**Title**

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

**Authors**

Asad Bhatty\*1,2,3, Chris Wilkinson\*4,5, Suleman Aktaa6, Gorav Batra7, Benjamin Beska8, Phyo H. Khaing8, Ali Wahab3,4,5, Keerthenan Raveendra3,4, Ahmed Taha5, Ramesh Nadarajah1,2,3, Deepak L. Bhatt9, Rod Stables10, A. John Camm11, Rajesh Kharbanda12, Dave Newby13, Mark Petrie14, Jianhua Wu15, Matthew R Sydes16,17.18, Chris P Gale3,4,5

\*Joint first authors

**Affiliations**

1. Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
2. Leeds Institute for Data Analytics, University of Leeds, Leeds, UK
3. Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
4. Hull York Medical School, University of York, York, UK
5. Academic Cardiovascular Unit, South Tees NHS Foundation Trust, James Cook University Hospital, Middlesbrough, UK
6. Department of cardiology, St. Paul’s Hospital, Vancouver, BC, Canada.
7. Department of Medical Sciences, Cardiology and Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden
8. Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
9. Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mount Sinai, New York, NY, USA
10. Liverpool Heart and Chest Hospital, Liverpool, UK
11. Division of Clinical Sciences, City St Georges University of London, London, UK
12. Oxford Heart Centre, Oxford University Hospitals, Oxford, UK
13. BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK
14. School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK
15. Wolfson Institute of Population Health, Queen Mary, University of London, UK
16. MRC Clinical Trials Unit at UCL, University College London, London, UK
17. BHF Data Science Centre, Health Data Research UK, HDR UK, London, UK
18. Data for R&D Programme, NHS England, London, UK

**Correspondence:**

Dr Asad Bhatty, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK. Email: A.N.Bhatty@leeds.ac.uk

Abstract: 263/300 words

Full text: 2999/3000 words

Figures: 6

Supplementary figures: 6

Tables: 2

Supplementary tables: 11

**Abstract**

**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.

**Methods**

Cardiovascular phase 3 or 4 randomised clinical trials (RCT) or multicentre observational studies published in the New England Journal of Medicine, Lancet or Journal of the American Medical Association between 1st January 2013 and 6th June 2024 from Embase and Ovid Medline were included. Two independent reviewers selected the studies and extracted the primary and secondary outcome measures from each publication.

**Results**

386 studies (83% RCTs; 17% observational) representing 10,699,147 participants were included. Studies investigated coronary heart disease (51%), cardiomyopathy / heart failure (22%), heart rhythm disease (15%), valvular heart disease (11%) and ‘other’ cardiovascular diseases (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 myocardial infarction (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, myocardial infarction and stroke varied across the studies.

**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.

**What is already known about the topic**

Major adverse cardiovascular events (MACE) are often used as a composite outcome measure in clinical studies of cardiovascular diseases. There is limited literature about the nature and definitions of outcome measures in cardiovascular studies, and how this may have changed over time.

**What this study adds**

For clinical studies of cardiovascular diseases, 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, as were primary outcome measures for cardiovascular death and myocardial infarction, making comparisons between studies difficult.

**How this study affects research**

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, cross-study comparisons and marketing applications 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.

**Introduction**

Primary outcome measures and their definitions are fundamental components of research that determine the sample size and evaluate the result of the study. A positive randomised clinical trial (RCT) can influence guideline recommendations and clinical practice.[1, 2] However, improving cardiovascular disease mortality,[3] an increasing time period to manifest the impact of interventions,[4] and an expansion in the use of routine data not originally collected for research purposes have catalysed changes to study design.[5-7] Approaches to increase the power of a study without increasing the sample size (and therefore not increasing costs) include using composite outcomes measures. Secondary outcome measures are employed to help interpret the primary outcome measure.

