.2 Gaps that the MD addresses

Guided by the gaps identified in the systematic and scoping reviews in CROs and PROMs the objectives of my MD have been met which were:

1. To complete a contemporary systematic review of the CROs employed by trials across the common CVD published in highly cited journals.

2. To develop a catalogue of internationally derived, standardised and defined outcome measures for HF utilising a modified Delphi method.

3. To aid the development of internationally derived and defined outcome measures for ACS/PCI, AF, TAVI and generic CVD utilising a modified Delphi method.

4. To complete a scoping review of HRQoL PROMs in the common CVD that performed a contemporary, comprehensive qualitative assessment using the COSMIN analysis.

5. To develop a ranking of existing HRQoL PROMs across the common CVD using the results from the scoping review based on preference by patients and trialists using the modified Delphi method.

6. To develop an internationally derived checklist that evaluates the intrinsic barriers to implementing PROMs utilising a modified Delphi method and informed by a scoping review.

By addressing these objectives, my MD provides novel and important findings that aid study design and research methodology that may help allows for trial results to be easily interpreted and generalisable. Consequently, this may improve health outcomes for patients living with CVD. As part of EuroHeart, the standardisation of both CROs and PROMs is the first step to establishing a CVD outcomes registry that may better understand contemporary CVD patterns, highlight health inequalities and areas for improvement across Europe. (9, 31, 54) Furthermore, by providing a platform for observational research and international quality improvement this work may help to reduce the health and economic burden of CVD by building upon the success of national registries such as the National Institute for Cardiovascular Outcomes Research in the UK, internationally. (466)

9.3 Summary findings of my MD

This thesis presents my involvement in a number of projects to achieve the central aim of my thesis which is to standardise the selection and definitions of key clinician and patient reported outcome measures for the common CVD conditions. The key findings of each component will now be summarised.

9.3.1 Systematic review of cardiovascular outcomes

The systematic review included 386 articles for full text review that were published in highly cited journals (JAMA, NEJM and the Lancet) investigating the common CVD between 1st January 2013 and 6th June 2024. The main findings were split into two sections: one exploring the type of primary outcome employed by trials and its temporal trends and another exploring the consistency in the definitions of primary outcome measures.

The review found that, overall, the most frequently reported primary outcome across each CVD category was a composite followed by all-cause mortality and a PROM in RCTs. The components of the composite ranged between two and ten and the most common components, across all studies, were MI (142 studies, 58%) and all-cause mortality (125 studies, 51%). Composite use increased almost two-fold over the last decade. The distribution of the components of the composite varied significantly and according to their frequency of use. Furthermore, the employment of secondary outcome measures varied, with a high proportion of studies reporting them in heart rhythm, valvular heart disease and coronary heart disease studies and lower rates in cardiomyopathy studies.

When investigating the common CVD outcome definitions, the review found that all-cause mortality, stroke and bleeding definitions were employed more consistently across the included trials. However, there were inconsistent outcome definitions for both CV mortality and MI. Over a third of studies, did not provide definitions for CV mortality (34%) and a minority for MI (17%) either in the trial protocol or manuscript. For studies employing CV mortality as an outcome measure only half (51%) gave a full definition that was aligned with a consensus definition (47%, 24% of total with the SCTI definitions in 2018 and 53%, 27% of total with others). For studies employing MI as an outcome

measure, most gave a clear definition that aligned with either the Third or Fourth Universal Definition of MI (63%).

The systematic review of CROs, to my knowledge, is the first to provide evidence of the heterogeneity in both the selection and definition of major CROs such as CV mortality and MI, expansion in the number of secondary outcomes employed and inconsistently classified and defined primary outcome composite measures such as MACE across the common CVD conditions published in highly-cited medical journals.

9.3.2 Standardising heart failure outcomes

The results of the systematic review formed the foundation to identify and define a catalogue of hierarchically classified standardised heart failure outcomes and their definitions that is internationally derived for use in both trials and registries.

By following the EuroHeart method for the development of CVD data standards,(171) we formed a WG consisting of 42 international heart failure experts that were mostly representatives from the HFA and 15 ESC WGs spanning 16 countries across Europe and North America. The HF WG reviewed 18 candidate variables and participated in a modified Delphi process to reach consensus over the selection and definitions of key HF outcome measures as either Level 1 (mandatory to include), optional (Level 2) within EuroHeart or to exclude.

The HF WG voted on the following Level 1 outcomes to be included; capture of left ventricular EF as a percentage. Where this is not possible, the category reported should be according to ESC guidance,(258) ii) all-cause hospitalisation, iii) HF hospitalisation, iv) implantation of left ventricular assist device and v) heart transplantation.

The Level 2 outcomes to be included were: device implantation and resuscitated ventricular arrhythmia. The WG proposed complementary heart failure outcomes in addition to the Level 1 and Level 2 HF outcome measures. These were: i) concurrent presence of AF; ii) NT-proBNP; iii) eGFR; iv) change in left ventricular EF and v) NYHA class.

9.3.3 Standardising cardiovascular outcomes for the common CVD

The standardisation of heart failure outcome measures was part of an overall project to harmonise important existing outcome measures and their definitions for ACS/PCI, AF, HF, TAVI and generic CVD (defined as those outcomes with potential applicability to all patients with CVD). We followed the five step EuroHeart process for data standard standardisation of which the systematic review of CROs formed the first step.(171)

We formed the Global Cardiovascular Outcomes Consortium that consisted of 82 international clinical and academic experts from each ESC working groups and associations or external experts independently approached due to their expertise. From the consortium we established five WGs to correspond with each condition with some experts participating in more than one group. The WG members voted on outcomes distilled from the systematic review in a modified Delphi process to be included as either Level 1, Level 2 or excluded.

For the generic domain, five outcomes were selected and defined for Level 1: all-cause mortality, cardiovascular mortality, MI, stroke, and new-onset HF. Agreed Level 2 outcome were: transient ischaemic attack, worsening HF, cardiogenic shock, mechanical circulatory support, heart transplant, bleeding events, device implantation, ICD therapy delivery, systemic embolism, pulmonary embolism, deep vein thrombosis, cardiac arrest, hospitalised ventricular tachycardia, newly diagnosed AF, all-cause re-hospitalisation, cause-specific hospitalisation, unplanned cardiac surgery, acute kidney injury.

For the ACS/PCI domain, eight Level 1 outcomes were selected: major bleeding event, acute kidney injury requiring renal replacement therapy, target vessel-related MI, unplanned target-vessel PCI, unplanned target-vessel CABG, target lesion stent thrombosis, HF hospitalisation, cardiac arrest. Agreed Level 2 outcomes were: minor bleeding event, vascular access complication, left ventricular EF, CCS class, cardiovascular hospitalisation, hospitalisation with unstable angina, attendance at cardiac rehabilitation.

For the AF domain, two Level 1 outcomes were selected: cardiovascular hospitalisation, and catheter ablation and the agreed Level 2 outcomes were implantable monitoring device, device implantation, recurrence of AF, burden of AF, all-cause hospitalisation and cardioversion.

For the TAVI domain, four Level 1 outcomes were selected: NYHA class, aortic regurgitation, device implantation, re-intervention on the aortic valve. The agreed Level 2 outcomes were: access-related non-vascular complications, endocarditis, cardiogenic shock, cardiac arrest, serum creatinine, CCS class, left ventricular EF, residual AS, other transcatheter heart valve procedure, CABG, PCI, all-cause rehospitalisation, new renal replacement therapy, new AF or atrial flutter, sternotomy or thoracotomy due to bleeding.

9.3.4 Scoping review of health-related quality of life PROMs

The scoping review into HRQoL PROMs included 220 articles that appraised 38 different PROMs for full text review that were developed or validated in the common CVD (IHD, AF, HF, AS and generic), from inception to 8th February 2025 using PubMed, Web of Science, CINAHL and Embase databases. The psychometric properties of all 38 PROMs (HF n = 17, 45%; AF n = 11, 29%; IHD n = 7, 18%; generic n = 2, 5%; AS n=1, 3%) and their validation articles were comprehensively evaluated in accordance with the nine-COSMIN criteria by two independent PROMs methodologists.(108) This includes: content validity, reliability, internal consistency, structural validity, criterion/convergent, cross-cultural validity, measurement error, hypothesis testing and responsiveness. Each PROMs overall suitability for use within routine clinical care was marked using the GRADE approach.(344)

We found that HRQoL PROMs for the common CVD vary in their psychometric properties; most require further validation studies prior to use, particularly for cross-cultural validity, measurement error and responsiveness. Overall, less than a third of all HRQoL PROMs in the common CVD met all nine COSMIN criteria and would be suitable to recommend for routine clinical care (11 PROMs; 29%). Whereas most required further validation work in cross cultural validity, measurement error and responsiveness prior to routine use within clinical care and research (n= 19, 50%) but eight PROMs were deemed inadequate for clinical use (21%).

Most of the HRQoL PROMs that met all nine COSMIN criteria were validated for HF (6 instruments, 55%), then IHD (4 instruments, 36%), and a minority were

validated for AF (1 instrument, 9%). Only one PROM was specifically designed to assess HRQoL for AS, and it did not meet all nine COSMIN criteria and required further validation work prior to using within routine clinical care.

9.3.5 Ranking PROMs across the common CVD

The completed scoping review and contemporary psychometric evaluation of all HRQoL PROMs formed the first step to standardise the selection of PROMs in the common CVD. Similar to the process for CDOs, we followed the EuroHeart method of standardisation that involved invited members to rank, in a modified Delphi process, on which PROMs would be most preferred to use in each disease domain. We approached the Global Cardiovascular Outcomes Consortium members as well CVD patient representatives from the ESC Patient Forum and other patient groups, external PROMs methodologists and academics with expertise with PROMs to contribute that amounted to 94 experts voting. We formed five WGs that mirrored the disease domains with some experts and patients voting in more than one domain. The Working Groups ranked their preference of each PROM using a Likert scale of 0 – 5 and for select domains (ACS/PCI, TAVI and generic) they voted on additional questions.

For the ACS/PCI domain, the CROQ was ranked highest with 3.9 out of 5, the 12 item KCCQ was ranked highest with 4.5 points for HF, TASQ with 3.0 points for TAVI, both AF Impact and AFEQT 3.9 points for AF and both the EQ5D and SF-36 questionnaires with 3.5 points for generic domain. Consistent feedback from each of the five WGs highlighted some PROMs may be more easily implemented over others due to intrinsic factors such as price of obtaining the questionnaire, availability of appropriate translations (for non-English speaking patients internationally) and duration. By not excluding any PROM from the ranking it allows international institutions to select other PROMs that are not highly ranked as they be more easily implemented than the preferred PROM.

9.3.6 Formation of the FACTOR3 checklist

Following the WGs comments I set out to develop a feasibility checklist that assesses the implementation characteristics of a PROM that could be used in

conjunction with psychometric analyses to aid the selection of the most appropriate PROM for research, routine care and regulatory affairs. Feasibility was defined as the intrinsic characteristics of a PROM that allows ease of implementation.(440)

I followed a five-step modified Delphi process, informed by a scoping literature review, to achieving a consensus amongst experts over which items to include in the checklist. Step 1 involved using a pre-defined search strategy to screen all prospective and retrospective articles and grey literature (335, 411, 418) assessing the feasibility of PROM implementation from inception to 6th March 2024. PubMed was searched and only articles published in English were screened and I identified 13 possible candidate items for inclusion which were condensed into 9 unique items.

I thereafter formed the design group to conduct round 1 of the modified Delphi to either include or exclude the 9 candidate items. The design group consisted of five PROMs methodologists, one biostatistician, two health economists, four healthcare providers, and two patient representatives. I conducted a series of meetings with the design group between 7th June 2024 and 10th June 2024, with subsequent voting on the nine items. The results were presented to representatives from international regulatory bodies such as NICE and the EMA and their feedback was sought.

