Data standards for clinical endpoints in cardiovascular disease

A literature review protocol

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**Review question**

What clinical endpoints are reported in the literature for patients with cardiovascular disease?

**Rationale**

The appropriate *a priori* selection of outcomes used in clinical research is essential for meaningful and unbiased research,1 and for drug and device monitoring. Registry-based randomised clinical trials (R-RCTs) are becoming increasingly common, and provide opportunities for efficient study delivery and gaining new insights into a range of health conditions.2 This requires a clear understanding of what clinical endpoints are currently in use for studies of people with cardiovascular disease, and also of how robust the evidence is supporting such clinical endpoints.3

This systematic review aims to identify the clinical endpoints that are used in contemporary major randomised clinical trials and multicentre observational studies of cardiovascular disease, examine their definitions, and assess the extent of heterogeneity to inform whether there is a need to develop harmonised definitions of these endpoints.

**Search sources**

MEDLINE, EMBASE

**Participants/population**

Adults with cardiovascular disease, to include:

* Heart rhythm disease
* Coronary artery disease and ischaemic heart disease
* Cardiomyopathy and heart failure
* Valvular heart disease

**Intervention(s), exposure(s)**

Cardiovascular disease or treatment for diagnosed cardiovascular disease

**Comparator(s)/control**

Any or none

**Types of study to be included**

Inclusion criteria:

* Phase 3 or 4 randomised control trial or multi centre observational cohort study
* Published in NEJM, Lancet, JAMA
* Publication date 2000 to present in English
* One or more clinical outcome (including biomarker, imaging, and patient reported outcome measures) is reported

Exclusion criteria:

* Conference abstracts or review articles
* Clinical outcomes not reported, or not defined
* Case control, cross-over and cross-sectional observational studies
* Studies in which the outcome is a risk stratification score or model
* Studies that include only cardiac surgical or post-operative care (with no cardiology care such as TAVI)
* Studies that evaluate diagnostic tests to identify presence or absence of cardiovascular disease
* Studies examining care during or immediately after cardiac arrest
* Sub-studies where the main study is already included in the review

**Main outcome(s)**

* Investigators choice of primary clinical endpoints
* The diagnostic criteria that defined the clinical endpoint

**Selection of studies**

* Titles and abstracts of all identified studies will be independently screened by two researchers, blinded to each other’s decisions.
* Disagreements will be resolved by a third reviewer
* Decisions will be recorded using Rayyan online software

**Search strategy**

Medline and Embase will be searched. Recommended search filters for RCT4 and observational (cohort and case-control)1 search filters were used. Previously published searches for heart disease were adapted.5-7 The search strategy is in Appendix A.

**Data extraction**

The following data will be extracted into an Excel spreadsheet, and then a sample will be checked for accuracy by a second reviewer

|  |  |
| --- | --- |
| Study title |  |
| Year of publication |  |
| Journal | JAMA/NEJM/Lancet |
| Study type | Randomised control trialMulti-centre observational cohort study |
| Number of countries recruited from |  |
| Cardiovascular condition |  |
| Intervention/exposure under investigation |  |
| Total number of participants |  |
| Median (IQR) / mean (SD) duration of follow-up, months |  |
| **Outcomes**  |  |
| Primary endpoint  |  |
| When was primary endpoint ascertained? |  |
| Definition of primary endpoint |  |
| Adjudication of primary endpoint |  |

**Quality assessment**

This will be completed at the same time as data extraction, using:

* Newcastle-Ottawa – for cohort studies.8
* RoB 2 – for randomised studies.9

A sample will be checked by a second reviewer.

**Analysis**

The cardiovascular condition will be categorised as in the inclusion criteria (eg. Atrial fibrillation, aortic stenosis etc.). Study data will be summarised as counts and percentages, stratified by cardiovascular condition under investigation.

The outcomes reported (e.g. ejection fraction, quality of life) will be thematically categorised, and these will be used to classify subsequent articles, whilst remaining open to adding additional categories if further themes emerge. The heterogeneity of clinical outcomes will be estimated, making use of the verbatim description of the outcome and the variation in definition. This will be summarised statistically and/or narratively, depending on the available data.

**References**

[1] BMJ Best Practice. Study design search filters. <https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/> (06/09/2021 last accessed).

[2] Solomon SD, Pfeffer MA. The Future of Clinical Trials in Cardiovascular Medicine. *Circulation* 2016; **133**: 2662-2670.

[3] Meah MN, Denvir MA, Mills NL, Norrie J, Newby DE. Clinical endpoint adjudication. *Lancet* 2020; **395**: 1878-1882.

[4] 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**: 556-563.

[5] 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**.