Major adverse cardiovascular events (MACE) are well-recognised composites, but there is heterogeneity in its classification and definition.[8-10] This can lead to uncertainty about the effectiveness of a treatment and is a potential signal of investigator bias.[11] Seemingly small differences in definitions, for example of peri-procedural myocardial infarction (MI), alter study conclusions and make comparisons between studies challenging.[12-14] To that end, in 2009 the US Food and Drug Administration established the Standardised Data Collection for Cardiovascular Trials.[15]

As part of the British Heart Foundation SCORE-CVD collaborative, we aimed to describe and summarise the use of outcome measures and their definitions in RCTs and multicentre observational studies of cardiovascular disease published in three highly-cited journals. Understanding the extent and depth of outcome measures in cardiovascular clinical studies helps improve the study design, conduct and result interpretability.

**Methods**

*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.[16] The protocol was pre-registered: <https://doi.org/10.25405/data.ncl.19264346>.

*Eligibility criteria*

Studies published in highly-cited journals included: New England Journal of Medicine (NEJM), Lancet and Journal of the American Medical Association (JAMA). Eligible studies were phase 3 or 4 RCTs or multicentre observational studies of patients with established cardiovascular disease or tested a cardiovascular intervention, published between 1st January 2013 and 6th June 2024. Cardiovascular disease was pre-specified as conditions typically managed by cardiologists: heart rhythm disease, coronary heart disease, cardiomyopathy and heart failure, and valvular heart disease.[17] Review articles, studies published in subsidiary journals, sub-studies of the main paper, secondary and meta-analyses, and studies in which outcome measures were not reported or not disclosed were excluded.

*Information sources and search strategy*

Embase and Ovid Medline was searched using a search strategy developed with a research librarian **(appendix 1)**. Recommended search filters for phase 3 and 4 RCTs and observational studies were used,[18, 19] and previously searches for heart disease were adapted.[20-22]

*Selection, data, and risk of bias*

Two reviewers (of CW, BB, PK, GB, SA, AT, AW, AB) independently selected studies. The titles and abstracts of studies were screened, and the full text was assessed for eligibility. Decisions were recorded using Rayyan software.[23] Disagreements were resolved through discussion with a third reviewer (CW). Seven reviewers contributed to study selection, and eight to data extraction.

Study characteristics included the journal, year of publication, continent(s) in which the study was delivered and the number of countries from which participants were recruited, funding sources (industry, non-industry or combined/both), cardiovascular disease category, number of participants, follow-up duration and study type (RCT or observational and device, drug or other). 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.[24] 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 and categorised according to their clinical topic or composite if there was more than one outcome measure considered, for example, all-cause mortality and stroke. We recorded the total number of primary and secondary outcomes provided in the manuscript.

**Data analysis**

*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. [25, 26]

*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 data synthesis on outcome measures was mapped by publication year, sample size, study design and cardiovascular disease. Outcome heterogeneity was described narratively by the author and their definitions were synthesised narratively. Stata 17 MP was used for analysis and R for data visualisation.

*Patient and public involvement (PPI)*

There was no PPI involvement in the conduct of this study. Results will be shared with a PPI working group who will co-author future work on patient reported outcome measures.[27]

**Role of funding source**

There was no funding for this study, however, the study was undertaken with the British Heart Foundation SCORE-CVD collaborative.

**Results**

*Study selection and characteristics*

Of 2,868 unique citations screened, 386 were included in the review after full-text evaluation **(figure 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. There were 10,699,147 participants recruited from six continents, most commonly from Europe (n=260, 67%). **(supplementary figure 1).** Most frequently, one country was included (n=162, 42%), and the maximum was 57 countries (median 3, IQR 1 to 12). During the study period, the median number of studies per year was 33 (IQR 26-40).

*Cardiovascular disease categories*

Most studies concerned coronary heart disease (n=197, 51%) followed by cardiomyopathy / heart failure (n=85, 22%), heart rhythm disease (n = 58, 15%), valvular heart disease (n = 42, 11%) and other (n = 4, 1%; **table 1**).

Overall, the most frequently reported primary outcome was a composite (243 studies, 63%; **figure 2**) and across each cardiovascular disease category. 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%) (**table 2** **and figure 3**). All-cause mortality and stroke were the most common components in the domains except for coronary heart disease (**table 2**).