I then formed the clinical domains group which consisted mainly of healthcare providers with expertise in cardiology (n=4), ophthalmology (n=3), dermatology (n=3), orthopaedics and rheumatology (n=3), medical oncology (n=2), mental health (n=1), neurology (n=1), clinical epidemiology (n=1), urology (n=1), medical device regulatory affairs (n=1), and a patient representative (n=1; total 21 members). A round 2 modified Delphi was conducted between 17th December 2024 and 6th February 2025 to vote on the checklist.

The final stage involved evaluating the feasibility of six commonly used questionnaires (EQ5D-5L, HeartQOL, the Oxford Hip Score, The EORTC Core Questionnaire QLQ-C30, Re-QOL-10 and NEI-VFQ-25) by 3 independent reviewers. The presence of each item of the feasibility item checklist was assigned a score of 1 and the overall score was recorded. Each reviewer's overall score for each PROM was evaluated using the ICC.

The final FACTOR3 checklist, condensed from a scoping review and two rounds of modified Delphi voting from a multi-disciplinary team of experts that had expertise within PROMs, identified eight unique candidate items to be included. These were: price; licensing, comprehensibility, duration, coverage, translations, electronic device compatibility; and minimal important difference. The ICC of the independent reviewer's evaluation of the six well known PROMs was 0.81 suggesting good reliability. The FACTOR3 is a feasibility item checklist to assess the implementation characteristics of PROMs in research, regulation and routine clinical care. It may be used in conjunction with existing psychometric evaluation and user guides for PROMS to facilitate their use in health care.

9.4 Findings in context of the literature

Standardising outcome measures that is utilised in a CVD outcomes registry provides the platform for observational studies that accurately portrays the variation in management and outcomes of common CVD conditions such as STEMI and NSTEMI.(166) Once accurately demonstrated it may be the basis for international quality improvement which may improve outcomes.(31)

For example, previous studies have highlighted significant variations in the standards of care for MI patients in select European countries.(17, 467) Each respective national registry had high case coverage and prospective data registration for MI patients which differs from previous MI observational studies across Europe.(468, 469) All patients admitted with STEMI between 2014-2017 were captured and their baseline characteristics, in hospital treatments and outcomes such as 1-year mortality were described.(467) Rates of modifiable risk factors such as smoking and hypertension significantly differed between countries ranging from 25.1% in Sweden to 38.0% in Norway for smoking and 39.2% in Norway to 78.6% in Estonia for hypertension, respectively.(467) In hospital treatments such as primary PCI ranged from 63.4% in Estonia to 80.6% in Hungary with 1-year mortality ranging from 21.1% in Estonia to 14.8% in Sweden.(467) High rates of modifiable risk factors and the variability of in-hospital treatments could partially explain the disparity in 1-year mortality rates. Furthermore, the variation in baseline characteristics for STEMI patients

highlights the need for efficient and tailored secondary prevention that is unique for each country. For example, smoking cessation clearly could be a national priority for Norway whereas aggressive treatment for hypertension may be prioritised in Estonia which could lower the CVD burden. However, a major limitation to these studies is the heterogeneous case variable definitions.(17, 467) Despite consistent definitions for most in-hospital and outcome definitions, the definitions for hypertension and hyperlipidaemia varied between countries **Table 9.1**.

Table 9.1. Comparison of select case definitions

	Case Variable	
National Registry	**Hypertension**	**Hyperlipidaemia**
Estonia MI registry	The person has been diagnosed with or treated for hypertension. Including when the person knows that he/she has hypertension but has not been taking any medicine for it	The patient has been diagnosed with or treated for hyperlipidaemia. Including when hyperlipidaemia is diagnosed during the current episode. The criteria are the following: total chol >4.5; LDL-C >2.5; HDL-C <1.0 for men and <1.2 for women; Trigl > 1,7 mmol/.
Hungarian MI registry	The person has been diagnosed with or treated for hypertension. Including when the person knows that he/she has hypertension but has not been taking any medicine for it	Documented abnormal lipid levels and/or the patient is taking lipid-lowering medication. Treatment: statin, ezetimibe, both, other
Norway MI Registry	Person is treated for hypertension	Patient is treated for hyperlipidaemia
SWEDEHEART	The person has been diagnosed with or treated for hypertension. Including when the person knows that he/she has hypertension but has not been taking any medicine for it	The person has been diagnosed with or treated for hyperlipidaemia. Including when the person knows that he/she has hyperlipidaemia but has not been taking any medicine for it

Adapted from (467)

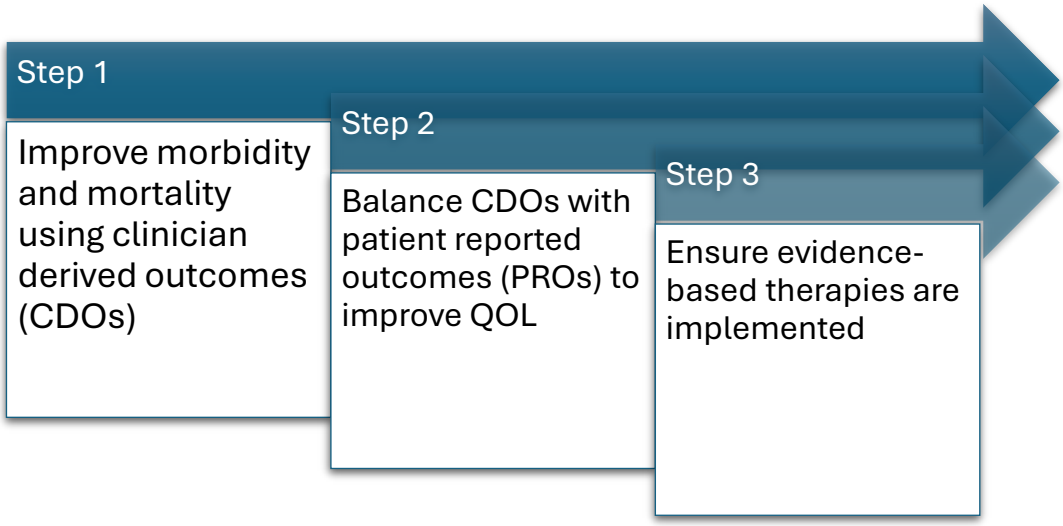
Therefore, some countries could underreport key baseline characteristics (such as Norway) whereas others may overreport (Hungary) thus hindering international comparisons and impede quality improvement.

With the standardisation of outcome definitions within EuroHeart, there is a potential to accurately portray contemporary standards of care for ACS (and other common CVD conditions), uncover health inequalities and feedback the results to each respective country to engage in quality improvement.(166) Recently, EuroHeart has published a cohort profile describing the STEMI admissions of seven vanguard countries including Estonia, Hungary and Sweden in 2022 with further updates anticipated soon.(166)

Standardising both CROs and PROMs is the first step to establishing a CVD outcomes registry across Europe that incorporates both CROs and PROMs may help to achieve a more patient centred approach to trial design (9) and provide a healthcare that balances outcomes of value to clinicians and patients alike.(10)

The rates of age standardised mortality for CVD has declined in recent years,(470) and establishing a CV outcomes registry to monitor and implement existing therapies for the common CVD conditions may contribute to reducing the significant health burden of CVD.(8) However, another explanation may be that current trials are too focused on ‘traditional’ outcomes that offer marginal gains over other emerging outcomes such as PROMs.(465) It may be that improving outcomes further involves a more holistic approach to CVD patients outside a coronary artery for example **Figure 9.2.**

Figure 9.2. Sequential manner of outcome utilisation.



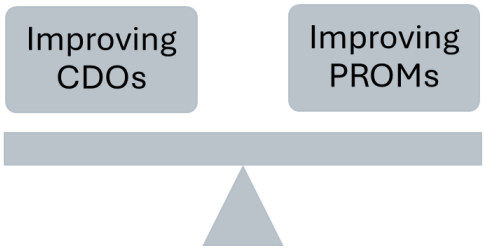
A contemporary example of a trial focusing on traditional outcomes is an RCT comparing catheter ablation to directed lifestyle modification (directed weight loss and physical exercise) with anti-arrhythmic drug treatment in patients who have paroxysmal AF and are obese.(471) The primary outcome was freedom of AF at 12 months but the secondary outcomes involved cardio-metabolic markers such as glycated haemoglobin (HbA1C), peak VO2 max, quality of life metrics using the AFEQT PROM scores. In the catheter ablation group, the percentage of patients with AF freedom at 12 months was 73.0% (95% CI: 64.3%-81.7%) and 34.6% (95% CI: 25.3%-43.9%) in the lifestyle modification group. The changes met statistical superiority for those that received catheter ablation (p = <0.001) and the authors concluded that patients with paroxysmal AF and a catheter ablation were more likely to be free from AF than patients with intensive lifestyle modifications alongside anti-arrhythmic therapy.(471) However, the between group differences demonstrated that HbA1C levels were significantly lower in the conservative arm (between group differences, 95% CI: 3.9 [1.4-6.3]; p < 0.001), peak VO2 was significantly higher in the conservative arm (+1.14 ± 3.90 mL/min per kg; *P* = 0.028) and overall quality of life, as assessed by AFEQT, was similar between both groups at follow-up.(471) Hence, freedom from AF appears to be less important when quality of life is not significantly altered and is accompanied by worsening cardiometabolic outcomes. One could argue that, paradoxically for patients with obesity and

paroxysmal AF, lifestyle interventions such as directed weight loss and physical exercise impact a patient's overall prognosis more than catheter ablation with regards to long term outcomes (as assessed by VO2 max and HbA1C levels) and offers similar impact in overall quality of life.

Conversely, focusing on increasing HRQoL without improving CROs can mislead conclusions over a treatment's efficacy. In the 'Transcatheter Valve Replacement in Severe Tricuspid Regurgitation' trial, 400 patients with severe tricuspid regurgitation were randomised to receive undergo either transcatheter tricuspid-valve replacement and medical therapy (valve replacement group) or medical therapy alone (control group).(472) The primary outcome was a hierarchical composite of all-cause mortality, right ventricular assist device or heart transplantation, tricuspid-valve intervention severity, heart failure hospitalisation, change in KCCQ score, NYHA and 6-minute walk distance. After one year follow up the win ratio overall favoured the valve replacement (2.02; 95% CI, 1.56 to 2.62; P<0.001). (472) However the overall positive findings were driven mainly by improving symptoms (NYHA 10.2% vs. 0.8%) and overall quality of life (KCCQ 23.1% vs. 6.0%) score over more objective markers. Although the valve replacement group had slightly more wins than the control with respect to all-cause mortality (14.8% vs 12.5%) and the six minute walk distance (1.1% vs 0.9%), the valve replacement group worsening heart failure hospitalisation (9.7% vs 10.0%), more bleeding (15.4% vs 5.3%; p=0.003) and required more permanent PPM insertion (17.4% vs 2.3%; p<0.001).

As a preliminary trial into the emerging field of transcatheter tricuspid valve intervention the results are encouraging however balancing improvements in quality of life with reciprocal changes in CROs are needed prior to widespread implementation to effectively tackle the health and economic burden of tricuspid valve disease for example **Figure 9.3**.

Figure 9.3. Balancing PROMs with CROs in step 2.



9.5 Implications of the MD

Creating an international unified CVD outcomes registry that employs the standardised CRO and PROM outcome sets is possible. Recently, EuroHeart has established a collaboration of European national registries for continuous prospective data collection for hospitalised patients with STEMI and non ST elevation MI (NSTEMI).(166, 170) The operational ACS/PCI registry initially involved seven vanguard countries within the EuroHeart network which were: Estonia, Hungary, Iceland, Portugal, Romania, Singapore, and Sweden.(166) Individual patient level data was recorded, collected and aligned with the previously published EuroHeart data standards for hospitalised patients with ACS, by participating countries.(170) After performing statistical analyses on the data each country would subsequently transfer anonymised aggregated data to the DSG for international reporting.

Between 1st January 2022 and 31st December 2022 EuroHeart captured and recorded 40 021 admissions (STEMI 46.7%, NSTEMI 53.3%) from a total of 192 hospitals across the participating countries.(166) The average age for the cohort was 67.9 (standard deviation 12.6) years, and it included 12 628 (31.6%) women.(166) Further publications describing the contemporary provision of care in more granularity for patients admitted with ACS across Europe is expected soon. But the previously published cohort profile provides a platform for quality improvement and registry-based trials.