[6] 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 of Systematic Reviews* 2021.

[7] 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 Cardiovascular Disorders* 2020; **20**: 38.

[8] 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-analyses2009.

[9] 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.

**Appendix A: Search strategy**

**Medline search**

|  |  |
| --- | --- |
| 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=2000-2021 |
| 68 | ("new england journal of medicine" or lancet or jama).jn. |
| 69 | 67 and 68 |

**Embase search**

|  |  |
| --- | --- |
| 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 atheroscleroses or arteriosclerosis or arterioscleroses or (coronary adj5 disease\*)).ti,ab,kw. |
| 19 | (hard\* adj3 arter\*).ti,ab,kw. |
| 20 | (plaque adj4 build\*).ti,ab,kw. |
| 21 | heart rehabilitation/ |
| 22 | ((cardiac\* or cardio\* or heart\*) adj5 (rehab\* or conditioning\*)).ti,ab,kw. |
| 23 | exp Aortic Valve/ |
| 24 | exp Aortic Valve Stenosis/ |
| 25 | exp Mitral Valve/ |
| 26 | exp mitral valve stenosis/ |
| 27 | valvular heart disease/ |
| 28 | exp mitral valve regurgitation/ |
| 29 | (left adj2 valv\*).af. |
| 30 | (native adj2 valve\*).af. |
| 31 | (mitral adj2 valv\*).af. |
| 32 | (aortic adj2 valv\*).af. |
| 33 | (valve adj2 (disease\* or stenos\* or insufficien\*)).tw. |
| 34 | heart valve replacement/ |
| 35 | heart valve prosthesis/ |
| 36 | (valve adj2 (surg\* or replace\* or repair\* or prosthe\* or implant\* or procedure\*)).tw. |
| 37 | MitraClip.tw. |
| 38 | transcatheter aortic valve implantation/ |
| 39 | TAVI.tw. |
| 40 | or/1-39 [cardiovascular diseases] |
| 41 | exp cohort analysis/ |
| 42 | exp longitudinal study/ |
| 43 | exp prospective study/ |
| 44 | exp follow up/ |
| 45 | cohort$.tw. |
| 46 | exp case control study/ |
| 47 | (case$ and control$).tw. |
| 48 | or/41-47 [BMJ Embase cohort and case-control strategy] |
| 49 | Randomized controlled trial/ |
| 50 | Controlled clinical study/ |
| 51 | random$.ti,ab. |
| 52 | randomization/ |
| 53 | intermethod comparison/ |
| 54 | placebo.ti,ab. |
| 55 | (compare or compared or comparison).ti. |
| 56 | ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. |
| 57 | (open adj label).ti,ab. |
| 58 | ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. |
| 59 | double blind procedure/ |
| 60 | parallel group$1.ti,ab. |
| 61 | (crossover or cross over).ti,ab. |
| 62 | ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. |
| 63 | (assigned or allocated).ti,ab. |
| 64 | (controlled adj7 (study or design or trial)).ti,ab. |
| 65 | (volunteer or volunteers).ti,ab. |
| 66 | human experiment/ |
| 67 | trial.ti. |
| 68 | or/49-67 |
| 69 | (random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) |
| 70 | Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) |
| 71 | (((case adj control$) and random$) not randomi?ed controlled).ti,ab. |
| 72 | (Systematic review not (trial or study)).ti. |
| 73 | (nonrandom$ not random$).ti,ab. |
| 74 | Random field$.ti,ab. |
| 75 | (random cluster adj3 sampl$).ti,ab. |
| 76 | (review.ab. and review.pt.) not trial.ti. |
| 77 | we searched.ab. and (review.ti. or review.pt.) |
| 78 | update review.ab. |
| 79 | (databases adj4 searched).ab. |
| 80 | (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 monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ |
| 81 | Animal experiment/ not (human experiment/ or human/) |
| 82 | or/69-81 |
| 83 | 68 not 82 [Cochrane Embase RCT filter] |
| 84 | 48 or 83 [Cohort or case control studies or Rcts] |
| 85 | 40 and 84 [cardiovascular diseases and cohort or case control studies or RCTs] |
| 86 | (exp adolescent/ or exp child/ or exp infant,newborn/) not exp adult/ |
| 87 | 85 not 86 [adult studies only] |
| 88 | lancet.jn. |
| 89 | new england journal of medicine.jn. |
| 90 | (jama or jama chicago ill or "jama journal of the american medical association").jn. |
| 91 | or/88-90 |
| 92 | 87 and 91 [results limited to specific journals] |
| 93 | limit 92 to yr="2000 - 2021" |
| 94 | remove duplicates from 93 |