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 **(figures 2 and 3)**. 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 **(figures 3).**

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 (**table 1**).

*Funding, intervention and outcome results*

Most studies (n=184, 48%) were industry funded, and most investigated devices (n=173, 45%) and drugs (n=169, 44%). A minority of studies investigated care processes or lifestyle measures (n=44, 11%). 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, **supplementary table 1 and 2**). Of these the most commonly 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, **supplementary table 1 and 2**).

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. (**supplementary table 3 and 4)**.

*Temporal trends*

The use of a composite primary outcome measure increased from 49% of studies in 2013 to a peak of 85% in 2018. The number of secondary outcomes per study increased from a mean of 3 in 2013 to 8 in 2023. 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 (**figures 4 and 5, supplementary table 5).** The median number of participants in RCTs appeared to decline over time (**figure 6**) and across funding sources and interventions apart from non-industry and ‘other’ RCTs where it appeared to increase **(supplementary table 6).** The median number of participants in observational trials increased from a median of 8,188 in 2013 to a median of 23,341 in 2023 with a peak of 114,871 in 2022 and was evident across funding sources and interventions (**supplementary table 6**).

*Outcome definitions*

*Mortality*

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

Cardiovascular mortality was reported in 107 studies (104 as part of the composite), and there was wide variation in the definitions used. The definitions were not always reported in the study manuscript, and were often absent from the protocol or supplementary materials (34%)[28-30] or were partially defined to include unexplained death only (15%)[31]. 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.[32, 33] This included: MI, pump failure, pulmonary embolism, stroke, presumed and confirmed sudden death, post procedural death and presumed cardiac death.[34]

Of the studies that reported partial definitions some included study specific definitions; presuming all deaths to be cardiovascular unless there was a clear demonstration of a non-cardiac cause,[35, 36] and having cardiovascular mortality as the first of two primary outcome measures (added post priori).[28]

*Myocardial infarction*

Myocardial infarction 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.[37-39]

Definitions (when given) varied. In 20% of studies, study-specific criteria were used. One study employed two definitions of MI, one for the primary outcome measure and the other for its secondary outcome measure,[40] to capture all types of MI. Another study changed the definition that was stated *a priori* to a contemporary definition,[41] with the adjudicating committee still blinded to the group allocation and results.[42] Recent consensus definitions such as the Third and Fourth Universal Definition of MI were deployed in the majority of studies (63%).[43-47] However, the definition of peri-procedural MI was inconsistent – for example, one required higher biomarker thresholds for defining an MI citing data that a more stringent definition ‘had greater prognostic significance than the universal definition types 4a and 5’.[43]

*Stroke*

In 50% of studies with stroke as the primary outcome measure, stroke was defined as a ‘non-traumatic focal neurologic deficit lasting greater than 24 hours’,[48] In 14% of studies a definition for stroke was not provided.[49] Consensus definitions included those by the Valve Academic Research Consortium-2 (VARC-2).[50]

*Bleeding*

Bleeding was a primary outcome measure in 42 studies (29 as part of a composite). Consensus definitions included the International Society on Thrombosis and Haemostasis (IISTH),[51] Thrombolysis in Myocardial Infarction (TIMI),[52] the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria[53] and the Bleeding Academic Research Consortium (BARC).[52] The most commonly used consensus definition was BARC (81%).

*Risk of bias*

Most (78%) of the 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 **(supplementary table 7).**

**Discussion**

In this systematic review of 386 RCTs and observational studies of cardiovascular diseases 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 this form of 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 leads to suboptimal interpretation and limits the comparison across similar studies.[11] 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 such as the universal definition of MI.[54] Adjudication within studies can differ due to multiple consensus definitions that are not aligned,[15, 46, 55], making meaningful comparisons between studies difficult. In contrast bleeding was an infrequent primary outcome (11% of all studies) with most definitions opting for BARC.[52] This could be because bleeding is becoming a less important outcome in intervention studies given the safety and efficacy of contemporary anti-thrombotic therapies.[56] 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 patients with low risk of bleeding were investigated.