This is predicated on the publications of each project and there are plans in place to disseminate the findings of each of the MD's projects. The systematic review into cardiovascular outcomes has been published in Heart,(334) and the

EuroHeart standardisation and hierarchical grading of HF outcomes and other CROs have all been published in the European Heart Journal Quality Clinical Care and Outcomes and the European Heart Journal respectively.(240, 241) Three manuscripts on the scoping review into HRQoL CVD PROMs and their psychometric analysis, the EuroHeart ranking of all HRQoL CVD PROMs and the development and formation of the FACTOR3 checklist have been prepared and submitted to various journals and awaiting reviewer comments.

9.6 Limitations to the MD

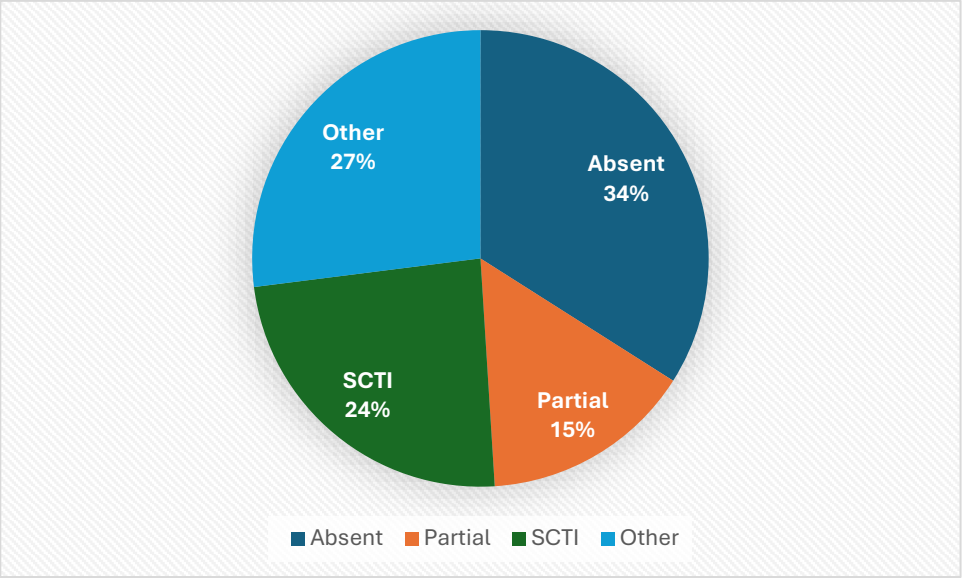
Specific limitations for each project within the MD has been addressed briefly within the main body of the thesis. However, in this section I will address some limitations to the MD in general.

9.6.1 Is lack of transparency the central problem?

As mentioned in **Chapter 3,** one aim of the cardiovascular outcomes systematic review was to evaluate if CROs employed by contemporary trials published in practice changing journals utilise inconsistent definitions for commonly used CROs such as MI across commonly occurring CVD conditions. Part of the results evaluated the five of the commonly employed outcome measures across trials, all-cause mortality, CV mortality, MI, stroke and bleeding.

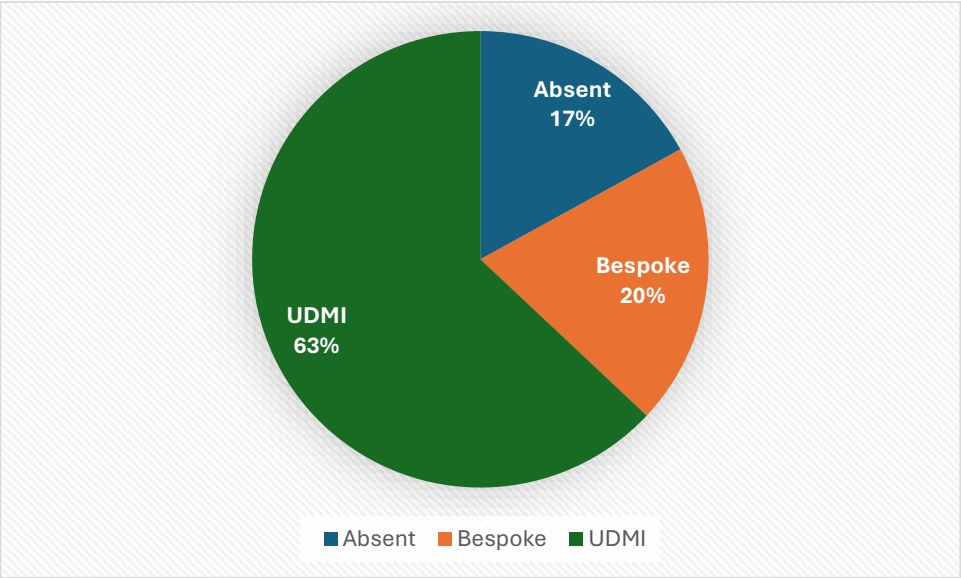
As previously stated in **section 3.5**., these outcome definitions were heterogenous however there is also a lack of transparency in reporting some outcome definitions by some trials. As demonstrated in **Figure 9.4 and Figure 9.5.**

Figure 9.4. Distribution of CVD mortality definitions identified from the systematic review.



Abbreviations: ***SCTI****: Standardized data collection for Cardiovascular Trials Initiative*

Figure 9.5. Distribution of MI definitions identified from the systematic review.



Abbreviations: ***UDMI:*** *Universal Definition of Myocardial Infarction*

When evaluating these five outcome measures, a definition is mostly provided (51% for CV mortality, 83% for MI, 86% for CVA, 100% for bleeding) albeit in a largely varied manner. **Figure 9.4, Figure 9.5, Figure 9.6 and Figure 9.7.**

Figure 9.6. Distribution of stroke definitions identified in the systematic review.

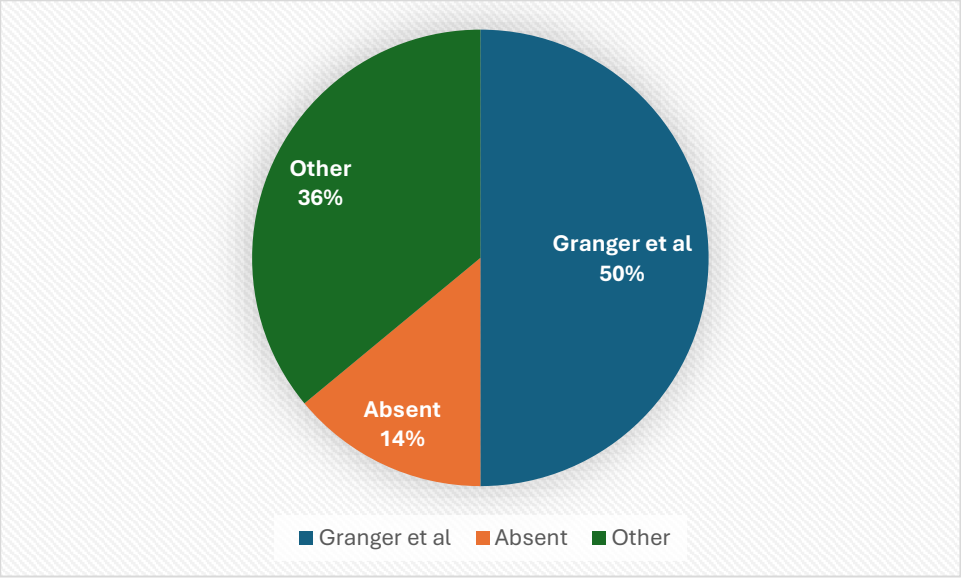
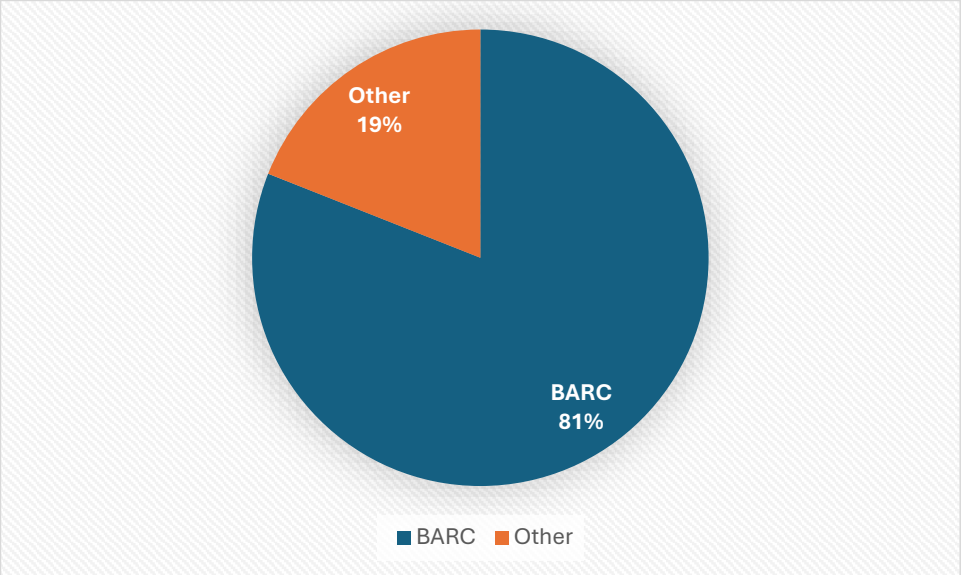


Figure 9.7. Distribution of bleeding definitions identified in the systematic review.



Abbreviations: ***BARC:*** *Bleeding Academic Research Consortium*

However, a further conclusion from the review may be the distinct lack of outcome definitions provided by major trials published in high profile journals. Particularly for CV mortality where almost half of definitions were either absent or partially defined (49%), one may argue that not reporting an outcome's definition clearly could lead to more misleading conclusions over a treatment's safety and efficacy than transparently reported alternative definitions.

This problem may be compounded if such absent definitions form part of a composite that was positive overall. For example, in the ‘Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease (CLARIFY)’ study, 22 672 patients were enrolled to observe the association between blood pressure and cardiovascular outcomes in patients with coronary artery disease and hypertension.(213) CV mortality, alongside MI and stroke, formed the primary outcome composite measure and after a median follow up of 5 years, systolic blood pressure higher than 140mmHg and lower than 120mmHg was associated with increased risk of the composite outcome measure (adjusted HR 1.56, 95% CI 1.36–1.81).(213) The incidence of each component of the composite outcome measure after a 5 year follow up was 1209 (5.3%) for CV mortality, 827 (3.6%) for MI and 526 (2.3%) for stroke patients, respectively.(213) However, CV mortality was not defined especially as the incidence rate was higher than other components and patients were enrolled from 45 countries as part of an international registry. Previous studies have proffered contradictory results by suggesting a potential benefit in reducing systolic blood pressure below 120mmHg.(473, 474) Hence, explaining CLARIFY’s results and how they differ from previous studies on defining the optimum blood pressure range becomes more difficult due to the absence of a definition given rather than using an alternative consensus definition. This problem has been identified in other specialties, such as dermatology, where a recent review found that up to two thirds of primary outcomes were given partial and incomplete definitions. (475)

To this end, the CONSORT statement was established to improve and enhance the quality and transparency of outcome reporting by recommending a minimum set of items to be included in a report of a trial by way of a checklist.(23) The CONSORT checklist was recently updated to include the rationale behind the primary outcome selection and whether their definitions were in alignment with a pre-defined core outcome set (COS) within the methods section of a trial.(23) It explicitly mentions, ‘*All outcomes, whether primary or secondary, should be described and completely defined’ as it allows for reproducibility of results*.’(23, 476) The major problem that CONSORT attempts to tackle here is the lack of

definition given to primary outcomes rather than transparently reported heterogenous outcomes.

9.6.2 The solution to heterogeneity is not more heterogeneity

The need to standardise outcome reporting in trials is well recognised and the 'Core Outcome Measures for Effectiveness Trials' (COMET) is an initiative established in 2010 that aims to develop, disseminate and collect COS in a database for a variety of health conditions.(477) By 2018, however, 364 outcome sets had been developed and registered on COMET for a variety of health conditions.(478) Therefore there is a danger that developing multiple standardised outcome sets without ensuring their uptake could in fact perpetuate heterogeneity rather than offer a solution.

As mentioned in **section 3.5**. there is significant heterogeneity in outcome definitions for the major CROs published in highly cited journals for CVD **Figure 9.4, Figure 9.5, Figure 9.6 and Figure 9.7.** To date, there are three international organisations that offer multiple consensus definitions for the majority of CROs in common CVD; ARC, SCTI, ICHOM.(51, 146, 148, 150, 289). Recently, *Beerman et al* performed a systematic review evaluating the COS uptake before 2015 and ICHOM's CAD COS uptake since its publication in 2015 in phase 3 or 4 RCTs registered on ClinicalTrials.gov from 2020 to 2023.(150, 314) The review found that pre 2015, relatively few trials adhered to an outcome set (11.5%) and since the ICHOM publication there was an increase in the mean percentage of COS-defined outcomes over time (0.1% per month) that was not statistically significant ($p = 0.12$, 95% CI = [− 0.02, 0.16]).(314) One explanation for this discrepancy was that ICHOM's CAD COS was too broad by encompassing angina, incident CAD as well as ACS. However, an alternative conclusion may be that the proliferation of COS in CVD may hinder standardisation.

To clarify if broad outcome sets impact implementation, *Duncan et al* performed a systematic review evaluating the uptake of the ESC's cardiology audit and registration data standards (CARDS) for PCI, in particular, that was published in 2018.(479, 480) Similar to the previous review,(314) data standards uptake in

PCI was low but increased marginally after the publication of the CARDS data standards (40% before CARDS to 55% after its availability, p=0.121).(480) Notably, the level of variability in outcome reporting is reduced after the publication of a well-known COS but still persists.(480) This suggests that implementing a narrowly defined COS helps implementation but developing another COS is not entirely the solution to heterogeneity in of itself. This mirrors the results of our systematic review on CROs in **Chapter 3**. A systematic review into the uptake of COS in the other common CVD has not, to my knowledge, been performed.

There are notable barriers to implementing a COS such as the lack of PPI involvement, trialists having their own preferences for COS reporting and lack of awareness from trialists for some COS.(314, 480, 481) For example, a recent survey of trialists' perceptions and knowledge of COS in their respective field.(481) The main barriers to COS implementation identified were poor knowledge about COS (69%) and difficulties identifying relevant COS (68%).(481) Whereas characteristics that trialists preferred in COS were clear understanding of what the COS entailed (82%) and perceived hierarchical importance of outcomes in the COS (71%).(481) It may be that to improve heterogeneity in outcome selection and definitions, one may attempt to improve awareness amongst trialists.

9.6.3 Marketing EuroHeart's outcome sets

The addition of another COS by EuroHeart may not encounter the same issues as previous COS. There was clear PPI involvement in each process, recruitment of multiple trialists from various international affiliated organisations (therefore increased awareness) and the presence of a unified international registry that has begun to prospectively collect patients admitted with ACS across the vanguard countries and is expected to form other registries for the other CVD.(166, 241) Furthermore a hallmark feature of the EuroHeart COS were hierarchical grading of outcomes according to the perceptions of relevant stakeholders which increases the likelihood of its dissemination into clinical practice.(240, 241)

However, as mentioned in **Section 9.6.1** and **9.6.2**, the CONSORT statement is a widely used checklist to appraises key elements in the conduct and design related to the internal and external validity for trials.(23) On selecting outcomes the CONSORT checklist encourages readers to refer to the COMET database for a list of standardised and clearly defined COS across many health conditions.(23, 477) Not collaborating with COMET or CONSORT represents a missed opportunity to increase the visibility and awareness of EuroHeart's COS in trials conducted by organisations outside of ESC affiliated ones. Moreover, previous EuroHeart projects have been designed and conducted to reflect contemporary ESC clinical practice guidelines and therefore applicable for widespread use for European healthcare systems and trials. (167-170) Marketing solely for a European context may exclude implementation and uptake in trials originating outside of Europe. As **Chapter 3** demonstrated a large proportion of studies published in highly cited journals recruit patients from North America (67%).(334)

A further missed opportunity includes not collaborating with major international regulators such as the EMA and FDA. One way to incorporate the regulators could be to obtain their feedback during stage 4 of the EuroHeart process, as a reference group. (171) As mentioned in **Chapter 8,** one advantage of our work in developing the FACTOR3 checklist was critical feedback from regulators but also increased awareness of an upcoming checklist. Trials utilising standardised and clearly defined outcomes provide important evidence for benefit versus risks assessments conducted by regulators by evaluating the safety and efficacy of an intervention.(98) One advantage of the SCTI outcomes was their collaboration with the FDA which maximises the visibility and awareness of the COS.(146)

9.6.4 PROMs ranking: Too much too soon?

Clinical registries are central in monitoring contemporary CVD care and may be used in quality improvement projects to improve clinical care and outcomes for CVD patients.(469, 482, 483) Yet current national registries, such as NICOR, are restricted to monitoring short term outcomes of interest to clinicians (such as in hospital baseline characteristics) and processes of care.(466) While

monitoring these are necessary there is a propensity for such registries to lack granularity over longer term outcomes (such as 1 or 5 year all cause mortality) and longitudinal outcomes such as PROMs (and HRQoL metrics) which provides a more holistic and comprehensive overview of contemporary CVD care.(76, 150) With the advent of electronic health record data and the rising popularity of PROMs, establishing an international unified CVD outcomes registry that incorporates PROMs may be possible.(8, 241)

It could be argued that prior to collecting and comparing PROMs scores internationally the next stage for EuroHeart may be to support integrating PROM into national registries and routine care across Europe. However, a major barrier to this will be implementing PROMs into existing national registries in Europe. As mentioned in **section 1.4.3.1 and 1.4.3.4**, there are clinical benefits to both patient and healthcare provider alike in implementing PROMs into routine clinical care.(58, 117, 281) Yet embedding PROMs into routine care across has been slow and confined to individual centres collecting PROMs for a single CVD condition, such as ACS, as mentioned in **Chapter 7**.(93) Widespread national CVD PROM collection and reporting is variable across Europe with the HF registry within Sweden (SwedeHF) acting as one of the few notable exceptions.(152, 484, 485) Other high income countries with well-established registries such as England and Wales are yet to include PROMs into the ACS registry for example.(486) This has been attempted within large tertiary hospitals within England and Wales.

For example, in 2017 a modified, and shortened, version of CROQ was piloted in patients treated with PCI and CABG regardless of indication (either elective or inpatient revascularisation) in 11 hospitals within England.(487) Patients completed the paper questionnaire at baseline within hospital and at 6 months follow up via post. A total of 6396 patients completed the questionnaire are baseline (CABG: n=2685; PCI: n=3711) but a total of 1706 patients completed the PROM at the recall period of 6 months (CABG: n= 869; PCI: n= 837).(487) The modified CROQ met the prespecified criteria for acceptability, reliability, internal consistency, construct validity (including convergent validity and hypothesis testing) and responsiveness.(487) As an example, significant change between the pre-revascularisation and post-vascularisation scores were demonstrated for both CABG and PCI ($p<0.001$). For CABG this was

predominantly driven by psychosocial and physical functioning and a small effect size for cognitive functioning (pre and post CROQ score effect size difference: 0.72, 0.91 and 0.28 respectively).(487) For PCI, there was a large effect size for symptoms, moderate effect sizes for physical functioning and psychosocial functioning and a very small effect size for cognitive functioning (pre and post CROQ score effect size difference: 0.82, 0.52, 0.59 and 0.19 respectively).(487) However, the pilot program was hampered by feasibility issues that explain the relatively low response rate at follow up such as completing the questionnaire by post, leading to missing data. As mentioned in **Chapter 8,** conducting the questionnaires using electronic devices may improve the response rate for patients. Therefore, international efforts to compare provider performance and quality care using PROMs scores across Europe may be undermined by extensive missing data.(128, 444)

The barriers to embedding PROMs into routine care is well known and documented which include; integrating PROMs electronically into existing administrative and clinical workflows that utilise electronic health records, managing administrative and patient respondent burden (duration of PROMs and data storage), cost of obtaining the license to use a PROM, negative clinician attitudes towards PROMs and how PROMs may inform clinical decision making.(129, 133, 137, 488) Our development of the FACTOR3 checklist addresses some of these barriers that will allow healthcare providers to select the most appropriate PROM for their institution and target population.

9.7 Recommendations for future research

Given that the MD encompassed broad topics within CVD care, there are several avenues, in my opinion, for further research that has emerged during this MD.

1. To develop a HRQoL PROM specifically for patients with AS treated with TAVI that has robust psychometric properties

2. To perform a qualitative study of CVD trialists in particular to better understand their COS selection.

3. To evaluate COS uptake in the other common CVD – HF, AF and TAVI.

4. Investigate contemporary standards of care for ACS across EuroHeart participating countries using EuroHeart data standards and outcomes for ACS.

5. To develop clinical consensus on the data standards, outcomes and PROMs for other heart valve diseases such as mitral and tricuspid valve interventions.

6. To register the EuroHeart COS on both CDOs and PROMs onto the COMET database

7. To investigate the feasibility of all HRQoL CVD PROMs considered for the EuroHeart ranking and pair that with the COSMIN analysis

8. To conduct a pilot feasibility study evaluating PROMS implementation for ACS across EuroHeart participating countries.

9.8 Conclusion

This thesis has sought to standardise the use of CROs and PROMs for commonly occurring CVD conditions that may be used in an international unified registry such as EuroHeart. To achieve this, I followed the EuroHeart method of building consensus amongst key stakeholders.

First, I provided evidence for heterogeneity in the definition and selection of contemporary CVD CROs published in highly cited journals across the common CVD conditions of IHD, HF, arrhythmia and valvular heart disease. These findings were then incorporated into a modified Delphi exercise to achieve consensus on a final set of cardiovascular outcomes by consulting 82 experts and trialists from the Global Cardiovascular Outcomes Consortium. The WGs identified and defined 25 mandatory (generic: 5, ACS: 8, AF: 2; HF: 5, TAVI: 4)

and 50 optional variables (generic: 18, ACS: 7, AF: 6, HF: 2, TAVI: 15). After discussion with the ESC Patient Forum it was decided that PROMs should not be excluded from the outcome set.

Similar to CROs, I provided evidence, from a scoping review and contemporary COSMIN analysis, that the majority of CVD PROMs required further validation studies prior to routine use in clinical care. The findings were presented to the Global Cardiovascular Outcomes Consortium, patients and PROMs experts ranked the 7 PROMs highly across the five clinical domains. A consistent theme identified by the Global Cardiovascular Outcomes Consortium was the feasibility aspects of PROMs that may hinder their implementation into routine care. I therefore formulated a unique 8 item feasibility checklist, termed FACTOR3, distilled from a modified Delphi process, informed by a scoping review of the literature and consisting of interdisciplinary international stakeholders including patients, PROMs methodologists, health economists, biostatisticians, trialists, PROM developers and clinicians.

The internationally derived and agreed EuroHeart CRO and PROM catalogues benefit from including key stakeholders into the consensus building such as patients, leading trialists and healthcare experts from inception which differs to other outcome sets. Furthermore, there is an opportunity to leverage the existing EuroHeart registries, such as the ACS/PCI registry, to promote the adoption of each set internationally. This may enable standardised measurement of key outcomes, provides the patient’s voice within observational studies and provide a platform for registry based RCTs and federated research.