Previous studies have demonstrated heterogeneity in how MACE is defined and classified. [8, 9] In this work, the components of composites were not limited to MACE, and up to six components were included. This is problematic as inappropriate combinations of composites may introduce bias because each component differs in clinical significance, [57, 58] particularly if they are not separated into safety and efficacy composites.[9] Subsequently, elevated event rates and treatment effects associated with less important components may ‘result in misleading impressions of the impact of treatment’.[59] As cardiovascular morbidity and mortality decline, studies need to be larger or combine outcomes measures to reach sufficient statistical power. 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.

Reporting bias can be compounded if outcome measures are not pre-specified and fully reported. It has been shown 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.[60] 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%).[32] This may occur because changing outcome definitions midway through a trial is unlikely to occur and could account for the small change as well as the presence of alternative consensus definitions for the common cardiovascular conditions. [50, 54, 61] 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.[11, 62, 63]

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.[18] Novel methods are employed to plan, conduct and interpret RCTs and observational studies, that include routinely collected data from electronic health records and registries.[64] 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,[65] as historically outcomes such as MI have limited specificity and sensitivity in administrative data.[66] The ADAPTABLE randomised 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.[67] Whilst adjudication of outcome measures is considered important to minimise noise and mitigate bias,[68] there are increasing data to support the use of routinely collected health data for outcome measure ascertainment.[68, 69] 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.[62]

In this carefully conducted review we present important findings that may guide improvements in the design and conduct of clinical research. However, there are limitations to our 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 studies including more observational trials from other journals with wide readership were not considered and the resultant analysis is therefore subject to publication bias. 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, [60] with limited analyses for outcomes that listed more than one primary outcome and of secondary outcome measures, for the main cardiovascular disease states. We therefore lack detail on outcomes that frequently appear as secondary outcome measures such as PROMS, and on outcomes for other cardiovascular diseases.

**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, cross-study comparisons and marketing applications 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.

**Competing interests**

All authors have completed the ICMJE uniform disclosure form at <https://www.icmje.org/disclosure-of-interest/> and declare:

CW, outside this work, reports research grants from British Heart Foundation and National Institute for Health Research and has unpaid roles with EHJ Quality of Care and Clinical Outcomes (Associate Editor), and NICE Indicator Advisory Committee.

GB, outside this work, received institutional grants / honoraria for lectures from Bayer, P.O. Zetterlings Foundation, Jeanssons Foundation, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Novo Nordisk, and Sanofi.

SA, outside this work, reports participation on a Data Safety Monitoring Board or Advisory Board for the British Coronary Intervention Society (BCIS) and leadership or fiduciary role in European Society of Cardiology quality of care programme.

RN, outside of this work, has received research grant / consulting fees from the British Heart Foundation, Leeds Hospital Charity, Daiichi Sankyo, British Heart Foundation Clinical Research Collaborative, Health Data Research UK, National Institute of Health and Care Research and Vitacam.

DLB, outside this work, reports research grants from Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, Cincor, Cleerly, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer Inc, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, 89bio, Otsuka, Alnylam, honoraria for lectures from American College of Cardiology, Baim Institute for Clinical Research, Belvoir Publications, Boston Scientific, Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Novartis, Population Health Research Institute, Rutgers University, Canadian Medical and Surgical Knowledge Translation Research Group, Cowen and Company, HMP Global, Journal of the American College of Cardiology, K2P, Level Ex, Medtelligence/ReachMD, MJH Life Sciences, Oakstone CME, Piper Sandler, Population Health Research Institute, Slack Publications, WebMD, Wiley, Society of Cardiovascular Patient Care, CSL Behring and royalties from Elsevier.

AJC, outside this work, reports consulting fees / honoraria for lectures from Bayer, Pfizer/BMS, Daiichi Sankyo, Acesion, InCarda, Abbott, Boston Scientific, Medtronic, Huya Bio, Biosense Webster, Sanofi and Menarini. AJC has leadership roles within Drug Safety Research Unit, Arrhythmia Alliance, Atrial Fibrillation Association and European Society of Cardiology.

RK, outside this work, reports research grants / honoraria for lectures from Boston Scientific Medtronic and Edwards and is the clinical lead for the UK TAVI registry.

DN, outside of this work, reports research grants from British Heart Foundation, Medical Research Council, Sir Jules Thorn and the Well come Trust.

MP, outside this work, reports research grants / honoraria for lectures from Boehringer Ingelheim, Roche, SQ Innovations, Astra Zeneca, Novartis, Novo Nordisk, Medtronic, Boston Scientific, Pharmacosmos, 3R LifeSciences, Abbott, Akero, Applied Therapeutics, Amgen, AnaCardio, Biosensors, Corteria, Novartis, Astra Zeneca, Abbvie, Bayer, Horizon Therapeutics, Foundry, Takeda, Cardiorentis, Siemens, Eli Lilly, Vifor, New Amsterdam, Moderna, Teikoku, LIB Therapeutics, Reprieve, FIRE 1, Corvia, Regeneron and is a member of Board of Heart Failure Association of ESC.

MRS reports research grants / speaker’s fees / consulting fees, outside this work, from Astellas, Clovis Oncology, Janssen, Pfizer, Novartis, Sanofi-Aventis, Eisai and Eli Lilly and is an independent unpaid member of many data monitoring committees from academic sponsors.

CPG has reports research grants / consulting / speakers fees, outside this work, from Alan Turing Institute, British Heart Foundation, National Institute for Health Research, Horizon 2020, Abbott Diabetes, Bristol Myers Squibb, European Society of Cardiology, AI Nexus, AstraZeneca, Amgen, Bayer, Boehrinher-Ingleheim, CardioMatics, Chiesi, Daiichi Sankyo, GPRI Research B.V., Menarini, Novartis, iRhythm, Organon, The Phoenix Group, Boston Scientific, Raisio Group, Wondr Medical, Zydus. C.P.G. is also a Deputy Editor: EHJ Quality of Care and Clinical Outcomes, NICE Indicator Advisory Committee member, Chair ESC Quality Indicator Committee member and participated on a Data Safety Monitoring Board or Advisory Board for DANBLCOK trial and TARGET CTCA trial.

All other authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Contributors**

CW, SA, GB and CPG conceived the study. AB, CW, SA, GB, BB, PHK, KR, AT contributed to data extraction. AB had full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. CW and AB drafted the manuscript. AB and AW performed the statistical analysis and provided the analysis of data. AB, CW and CPG provided interpretation of data. AB, CW, SA, RN, DLB, RS, AJC, RK, DN, MP, JW, MRS, CPG, contributed to the critical revision of the manuscript for important intellectual content. CPG and CW supervised the study and CPG is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Acknowledgements**

None

**Funding and grant/award information**

There was no funding for this study, however, the study was undertaken with the British Heart Foundation SCORE-CVD collaborative.

**Ethical approval information**

Not applicable.

**Data sharing statement**

All data requests should be submitted to c.p.gale@leeds.ac.uk for consideration.

**Patient and Public Involvement**

There was no PPI involvement in the conduct of this study. Results will be shared with a PPI working group who will co-author future work on patient reported outcome measures.

**Table 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 heart failure | 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 | | | | | | | | | |

**Table 2**: Characteristics of the most commonly reported outcome measures by cardiovascular disease category and study design