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Appendix A

A.1 Search Strategy

A.1.1 Ovid MEDLINE search strategy

Appendix Table 0.1

1	exp Heart Failure/
2	((heart or cardiac* or cardio* or myocardial* or diastolic* or systolic* or paroxysmal*) adj5 (failure* or edema* or oedema* or decompensation* of dyspnea* or asthma* or chronic* or insufficient*)).ti,ab,kf.
3	((preserved ejection* or reduced ejection*) adj5 fraction*).ti,ab,kf.
4	(congestive heart* adj5 disease*).ti,ab,kf.
5	((cardio renal* or cardiorenal* or reno cardiac* or renocardiac*) adj5 syndrome*).ti,ab,kf.
6	exp Arrhythmias, Cardiac/
7	(arrhythmia* or dysrhythmia* or bradycardia* or bradyarrhythmia* or tachycardia* or tachyarrhythmia*).ti,ab,kf.
8	((irregular* or slow* or rapid* or fast or junctional*) adj3 (heartbeat* or heart beat* or rhythm*)).ti,ab,kf.
9	((atrial or auricular or ventricular) adj5 (fibrillation* or flutter*)).ti,ab,kf.
10	((heart rhythm* or cardiac rhythm*) adj5 disorder*).ti,ab,kf.
11	(premature adj3 (atrial or ventricular or junctional or cardiac) adj3 (contraction* or complex*)).ti,ab,kf.
12	((accelerat* or junctional*) adj5 rhythm*).ti,ab,kf.
13	(extra beats or heart block or heart blocks or AV block or AV blocks).ti,ab,kf.
14	Coronary Artery Disease/
15	(atherosclerosis or atheroscleroses or arteriosclerosis or arterioscleroses or (coronary adj5 disease*)).ti,ab,kf.
16	(hard* adj3 arter*).ti,ab,kf.
17	(plaque adj4 build*).ti,ab,kf.
18	acute coronary syndrome/
19	exp Myocardial Infarction/
20	exp Percutaneous Coronary Intervention/

21 Cardiac Rehabilitation/

22 ((cardiac* or cardio* or heart*) adj5 (rehab* or conditioning*)).ti,ab,kf.

23 exp Aortic Valve/

24 exp Aortic Valve Stenosis/

25 exp Mitral Valve/

26 exp mitral valve stenosis/

27 exp mitral valve insufficiency/

28 exp mitral valve regurgitation/

29 Heart Valve Diseases/

30 (left adj2 valv*).af.

31 (native adj2 valve*).af.

32 (mitral adj2 valv*).af.

33 (aortic adj2 valv*).af.

34 (valve adj2 (disease* or stenos* or insufficien*)).tw.

35 Heart Valve Prosthesis Implantation/

36 Heart Valve Prosthesis/

37 (valve adj2 (surg* or replace* or repair* or prosthe* or implant* or procedure*)).tw.

38 MitraClip.tw.

39 Transcatheter Aortic Valve Replacement/

40 TAVI.tw.

41 pacemaker, artificial/ or cardiac resynchronization therapy devices/

42 Defibrillators, Implantable/

43 or/1-42 [cardiovascular diseases]

44 exp cohort studies/

45 cohort$.tw.

46 controlled clinical trial.pt.

47 epidemiologic methods/

48 limit 47 to yr=1966-1989

49 exp case-control studies/

50 (case$ and control$).tw.

51	or/44-46,48-50
52	Randomized controlled trial.pt.
53	controlled clinical trial.pt.
54	randomized.ab.
55	placebo.ab.
56	drug therapy.fs.
57	randomly.ab.
58	trial.ab.
59	groups.ab.
60	or/52-59
61	51 or 60
62	43 and 61
63	(exp Child/ or Adolescent/ or exp Infant/) not exp Adult/
64	62 not 63
65	exp animals/ not humans.sh.
66	64 not 65
67	limit 66 to yr=2013-2024
68	("new england journal of medicine" or lancet or jama).jn.
69	67 and 68

A.1.2 Embase search strategy:

Appendix table 0.2

1	exp heart failure/
2	((heart or cardiac* or cardio* or myocardial* or diastolic* or systolic* or paroxysmal*) adj5 (failure* or deem* or deem* or decompensation* or dyspnea* or asthma* or chronic* or insufficient*)).ti,ab,kw.
3	((preserved ejection* or reduced ejection*) adj5 fraction*).ti,ab,kw.
4	(congestive heart* adj5 disease*).ti,ab,kw.
5	((cardio renal* or cardiorenal* or reno cardiac* or renocardiac*) adj5 syndrome*).ti,ab,kw.

6 exp heart arrhythmia/

7 (arrhythmia* or dysrhythmia* or bradycardia* or bradyarrhythmia* or tachycardia* or tachyarrhythmia*).ti,ab,kw.

8 ((irregular* or slow* or rapid* or fast or junctional*) adj3 (heartbeat* or heart beat* or rhythm*)).ti,ab,kw.

9 ((atrial or auricular or ventricular) adj5 (fibrillation* or flutter*)).ti,ab,kw.

10 ((heart rhythm* or cardiac rhythm*) adj5 disorder*).ti,ab,kw.

11 (premature adj3 (atrial or ventricular or junctional or cardiac) adj3 (contraction* or complex*)).ti,ab,kw.

12 ((accelerat* or junctional*) adj5 rhythm*).ti,ab,kw.

13 (extra beats or heart block or heart blocks or AV block or AV blocks).ti,ab,kw.

14 exp cardiac implantable electronic device/

15 exp heart pacing/

16 exp implantable cardioverter defibrillator/

17 exp coronary artery disease/

18 (atherosclerosis or atherosclerоses or arteriosclerosis or arteriosclerоses or (coronary adj5 disease*)).ti,ab,kw.

19 (hard* adj3 arter*).ti,ab,kw.

20 (plaque adj4 build*).ti,ab,kw.

21 acute coronary syndrome/

22 heart infarction/

23 percutaneous coronary intervention/

24 heart rehabilitation/

25 ((cardiac* or cardio* or heart*) adj5 (rehab* or conditioning*)).ti,ab,kw.

26 exp Aortic Valve/

27 exp Aortic Valve Stenosis/

28 exp Mitral Valve/

29 exp mitral valve stenosis/

30 valvular heart disease/

31 exp mitral valve regurgitation/

32 (left adj2 valv*).af.

33 (native adj2 valve*).af.

34 (mitral adj2 valv*).af.

35 (aortic adj2 valv*).af.

36 (valve adj2 (disease* or stenos* or insufficien*)).tw.

37 heart valve replacement/

38 heart valve prosthesis/

39 (valve adj2 (surg* or replace* or repair* or prosthe* or implant* or procedure*)).tw.

40 MitraClip.tw.

41 transcatheter aortic valve implantation/

42 TAVI.tw.

43 or/1-42 [cardiovascular diseases]

44 exp cohort analysis/

45 exp longitudinal study/

46 exp prospective study/

47 exp follow up/

48 cohort$.tw.

49 exp case control study/

50 (case$ and control$).tw.

51 or/44-50 [BMJ Embase cohort and case-control strategy]

52 Randomized controlled trial/

53 Controlled clinical study/

54 random$.ti,ab.

55 randomization/

56 intermethod comparison/

57 placebo.ti,ab.

58 (compare or compared or comparison).ti.

((evaluated or evaluate or evaluating or assessed or assess) and (compare or
59 compared or comparing or comparison)).ab.

60 (open adj label).ti,ab.

61 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

62 double blind procedure/

63 parallel group$1.ti,ab.

64 (crossover or cross over).ti,ab.

((assign$ or match or matched or allocation) adj5 (alternate or group$1 or
65 intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.

66 (assigned or allocated).ti,ab.

67 (controlled adj7 (study or design or trial)).ti,ab.

68 (volunteer or volunteers).ti,ab.

69 human experiment/

70 trial.ti.

71 or/52-70

(random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or
database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed
72 controlled.ti,ab. or randomly assigned.ti,ab.)

Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or
73 controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

74 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

75 (Systematic review not (trial or study)).ti.

76 (nonrandom$ not random$).ti,ab.

77 Random field$.ti,ab.

78 (random cluster adj3 sampl$).ti,ab.

79 (review.ab. and review.pt.) not trial.ti.

80 we searched.ab. and (review.ti. or review.pt.)

81 update review.ab.

82 (databases adj4 searched).ab.

(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or
83 monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

84 Animal experiment/ not (human experiment/ or human/)

85 or/72-84

86 71 not 85 [Cochrane Embase RCT filter]

87 51 or 86 [Cohort or case control studies or Rcts]

88 43 and 87 [cardiovascular diseases and cohort or case control studies or RCTs]

89 (exp adolescent/ or exp child/ or exp infant,newborn/) not exp adult/

90 88 not 89 [adult studies only]

91 lancet.jn.

92 new england journal of medicine.jn.

93 (jama or jama chicago ill or "jama journal of the american medical association").jn.

94 or/91-93

95 90 and 94 [results limited to specific journals]

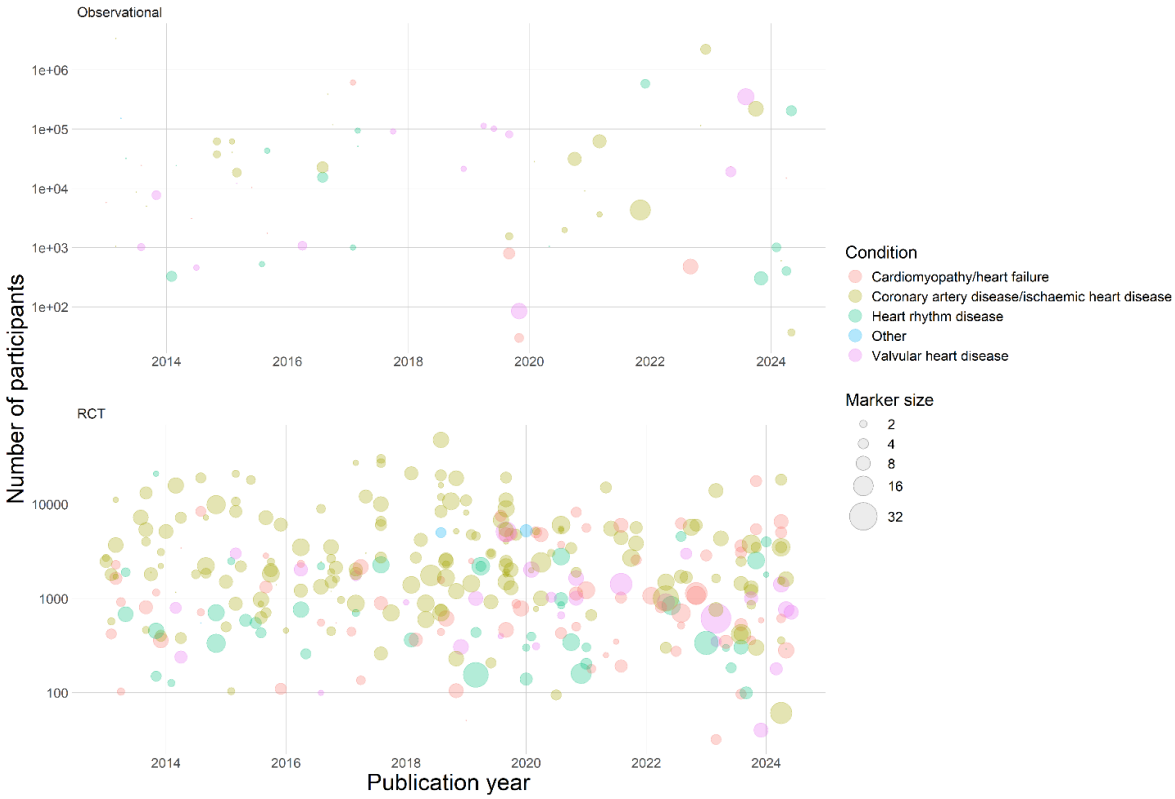
96 limit 95 to yr="2013 - 2024"