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Study type** | **Number of studies**  **(% of category)** | **Most common primary outcome Most common components**  **(n = number of studies, % of category)** | |
| Coronary disease and ischaemia | RCT | 172 (87) | Composite  (142, 82%) | MI  (125, 88%)  CV mortality  (77, 54%). |
|  | Observational | 25 (13) | All-cause mortality  (11, 48%) | - |
| Cardiomyopathy and heart failure | RCT | 74 (87) | Composite  (45, 61%) | Cause specific hospitalisation  (28, 62%)  All-cause mortality  (26, 58%) |
|  | Observational | 11 (13) | All-cause mortality  (5, 46%) |  |
| Heart rhythm | RCT | 43 (74) | Composite  (14, 31%) | Stroke  (8, 57%)  Systemic embolism  (6, 43%) |
|  | Observational | 15 (26) | Composite  (7, 54%) | All-cause mortality  (5, 71%)  Stroke  (4, 57%) |
| Valvular heart disease | RCT | 28 (67) | Composite  (18, 64%) | All-cause mortality  (17, 94%)  Stroke  (13, 72%) |
|  | Observational | 14 (33) | Composite  (6, 43%) | Stroke  (5, 83%)  All-cause mortality  (5, 83%) |

Abbreviations: RCT: randomised clinical trial, Obs: observational studies, MI: Myocardial Infarction, CV mortality: Cardiovascular mortality

**References**

* 1. Stanley K. Design of Randomized Controlled Trials. Circulation. 2007;115(9):1164-9.
* 2. Jüni P, Antoniou S, Arbelo E, Buccheri S, Cikes M, da Costa BR, et al. 2024 Revision of the level of evidence grading system for ESC clinical practice guideline recommendations I: therapy and prevention. European Heart Journal. 2025.
* 3. Wang H NM, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459-544.
* 4. Soloveva A, Gale CP, Han NT, Hurdus B, Aktaa S, Palin V, et al. Associations of health-related quality of life with major adverse cardiovascular and cerebrovascular events for individuals with ischaemic heart disease: systematic review, meta-analysis and evidence mapping. Open Heart. 2023;10(2).
* 5. Karanatsios B, Prang K-H, Verbunt E, Yeung JM, Kelaher M, Gibbs P. Defining key design elements of registry-based randomised controlled trials: a scoping review. Trials. 2020;21(1):552.
* 6. Gale CP, Stocken DD, Aktaa S, Reynolds C, Gilberts R, Brieger D, et al. Effectiveness of GRACE risk score in patients admitted to hospital with non-ST elevation acute coronary syndrome (UKGRIS): parallel group cluster randomised controlled trial. BMJ. 2023;381:e073843.
* 7. Hayward CJ, Batty JA, Westhead DR, Johnson O, Gale CP, Wu J, Hall M. Disease trajectories following myocardial infarction: insights from process mining of 145 million hospitalisation episodes. EBioMedicine. 2023;96:104792.
* 8. Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC Med Res Methodol. 2021;21(1):241.
* 9. Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. J Am Coll Cardiol. 2008;51(7):701-7.
* 10. Shepshelovich D, Yahav D, Rome DR, Goldvaser H, Richter I, Hermann EA, Barr RG. Heterogeneity of Primary Outcomes in Large Atherosclerotic Cardiovascular Disease Trials Published in Prominent Medical Journals. JAMA Intern Med. 2025.
* 11. Bhatty A, Wilkinson, C, Sydes, M, Gale, C. P,. Defining the need for cardiovascular event definitions. Eur Heart J Qual Care Clin Outcomes. 2024;10(2):105-7.
* 12. Hara H, Serruys PW, Takahashi K, Kawashima H, Ono M, Gao C, et al. Impact of Peri-Procedural Myocardial Infarction on Outcomes After Revascularization. J Am Coll Cardiol. 2020;76(14):1622-39.
* 13. Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice M-C, Puskas J, et al. Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease. New England Journal of Medicine. 2019;381(19):1820-30.
* 14. Cohen D, Brown E. New England Journal of Medicine reviews controversial stent study. BMJ. 2020;368:m878.
* 15. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation. 2018;137(9):961-72.
* 16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372:n71.
* 17. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021.
* 18. BMJ Best Practice. Study design search filters [Available from: <https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/>.
* 19. Glanville J, Kotas E, Featherstone R, Dooley G. Which are the most sensitive search filters to identify randomized controlled trials in MEDLINE? J Med Libr Assoc. 2020;108(4):556-63.
* 20. Clark A, Sousa B, Smith A, Steele D, Rader T, MacDougall D, et al. Remote monitoring programs for cardiac conditions. Canadian Journal of Health Technologies. 2021;1(9).
* 21. Abraham LN, Sibilitz KL, Berg SK, Tang LH, Risom SS, Lindschou J, et al. Exercise-based cardiac rehabilitation for adults after heart valve surgery. Cochrane Database Syst Rev. 2021;5(5):Cd010876.
* 22. Roule V, Verdier L, Blanchart K, Ardouin P, Lemaitre A, Bignon M, et al. Systematic review and meta-analysis of the prognostic impact of cancer among patients with acute coronary syndrome and/or percutaneous coronary intervention. BMC Cardiovasc Disord. 2020;20(1):38.
* 23. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
* 24. Huffman MD, Mohanan PP, Devarajan R, Baldridge AS, Kondal D, Zhao L, et al. Effect of a Quality Improvement Intervention on Clinical Outcomes in Patients in India With Acute Myocardial Infarction: The ACS QUIK Randomized Clinical Trial. Jama. 2018;319(6):567-78.
* 25. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898.
* 26. Wells GA SB, O’Connell D, Peterson J, Welch V, Losos M, Tugwell P,. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2009.
* 27. 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; Aug 20:qcae073. doi: 10.1093/ehjqcco/qcae073.
* 28. Packer M, O'Connor C, McMurray JJV, Wittes J, Abraham WT, Anker SD, et al. Effect of ularitide on cardiovascular mortality in acute heart failure. New England Journal of Medicine. 2017;376(20):1956-64.
* 29. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: A randomized clinical trial. JAMA - Journal of the American Medical Association. 2017;318(8):713-20.
* 30. Maeng M, Tilsted HH, Jensen LO, Krusell LR, Kaltoft A, Kelbaek H, et al. Differential clinical outcomes after 1 year versus 5 years in a randomised comparison of zotarolimus-eluting and sirolimus-eluting coronary stents (the SORT OUT III study): a multicentre, open-label, randomised superiority trial. Lancet. 2014;383(9934):2047-56.
* 31. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA. 2014;312(19):1988-98.
* 32. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, et al. 2017 cardiovascular and stroke endpoint definitions for clinical trials. Circulation. 2018;137(9):961-72.
* 33. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet. 2016;388(10055):2015-22.
* 34. McMurray JJ, Krum H, Abraham WT, Dickstein K, Kober LV, Desai AS, et al. Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure. New England Journal of Medicine. 2016;374(16):1521-32.
* 35. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet. 2017;390(10104):1747-57.