97 remove duplicates from 96

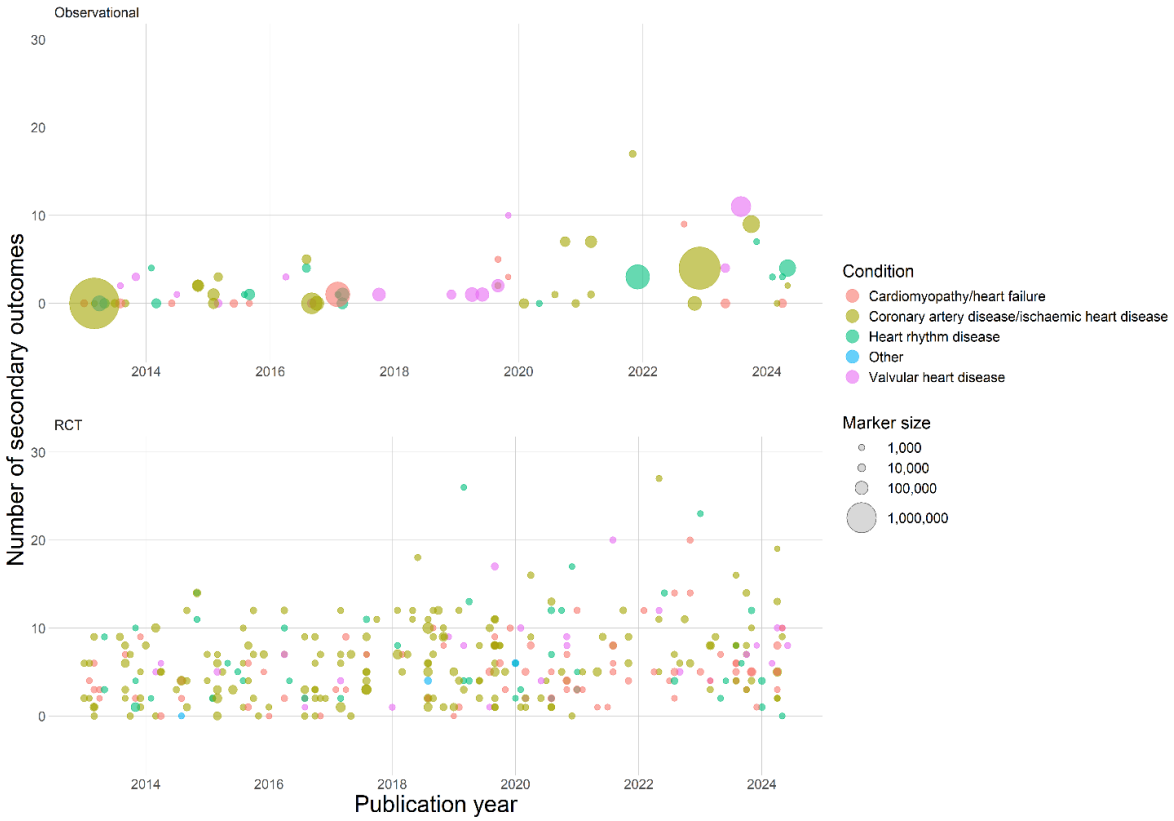
A.2 Evidence Map

Evidence map of A) temporal trends of the number of participants in observational studies and randomised clinical trials, and B) temporal trends in the reporting of secondary outcome measures in observational studies and randomised clinical trials.

A)



B)


Observational
RCT
Number of secondary outcomes
Publication year
30
20
10
0
2014
2016
2018
2020
2022
2024
Condition
Cardiomyopathy/heart failure
Coronary artery disease/ischaemic heart disease
Heart rhythm disease
Other
Valvular heart disease
Marker size
1,000
10,000
100,000
1,000,000

A.3 Risk of Bias

Article	Journal	Year	Randomization	Deviations (assignment)	Deviations (adherence)	Missing data	Measurement	Reporting	Overall
Abdallah et al	JAMA	2013	Low	Low	Low	Low	Low	Low	Low
Abdel-Wahab et al	JAMA	2014	Low	Low	Low	Low	Low	Low	Low
Abed et al	JAMA	2013	Low	Low	Low	Low	Low	Low	Low
Abraham et al	Lancet	2016	Low	Low	Low	Low	Low	Low	Low
Adams et al	NEJM	2014	Low	Low	Low	Low	Low	Low	Low
Ali et al	Lancet	2016	Low	Low	Low	Low	Low	Low	Low
Ali et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Al-Kaisey et al	JAMA	2023	Low	Low	Low	Low	Low	Low	Low
Al-Lamee et al	Lancet	2018	Low	Low	Low	Low	Low	Low	Low
Andrade et al	NEJM	2021	Low	Low	Low	Low	Low	Low	Low
Anker et al	NEJM	2021	Low	Low	Low	Low	Low	Low	Low
Appelboam et al	Lancet	2015	Low	Low	Low	Low	Low	Low	Low
Armstrong et al	NEJM	2013	Low	Some concern	Low	Low	Some concern	Low	Some concern
Armstrong et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
Assmus et al	JAMA	2013	Low	Low	Low	Low	Low	Low	Low

Bangalore et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
Baumbach et al	Lancet	2024	low	Low	Low	Low	Low	Low	Low
Berwanger et al	JAMA	2018	Low	Low	Low	Low	Low	Low	Low
Bhatt et al	NEJM	2021	Low	Low	Low	Low	Some concern	Low	Low
Bhatt et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Bhatt et al	NEJM	2013	Low	Low	Low	Low	Some concern	Low	Low
Bhatt et al	Lancet	2019	Low	Low	Low	Low	Low	Low	Low
Birnie et al	NEJM	2013	Low	Low	Low	Low	Low	Low	Low
Biscaglia et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Blankenberg et al	NEJM	2024	low	Low	Low	Low	Low	Low	Low
Blomstrom-Lundqvist et al	JAMA	2019	Low	Low	Low	Low	Low	Low	Low
Bohm et al	NEJM	2024	Low	Low	Low	Low	Low	Low	Low
Bohula et al	NEJM	2018	Low	Low	Low	Low	Low	Low	Low
Bonaa et al	NEJM	2016	Low	Low	Low	Low	Low	Low	Low
Bonaca et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Borlaug et al	JAMA	2018	Low	Low	Low	Low	Low	Low	Low
Bowman et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Brilakis et al	Lancet	2018	Low	Low	Low	Low	Low	Low	Low

Brouwer et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
Brugts et al	Lancet	2023	Low	Low	Low	Low	Low	Low	Low
Butler et al	NEJM	2024	Low	Low	Some concern	Low	Low	Low	Some concern
Byrne et al	Lancet	2013	Low	Low	Low	Low	Low	Low	Low
Calkins et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Cannon et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Cannon et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Carson et al	NEJM	2023	Low	Low	Low	Low	Some concern	Low	Some concern
Cayla et al	Lancet	2016	Low	Low	Low	Low	Low	Low	Low
Chen et l	JAMA	2013	Low	Low	Low	Low	Low	Low	Low
Chow et al	JAMA	2015	Low	Low	Low	Low	Low	Low	Low
Christiansen et al	Lancet	2013	Low	Low	Low	Low	Low	Low	Low
Claassens et al	NEJM	2019	Low	Some concern	Low	Low	Low	Low	Low
Connolly et al	NEJM	2022	Low	Low	Low	Low	Low	Low	Low
Cowie et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Cung et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Curtis et al	NEJM	2013	Low	Low	Low	Low	Low	Low	Low

Dangas et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
de Winter et al	Lancet	2018	Low	Low	Low	Low	Low	Low	Low
Delgado-Lista et al	Lancet	2022	Low	Low	Some concern	Low	Low	Low	Some concern
Desai et al	JAMA	2019	Low	Low	Low	Low	Low	Low	Low
Devereaux et al	Lancet	2018	Low	Low	Low	Low	Low	Low	Low
Devore et al	JAMA	2021	Low	Low	Low	Low	Low	Low	Low
Dewilde et al	Lancet	2013	Low	Low	Low	Low	Low	Low	Low
Diletti et al	Lancet	2023	Low	Low	Low	Low	Low	Low	Low
Ducrocq et al	JAMA	2021	Low	Low	Low	Low	Low	Low	Low
Edelmann et al	JAMA	2013	Low	Low	Low	Low	Some concern	Low	Low
Eikelboom et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Ellis et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Engstrom et al	Lancet	2015	Low	Low	Low	Low	Low	Low	Low
Erlinge et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Ezekowitz et al	Lancet	2022	Low	Low	Low	Low	Some concern	Low	Some concern
Fearon et al	NEJM	2022	Low	Low	Low	Low	Low	Low	Low
Feldman et al	JAMA	2018	Low	Low	Low	Low	Low	Low	Low

Felker et al	JAMA	2017	Low	Low	Low	Low	Low	Low	Low
Feres et al	JAMA	2013	Low	Low	Low	Low	Low	Low	Low
Ferrari et al	Lancet	2020	Low	Low	Low	Low	Low	Low	Low
Foley et al	Lancet	2024	Low	Low	Low	Low	Low	Low	Low
Fox et al	NEJM	2014	Low	Low	Low	Low	Low	Low	Low
Freund et al	JAMA	2020	Low	Low	Low	Low	Low	Low	Low
Frobert et al	NEJM	2013	Low	Low	Low	Low	Low	Low	Low
Gasparini et al	JAMA	2013	Low	Low	Low	Low	Low	Low	Low
Ge et al	Lancet	2024	Low	Low	Low	Low	Low	Low	Low
Gheorghiade et al	JAMA	2013	Low	Low	Low	Low	Low	Low	Low
Gibson et al	NEJM	2016	Low	Low	Low	Low	Low	Low	Low
Gibson et al	NEJM	2024	Low	Low	Low	Low	Some concern	Low	Some concern
Gimbel et al	Lancet	2020	Low	Low	Low	Low	Low	Low	Low
Goette et al	Lancet	2016	Low	Low	Low	Low	Low	Low	Low
Gotberg et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Guigliano et al	NEJM	2013	Low	Low	Low	Low	Low	Low	Low
Guimaraes et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
Hahn et al	Lancet	2018	Low	Low	Low	Low	Low	Low	Low

Hahn et al	JAMA	2019	Low	Low	Low	Low	Low	Low	Low
Halliday et al	Lancet	2019	Some concern	Low	Low	Low	Low	Low	Some concern
Han et al	JAMA	2015	Low	Low	Low	Low	Low	Low	Low
Hausenloy et al	Lancet	2019	Low	Low	Low	Low	Low	Low	Low
Haussig et al	JAMA	2016	Low	Low	Low	Low	Low	Low	Low
Healey et al	Lancet	2015	Low	Low	Low	Low	Low	Low	Low
Healey et al	NEJM	2024	Low	Low	Low	Low	Low	Low	Low
Hernandez et al	Lancet	2018	low	Low	Low	Low	Some concern	Low	Some concern
Herrmann et al	NEJM	2024	Low	Low	Low	Low	Low	Low	Low
Hindricks et al	Lancet	2014	Some concern	Low	Low	Low	Low	Low	Some concern
Hofmann et al	NEJM	2017	low	Some concern	Some concern	Low	Low	Low	Some concern
Holm et al	Lancet	2020	low	Low	Low	Low	Low	Low	Some concern
Holm et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Hong et al	JAMA	2015	Some concern	Low	Low	Low	Low	Low	Some concern

Hong et al	JAMA	2023	Low	Some concern	Some concern	Low	Low	Low	Some concern
Huffman et al	JAMA	2018	Some concern	Low	Low	Low	Low	Low	Some concern
Iglesias et al	Lancet	2019	low	Low	Some concern	Low	Low	Some concern	Some concern
Iglesias et al	Lancet	2023	Low	Low	Low	Low	Low	Low	Low
Iversen et al	NEJM	2019	Low	Low	Some concern	Some concern	Low	Low	Some concern
Jabbar et al	JAMA	2020	Low	Low	Low	Low	Low	Low	Low
Jacobs et al	NEJM	2013	low	Low	Low	Some concern	Low	Low	Some concern
Jeger et al	Lancet	2018	Some concern	Low	Low	Low	Low	Low	Some concern
Jolly et al	NEJM	2015	low	Low	Low	Low	Low	Some concern	Some concern
Jones et al	NEJM	2021	low	Low	Low	Low	Low	Low	Low
Kalra et al	Lancet	2022	Low	Low	Low	Low	Low	Low	Low
Kandzari et al	Lancet	2016	Low	Low	Low	Low	Low	Low	Low
Kapadia et al	Lancet	2015	low	Low	Some concern	Low	Low	Low	Some concern

Kapadia et al	NEJM	2022	Low	Low	Low	Low	Low	Low	Low
Kaul et al	NEJM	2015	Some concern	Low	Low	Low	Low	Low	Some concern
Kelbaek et al	Lancet	2016	low	Low	Some concern	Low	Low	Low	Some concern
Kereiakes et al	JAMA	2015	Some concern	Low	Low	Some concern	Low	Low	Some concern
Kim et al	JAMA	2020	Some concern	Low	Low	Low	Low	Low	Some concern
Kim et al	Lancet	2020	Some concern	Low	Some concern	Low	Low	Low	Some concern
Kim et al	Lancet	2021	Low	Low	Some concern	Low	Low	Low	Some concern
Kirchhof et al	NEJM	2020	low	Low	Some concern	Low	Low	Low	Some concern
Kirchhof et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Kistler et al	JAMA	2023	Low	Low	Low	Low	Low	Low	Low
Kitzman et al	JAMA	2016	Low	Low	Some concern	Low	Low	Low	Some concern
Kitzman et al	NEJM	2021	Low	Low	Some concern	Low	Low	Low	Some concern

Knops et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
Knops et al	NEJM	2023	Some concern	Low	Low	Low	Low	Some concern	Some concern
Knops et al	NEJM	2024	Low	Low	Low	Low	Low	Low	Low
Kober et al	NEJM	2016	low	Low	Some concern	Low	Low	Low	Some concern
Koehler et al	Lancet	2018	low	Low	Low	Low	Low	Some concern	Some concern
Koo et al	Lancet	2021	Low	Low	Low	Low	Low	Low	Low
Koo et al	NEJM	2022	Low	Low	Some concern	Low	Low	Low	Some concern
Kosiborod et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Kosiborod et al	NEJM	2024	Low	Low	Low	Low	Low	Low	Low
Kotecha et al	JAMA	2020	Low	Low	Low	Low	Low	Some concern	Some concern
Kozhuharov et al	JAMA	2019	Low	Low	Low	Low	Low	Low	Low
Kuck et al	NEJM	2016	low	Low	Low	Low	Low	Low	Low
Lagerqvist et al	NEJM	2014	low	Low	Some concern	Low	Low	Low	Some concern
Lamas et al	JAMA	2013	low	Low	Low	Low	Low	Low	Low

Lansky et al	Lancet	2018	low	Low	Some concern	Low	Low	Low	Some concern
Lanz et al	Lancet	2019	Some concern	Low	Low	Low	Some concern	Low	Some concern
Lee et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Lee et al	NEJM	2023	Some concern	Low	Low	Low	Some concern	Low	Some concern
Leon et al	NEJM	2016	Some concern	Low	Low	Low	Low	Low	Some concern
Lewis et al	JAMA	2022	Low	Low	Low	Low	Low	Low	Low
Lexis et al	JAMA	2014	Some concern	Low	Low	Low	Low	Low	Some concern
Li et al	Lancet	2022	Low	Some concern	Some concern	Low	Low	Low	Some concern
Li et al	Lancet	2024	Low	Low	Low	Low	Low	Low	Low
Lincoff et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Lincoff et al	Lancet	2016	low	Low	Some concern	Low	Low	Low	Some concern
Lincoff et al	JAMA	2014	low	Low	Low	Low	Low	Some concern	Some concern

Lincoff et al	NEJM	2017	low	Low	Some concern	Low	Low	Low	Some concern
Lindenfeld et al	Lancet	2021	low	Low	Some concern	Low	Low	Low	Some concern
Lopes et al	NEJM	2019	low	Low	Low	Low	Some concern	Low	Some concern
Mack et al	NEJM	2019	Low	Low	Low	Low	Low	Some concern	Some concern
Mack et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Mackenzie et al	Lancet	2022	Low	Low	Low	Some concern	Low	Low	Some concern
Macle et al	Lancet	2015	Low	Low	Low	Low	Low	Low	Low
Maeng et al	Lancet	2014	Low	Low	Low	Low	Some concern	Low	Some concern
Makikallio et al	Lancet	2016	Low	Low	Low	Low	Low	Low	Low
Makkar et al	Lancet	2020	Low	Low	Some concern	Low	Low	Low	Some concern
Makkar et al	NEJM	2020	Low	Low	Some concern	Low	Low	Low	Some concern
Mark et al	JAMA	2019	Low	Low	Low	Low	Low	Low	Low
Maron et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low

Maron et al	NEJM	2024	Low	Low	Low	Low	Low	Low	Low
Marrouche et al	NEJM	2018	Low	Low	Low	Low	Low	Low	Low
Marrouche et al	JAMA	2022	Low	Low	Low	Low	Low	Low	Low
Mathew et al	NEJM	2021	Low	Low	Low	Low	Low	Low	Low
Maurer et al	NEJM	2018	Low	Low	Low	Low	Low	Low	Low
Maurer et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Mauri et al	NEJM	2014	Low	Low	Low	Low	Low	Low	Low
McManus et al	JAMA	2014	Low	Low	Low	Some concern	Low	Low	Some concern
McMurray et al	NEJM	2016	Low	Low	Low	Low	Low	Low	Low
McMurray et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
McMurray et al	NEJM	2014	Low	Low	Low	Low	Low	Low	Low
Mebazaa et al	Lancet	2022	Low	Low	Low	Low	Low	Some concern	Some concern
Mehra et al	JAMA	2023	Low	Low	Low	Low	Low	Low	Low
Mehra et al	NEJM	2018	Low	Low	Low	Low	Low	Low	Low
Mehran et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Mehta et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Mentz et al	JAMA	2023	Low	Low	Low	Low	Low	Low	Low

Mentz et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Messas et al	Lancet	2023	Low	Low	Low	Low	Low	Low	Low
Metra et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Mohr et al	Lancet	2013	Low	Low	Low	Low	Low	Low	Low
Moller et al	NEJM	2024	Low	Low	Some concern	Low	Low	Low	Some concern
Montalescot et al	NEJM	2014	Low	Low	Low	Low	Low	Low	Low
Montalescot et al	NEJM	2013	Low	Low	Low	Low	Low	Low	Low
Morillo et al	JAMA	2014	Low	Low	Low	Low	Low	Low	Low
Morillo et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Mueller et al	JAMA	2021	Low	Low	Low	Low	Low	Low	Low
Mullens et al	NEJM	2022	Low	Low	Low	Low	Low	Low	Low
Nagel et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Newby et al	NEJM	2018	low	Some concern	Low	Low	Low	Low	Some concern
Nicholls et al	JAMA	2016	Low	Low	Low	Low	Low	Low	Low
Nicholls et al	JAMA	2014	Low	Low	Low	Low	Low	Low	Low
Nidorf et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
Nijenhuis et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low

Nissen et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Obadia et al	NEJM	2018	Low	Low	Low	Low	Low	Low	Low
O'Donoghue et al	JAMA	2016	Low	Low	Low	Low	Low	Low	Low
Ohman et al	Lancet	2017	Low	Low	Low	Low	Low	Low	Low
Okumura et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
Olgin et al	NEJM	2018	Low	Low	Low	Low	Low	Low	Low
Olivotto et al	Lancet	2020	Low	Low	Low	Low	Low	Low	Low
Packer et al	NEJM	2017	Low	Low	Low	Low	High	Low	Some concern
Packer et al	JAMA	2019	Low	Low	Low	Low	Low	Low	Low
Packer et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
Park et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Park et al	NEJM	2022	Low	Some concern	Low	Low	Low	Low	Some concern
Park et al	Lancet	2024	Low	Low	Low	Low	Low	Low	Low
Patterson et al	Lancet	2023	Low	Low	Low	Low	Low	Some concern	Some concern
Pereira et al	JAMA	2020	Low	Low	Low	Low	Low	Low	Low
Perera et al	NEJM	2022	Low	Low	Low	Low	Low	Low	Low
Petrie et al	JAMA	2020	Low	Low	Low	Low	Low	Low	Low

Pfeffer et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Pfeffer et al	NEJM	2021	Low	Low	Low	Low	Low	Low	Low
Pieske et al	JAMA	2021	Low	Low	Low	Low	Low	Low	Low
Pilgrim et al	Lancet	2014	Low	Low	Low	Low	Low	Low	Low
Pirmohamed et al	NEJM	2013	Low	Low	Low	Low	Low	Low	Low
Pitt et al	NEJM	2014	Low	Low	Low	Low	Low	Low	Low
Pluymaekers et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Ponikowski et al	Lancet	2020	Low	Low	Low	Low	Low	Low	Low
Raber et al	JAMA	2022	Low	Low	Low	Low	Low	Low	Low
Rajkumar et al	NEJM	2023	Low	Low	Low	Some concern	Low	Low	Some concern
Raungaard et al	Lancet	2015	Low	Low	Low	Low	Low	Low	Low
Ray et al	JAMA	2020	Low	Low	Low	Low	Low	Low	Low
Reardon et al	NEJM	2017	low	Low	Low	Low	Some concern	Low	Some concern
Reddy et al	JAMA	2014	Low	Low	Low	Low	Low	Low	Low
Reddy et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Reddy et al	JAMA	2023	Low	Low	Low	Low	Low	Low	Low
Redfield et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low

Ridker et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Ridker et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Rissanen et al	Lancet	2019	Low	Low	Low	Low	Low	Low	Low
Rogers et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Roshandel et al	Lancet	2019	Low	Low	Low	Low	Low	Low	Low
Ruschitzka et al	NEJM	2013	Low	Low	Low	Low	Low	Low	Low
Sabate et al	Lancet	2016	Low	Low	Low	Low	Low	Low	Low
Sabatine et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Saberi et al	JAMA	2017	Low	Low	Some concern	Low	Low	Low	Some concern
Sapp et al	NEJM	2016	Low	Low	Low	Low	Low	Low	Low
Sapp et al	NEJM	2024	Low	Low	Low	Low	Low	Low	Low
Schupke et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Schwartz et al	NEJM	2018	Low	Low	Low	Low	Low	Low	Low
Serruys et al	Lancet	2015	Low	Low	Low	Low	Low	Low	Low
Shah et al	Lancet	2018	Low	Low	Low	Low	Low	Low	Low
Shah et al	Lancet	2022	Low	Low	Low	Low	Low	Low	Low
Shahzad et al	Lancet	2014	Low	Low	Low	Low	Low	Low	Low
Sibbing et al	Lancet	2017	Low	Low	Low	Low	Low	Low	Low

Silvain et al	Lancet	2020	Some concern	Low	Low	Low	Low	Low	Low
Smits et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Smits et al	Lancet	2013	Low	Low	Low	Low	Low	Low	Low
Sohns et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Solomon et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Solomon et al	NEJM	2022	Low	Low	Low	Low	Low	Low	Low
Sorajja et al	NEJM	2023	Low	Low	Low	Low	Low	Low	Low
Spall et al	JAMA	2019	Some concern	Low	Low	Low	Low	Low	Low
Spertus et al	Lancet	2021	Low	Low	Some concern	Low	Low	Low	Some concern
Stahli et al	NEJM	2023	Low	Some concern	Low	Low	Low	Low	Some concern
Stambler et al	Lancet	2023	Low	Low	Low	Low	Low	Low	Low
Steg et al	NEJM	2013	Low	Low	Low	Low	Low	Low	Low
Steg et al	JAMA	2013	Low	Low	Low	Low	Low	Low	Low
Steg et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Steinberg et al	JAMA	2020	Low	Some concern	Low	Low	Low	Low	Some concern
Stewart et al	Lancet	2014	Low	Low	Low	Low	Low	Low	Low
Stiell et al	Lancet	2020	Low	Low	Low	Low	Low	Low	Low