* 36. Brilakis ES, Edson R, Bhatt DL, Goldman S, Holmes DR, Jr., Rao SV, et al. Drug-eluting stents versus bare-metal stents in saphenous vein grafts: a double-blind, randomised trial. Lancet. 2018;391(10134):1997-2007.
* 37. Nickenig G, Weber M, Lurz P, von Bardeleben RS, Sitges M, Sorajja P, et al. Transcatheter edge-to-edge repair for reduction of tricuspid regurgitation: 6-month outcomes of the TRILUMINATE single-arm study. Lancet. 2019;394(10213):2002-11.
* 38. Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet. 2016;388(10056):2142-52.
* 39. Ray KK, Nicholls SJ, Buhr KA, Ginsberg HN, Johansson JO, Kalantar-Zadeh K, et al. Effect of Apabetalone Added to Standard Therapy on Major Adverse Cardiovascular Events in Patients With Recent Acute Coronary Syndrome and Type 2 Diabetes: A Randomized Clinical Trial. JAMA. 2020;323(16):1565-73.
* 40. Bangalore S, Maron DJ, O'Brien SM, Fleg JL, Kretov EI, Briguori C, et al. Management of coronary disease in patients with advanced kidney disease. New England Journal of Medicine. 2020;382(17):1608-18.
* 41. Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention. 2010;5(7):871-4.
* 42. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: The OPTIMIZE randomized trial. Jama. 2013;310(23):2510-22.
* 43. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. N Engl J Med. 2020;382(15):1395-407.
* 44. Windecker S, Latib A, Kedhi E, Kirtane AJ, Kandzari DE, Mehran R, et al. Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk. N Engl J Med. 2020;382(13):1208-18.
* 45. Puymirat E, Cayla G, Simon T, Steg PG, Montalescot G, Durand-Zaleski I, et al. Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction. N Engl J Med. 2021;385(4):297-308.
* 46. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-35.
* 47. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. New England Journal of Medicine. 2023;388(15):1353-64.
* 48. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-92.
* 49. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA. 2014;312(19):1988-98.
* 50. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg. 2012;42(5):S45-60.
* 51. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692-4.
* 52. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized Bleeding Definitions for Cardiovascular Clinical Trials. Circulation. 2011;123(23):2736-47.
* 53. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med. 1993;329(10):673-82.
* 54. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138(20):e618-e51.
* 55. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, et al. Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. Circulation. 2018;137(24):2635-50.
* 56. Kamran H, Jneid H, Kayani WT, Virani SS, Levine GN, Nambi V, Khalid U. Oral Antiplatelet Therapy after Acute Coronary Syndrome: A Review. JAMA - Journal of the American Medical Association. 2021;325(15):1545-55.
* 57. Cordoba G, Schwartz L, Woloshin S, Bae H, Gotzsche PC. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. BMJ. 2010;341:c3920.
* 58. Lim E, Brown A, Helmy A, Mussa S, Altman DG. Composite outcomes in cardiovascular research: a survey of randomized trials. Ann Intern Med. 2008;149(9):612-7.
* 59. Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ. 2007;334(7597):786.
* 60. Goldacre B, Drysdale H, Dale A, Milosevic I, Slade E, Hartley P, et al. COMPare: a prospective cohort study correcting and monitoring 58 misreported trials in real time. Trials. 2019;20(1):118.
* 61. Abraham WT, Psotka MA, Fiuzat M, Filippatos G, Lindenfeld J, Mehran R, et al. Standardized Definitions for Evaluation of Heart Failure Therapies: Scientific Expert Panel From the Heart Failure Collaboratory and Academic Research Consortium. JACC Heart Fail. 2020;8(12):961-72.
* 62. Wilkinson C, Bhatty A, Batra G, Aktaa S, Smith AB, Dwight J, 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.
* 63. Bhatty A, Wilkinson C, Batra G, Aktaa S, Smith AB, Wahab A, 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. 2024.
* 64. BHF Data Science Centre. Standardising Clinical Outcome measures in Routinely-collected Electronic healthcare systems data (SCORE-CVD) Initial Report. . Zenodo. 2023.
* 65. Lauer MS, D'Agostino RB, Sr. The randomized registry trial--the next disruptive technology in clinical research? N Engl J Med. 2013;369(17):1579-81.
* 66. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of Myocardial Infarction Diagnoses in Administrative Databases: A Systematic Review. PLOS ONE. 2014;9(3):e92286.
* 67. Marquis-Gravel G, Hammill BG, Mulder H, Roe MT, Robertson HR, Wruck LM, et al. Validation of Cardiovascular End Points Ascertainment Leveraging Multisource Electronic Health Records Harmonized Into a Common Data Model in the ADAPTABLE Randomized Clinical Trial. Circ Cardiovasc Qual Outcomes. 2021;14(12):e008190.
* 68. Meah MN, Denvir MA, Mills NL, Norrie J, Newby DE. Clinical endpoint adjudication. Lancet. 2020;395(10240):1878-82.
* 69. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet. 2015;385(9985):2383-91.

**Legends:**

**Figure 1.** PRISMA diagram of included studies.

**Figure 2.** Temporal trends in primary outcome measures for A) randomised clinical trials and B) observational studies.

**Figure 3.** Temporal trends in the most common components of composite outcome measures in A) randomised clinical trials and B) observational studies.

**Figure 4**. Median number of secondary outcome measures by study design and funding.

**Figure 5.** Temporal trends in the median number of components of primary and secondary outcomes by study type.

**Figure 6.** 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.