Stone et al	NEJM	2018	Low	Low	Low	Low	Low	Low	Low
Stone et al	NEJM	2016	Low	Low	Low	Low	Low	Low	Low
Stone et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Stone et al	Lancet	2018	Low	Low	Low	Low	Low	Low	Low
Stone et al	NEJM	2023	Low	Low	Low	Low	Low	Some concern	Some concern
Swedberg et al	NEJM	2013	Low	Low	Low	Low	Low	Low	Low
Tardif et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Teerlink et al	Lancet	2013	Low	Low	Low	Low	Low	Low	Low
Teerlink et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
Tegn et al	Lancet	2016	Low	Low	Low	Low	Low	Low	Low
Thiele et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Thiele et al	NEJM	2018	Low	Low	Low	Low	Low	Low	Low
Thiele et al	NEJM	2023	low	low	low	low	low	low	low
Thuijs et al	Lancet	2019	Low	Low	Low	Low	Low	Low	Low
Toff et al	JAMA	2022	Low	Low	Low	Low	Low	Low	Low
Urban et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Vahl et al	Lancet	2024	Low	Low	Low	Low	Low	Low	Low
Valderrabano et al	JAMA	2020	Low	Low	Low	Low	Low	Low	Low

Valgimigli et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Valgimigli et al	Lancet	2015	Low	Low	Low	Low	Low	Low	Low
Valgimigli et al	Lancet	2018	Low	Low	Low	Low	Low	Low	Low
Valgimigli et al	NEJM	2021	Low	Low	Low	Low	Low	Low	Low
van Miegham et al	NEJM	2021	Low	Low	Low	Low	Low	Low	Low
Vardeny et al	JAMA	2020	Low	Low	Low	Low	Low	Low	Low
Varenne et al	Lancet	2018	Low	Low	Low	Low	Low	Low	Low
Velazquez et al	NEJM	2019	low	low	Some concern	Low	Low	Low	Some concern
Verheye et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Verma et al	NEJM	2015	Low	Low	Low	Low	Low	Low	Low
Vinereanu et al	Lancet	2017	Low	Low	Low	Low	Low	Low	Low
von Birgelen et al	Lancet	2013	Low	Low	Low	Low	Low	Low	Low
von Birgelen et al	Lancet	2018	Low	Low	Low	Low	Low	Some concern	Some concern
von Birgelen et al	Lancet	2016	Low	Low	Low	Low	Low	Low	Low
Voskoboinik et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
Vranckx et al	Lancet	2019	Low	Low	Low	Low	Low	Low	Low
Vranckx et al	Lancet	2018	Low	Low	Low	Low	Some concern	Low	Low

Wald et al	NEJM	2013	Low	Low	Low	Low	Low	Low	Low
Wallentin et al	Lancet	2016	Low	Low	Low	Low	Some concern	Low	some concern
Wang et al	JAMA	2019	Low	Low	Low	Low	Low	Low	Low
Watanabe et al	JAMA	2019	Low	Low	Low	Low	Low	Low	Low
Wazni et al	NEJM	2021	Low	Low	Low	Low	Low	Low	Low
Weisbord et al	NEJM	2018	Low	Low	Low	Low	Some concern	Low	Low
Weisz et al	Lancet	2016	Low	Low	Low	Low	Low	Low	Low
White et al	NEJM	2013	Low	Low	Low	Low	Low	Low	Low
White et al	NEJM	2014	low	Low	Some concern	Low	Low	Low	Some concern
Wilkoff et al	Lancet	2023	Low	Low	Low	Low	Low	Low	Low
Windecker et al	NEJM	2020	Low	Low	Low	Low	Low	Low	Low
Wykrzykowska et al	NEJM	2017	Low	Low	Low	Low	Low	Low	Low
Xaplanteris et al	NEJM	2018	Low	Low	Low	Low	Low	Low	Low
Xu et al	Lancet	2021	Low	Low	Low	Low	Low	Low	Low
Yang et al	JAMA	2023	Low	Low	Low	Low	Low	Low	Low
Yasuda et al	NEJM	2019	Low	Low	Low	Low	Low	Low	Low
Yndigegn et al	NEJM	2024	Low	Low	Low	Low	Low	Low	Low

Zaman et al	Lancet	2019	Low	Low	Low	Low	Low	Low	Low
Zannad et al	NEJM	2018	Low	Low	Low	Low	Low	Low	Low

A.4 List of included articles

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Appendix B

B.1 Heart Failure Outcome Measures Consortium

Ana G Almeida, Dan Atar, Antoni Bayés-Genís, Claudio Ceconi, Ovidiu Chioncel, Michele Ciccarelli, Sarah Moharem Elgamal, Justin A Ezekowitz, Gregg Fonarow, George Giannakoulas, Bruna Gigante, Can Gollmann-Tepeköylü, Stephen J Greene, Magnus T Jensen, Malgorzata Lelonek, Luca Liberale, Roberto Lorusso, Marco Metra, Cinzia Perrino, Peter P Rainer, Giuseppe MC Rosano, Gianluigi Savarese, Samuel Sossalla, Roderick W Treskes, Izabella Uchmanowicz, Jacob A Udell, Roland RJ van Kimmenade, Marija Zdravkovic

Appendix C

C.1 Members of the Global Cardiovascular Consortium

Victor Aboyans, Ana G. Almeida, Dan Atar, Gorav Batra, Antoni Bayés-Genís, Asad Bhatty, Giuseppe Biondi-Zoccai, Marc P. Bonaca, Nikolaos Bonaros, Bianca J.J.M. Brundel, Raffaele Bugiardini, Gianluca Campo, Barbara Casadei, Ruben Casado-Arroyo, Claudio Ceconi, Edina Cenko, Ovidiu Chioncel, Michele Ciccarelli, Louise Coats, Jean-Philippe Collet, Gheorghe-Andrei Dan, Victoria Delgado, Polychronis Dilaveris, Dobromir Dobrev, Erwan Donal, David Duncker, Sarah Moharem Elgamal, Justin A. Ezekowitz, Gregg Fonarow, Alan G. Fraser, Chris P. Gale, George Giannakoulas, Bruna Gigante, Massimiliano Gnecchi, Can Gollmann-Tepeköylü, Stephen J. Greene, Jordi Heijman, Jonathan Howes, Bernard Iung, Stefan James, Magnus T. Jensen, Vijay Kunadian, Malgorzata Lelonek, Sergio Leonardi, Erik Lerkevang Grove, Luca Liberale, Riccardo Liga, A. Michael Lincoff, Roberto Lorusso, Aldo P. Maggioni, Mamas Mamas, Olivia Manfrini, Fabio Mangiacapra, Nina Ajmone Marsan, María Martín-Fernandez, Jose L. Merino, Marco Metra, Alessandro Parolari, Cinzia Perrino, Lorenz Räber, Benyamin Rahmani, Peter P. Rainer, Giuseppe M.C. Rosano, Alexia Rossi, Andrea Rubboli, Tanja Rudolph, Sigrid Sandner, Gianluigi Savarese, Jolanta Siller-Matula, Samuel Sossalla, Cristiano Spadaccio, Eugenio Stabile, David Tanne, Jurrien ten Berg, Matthias Thielmann, Roderick W. Treskes, Izabella Uchmanowicz, Jacob A. Udell, Roland R.J. van Kimmenade, Lars Wallentin, Chris Wilkinson, and Marija Zdravkovic.

Appendix D

D.1 Search Strategy

Search was performed 08/02/2025.

Following keywords were used:

Population: ‘cardiovascular disease’, ‘heart failure’, ‘cardiomyopathies’, ‘heart valve disease’, ‘aortic stenosis’, ‘acute coronary syndrome’, ‘atrial fibrillation’, ‘percutaneous coronary intervention’ ,‘transcatheter aortic valve intervention’, ‘coronary artery disease’, ‘myocardial infarction’, ‘heart diseases’, ‘HF’, ‘HFpEF’, ‘HFmrEF’, ‘HFrEF’, ‘MI’, ‘ACS’, ‘PCI’, ‘CVD’, ‘TAVI’, ‘CAD’.

‘Patient-reported outcomes’, ‘patient outcome assessment’, PRO, PROM, ‘quality of life’, perceived health and health-related quality of life’ along with the associated abbreviations (QoL, HRQoL) was used.

An electronic literature search was conducted using three databases (PubMed, Web of Science, and Embase.

D.2 COSMIN criteria for good measurement properties

Measurement property	Rating	Criteria
Content validity	+	Included items are relevant for the construct, target population, and context of use, and response options and recall period are appropriate AND No key concepts are missing AND PROM items and response options are appropriately worded and PROM instructions, items and response options understood by the population of interest as intended.
	-	Items not relevant for construct or the target group, key concepts missing, response options not appropriate
	?	Not enough information reported
Structural validity	+	CTT: EFA/PCA: factor loadings of each item on its factor ≥ 0.30 AND

		Maximum 10% of the items have factor loadings ≥ 0.30 on multiple factors AND Explained variance ≥ 50% and structure is in line with the theory about the construct to be measured OR results on scree plot or Kaiser criterion (Eigenvalues > 1) are in line with the theory about the construct to be measured CFA: CFI or TLI or comparable measure > 0.95 OR RMSEA < 0.06 OR SRMR < 0.08. IRT/RASCH No violation of ***unidimensionality***: CFI or TLI or comparable measure > 0.95 *OR* RMSEA < 0.06 *OR* SRMR < 0.08 *AND* No violation of ***local independence***: residual correlations among the items after controlling for dominant factor < 0.20 *OR* Q3s < 0.37 *AND* No violation of ***monotonicity***: adequate looking graphs *OR* item scalability > 0.30 *AND* Adequate ***model fit****:* IRT: χ^2 > 0.01, Rasch: infit and outfit mean squares ≥ 0.5 and ≤ 1.5 *OR* Z-standardized values >-2 and < 2 Criteria for + not met Not enough information reported

	-	
	?	
Hypothesis testing for construct	+	≥ 75% of the results is in accordance with predefined hypotheses
	-	≥ 75% of the results deviates from predefined hypotheses
	?	No relevant results were found
Cross cultural validity	+	No important differences found between group factors (such as age, gender, language) in multiple group factor analysis OR no important DIF for group factors (McFadden's $R^2 < 0.02$)

	-	Important differences between groups/factors or DIF found
	?	Not enough information reported
Criterion validity	+	Correlation with gold standard ≥ 0.70 OR area under curve (AUC) ≥ 0.70
	-	Correlation with gold standard < 0.70 OR AUC < 0.70
	?	Not enough information reported
Reliability	+	Intra-class correlation coefficient (ICC), or weighted Kappa ≥ 0.70, Spearman/Pearson correlation ≥ 0.70
	-	ICC or (weighted) kappa or Pearson/Spearman correlation < 0.70
	?	Not enough information reported
Internal consistency	+	At least low evidence for sufficient unidimensionality

		AND Cronbach's alpha ≥ 0.70
	-	At least low quality evidence for sufficient unidimensionality AND Cronbach's alpha < 0.70
	?	Criteria for "at least low evidence for sufficient unidimensionality" not met OR Evidence for insufficient unidimensionality OR Not enough information reported
Measurement error/measurement invariance	+	Smallest detectable change (SDC) or limits of agreement (LoA) < minimal important change (MIC)
	-	SDC or LoA > MIC
	?	MIC not defined OR not enough information reported

Responsiveness	+	≥ 75% of the results is in accordance with predefined hypotheses OR AUC ≥ 0.70
	-	≥ 75% of the results deviates from predefined hypotheses OR AUC < 0.70
	?	No relevant results were found

Abbreviations: + Sufficient ? Indeterminate, - Insufficient. AUC = area under the receiver operating characteristic curve, CFA = confirmatory factor analysis, CFI = comparative fit index, CTT = classical test theory, DIF = differential item functioning, EFA = exploratory factor analysis, ICC = intraclass correlation coefficient, IRT = item response theory, LoA = limits of agreement, MIC = minimal important change, PCA = principal component analyses, RMSEA: Root Mean Square Error of Approximation, SEM = Standard Error of Measurement, SDC = smallest detectable change, SRMR: Standardized Root Mean Residuals, TLI = Tucker-Lewis index

D.3 List of included articles

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Appendix E

E.1 Search strategy

Search strategy for scoping review included the following terms:

“Patient reported outcome measure” OR “Patient reported outcome” OR “PROM” OR “PRO” AND “Feasibility” OR “Feasible” OR “Practical” AND “Implementation” OR “Implement” OR “Barrier”

E.2 FACTOR3 consortium

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