

Original citation:

Haywood, Kirstie L., Whitehead, Laura, Nadkarni, Vinay M., Achana, Felix A., Beesems, Stefanie, Böttiger, Bernd W., Brooks, Anne, Castrén, Maaret, Ong, Marcus E. H., Hazinski, Mary Fran, Koster, Rudolph W., Lilja, Gisela, Long, John, Monsieurs, Koenraad G., Morley, Peter T., Morrison, Laurie, Nichol, Graham, Oriolo, Valentino, Saposnik, Gustavo, Smyth, Michael A., Spearpoint, Ken, Williams, Barry and Perkins, Gavin D. (2018) COSCA (Core Outcome Set for Cardiac Arrest) in adults : an advisory statement from the International Liaison Committee on Resuscitation. *Circulation* . doi:10.1161/CIR.0000000000000562

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Core Outcome Set for Cardiac Arrest (COSCA) in adults: An Advisory Statement

From the International Liaison Committee on Resuscitation

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1 [h1]Abstract

2 Cardiac arrest effectiveness trials have traditionally reported outcomes that focus on survival.
3 A lack of consistency in outcome reporting between trials limits the opportunities to pool
4 results for meta-analysis. The Core Outcome Set for Cardiac Arrest (COSCA) initiative, a
5 partnership between patients, their partners, clinicians, research scientists, and the
6 International Liaison Committee on Resuscitation, sought to develop a consensus core
7 outcome set for cardiac arrest for effectiveness trials. Core outcome sets are primarily
8 intended for large, randomized clinical effectiveness trials (sometimes referred to as
9 *pragmatic trials, phase III/IV trials*) rather than for pilot or efficacy studies.

10

11 A systematic review of the literature combined with qualitative interviews among cardiac
12 arrest survivors was used to generate a list of potential outcome domains. This list was
13 prioritized through a Delphi process, which involved clinicians, patients, and their
14 relatives/partners. An international advisory panel narrowed these down to 3 core domains by
15 debate leading to consensus. The writing group refined recommendations for when these
16 outcomes should be measured and further characterized relevant measurement tools.

17

18 Consensus emerged that a core outcome set for reporting on effectiveness studies of cardiac
19 arrest (COSCA) in adults should include survival, neurologic function, and health-related
20 quality of life. This should be reported as survival status and modified Rankin Scale score at
21 hospital discharge and / or 30 days. Health-related quality of life should be measured by
22 using 1 or more tools from Health Utilities Index version 3, Short-Form 36-Item Health
23 Survey, EuroQol 5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest,
24 if resources allow.

25

1 [h1]Introduction

2 Sudden cardiac arrest is one of the leading causes of death in industrialized nations. In the
3 United States, approximately 360 000 cardiac arrests are attended by emergency services
4 each year, with only 10.6% of patients surviving to hospital discharge.¹ Similar statistics
5 apply across Europe and all other industrialized areas worldwide.^{2, 3} However, survival rates
6 vary widely both globally⁴ and regionally,^{5, 6} with 4-fold or more regional variations reported.
7 These low and variable survival rates highlight the importance of research that seeks to
8 improve patient outcomes.

9
10 Randomized trials are important tools for evaluating the clinical and cost-effectiveness of
11 interventions for in- and out-of-hospital cardiac arrest. Two broad types of trials have been
12 described—efficacy and effectiveness. Efficacy (sometimes called *explanatory*) trials aim to
13 test whether an intervention works under optimal situations. Effectiveness (sometimes called
14 *pragmatic*) trials are designed to assess how well an intervention works in routine clinical
15 practice.⁷ Ordinarily, efficacy trials focus on assessing the impact of an intervention on a
16 short-term outcome that is well-correlated with long-term prognosis. Effectiveness trials seek
17 to provide evidence of the longer-term health impact of an intervention.^{8, 9} Evaluated
18 outcomes may include clinical, clinician-reported, and patient-reported outcomes and
19 resource use or economic impact. Clinical trials provide essential evidence of the relative
20 benefit of an intervention for stakeholders as diverse as clinicians, patients, and policy
21 makers. Outcome selection is, therefore, an important aspect of trial design.^{9, 10}

22
23 Sometimes multiple trials may evaluate the same intervention in different settings.
24 Reconciling disparate trial results can be challenging if each trial evaluated different
25 outcomes at different timepoints. A systematic review of cardiac arrest trials published

1 between 2000 and 2012 included 61 publications that identified more than 160 different trial
2 outcomes.¹¹ No single outcome was reported across all trials. The majority of outcomes
3 reflected short-term clinical and clinician-reported outcomes, focusing on pathophysiologic
4 manifestations and process-based measures. While survival was the most commonly reported
5 outcome, 39 different definitions of survival were used. Patient-reported outcomes¹² were
6 rarely reported, although more recent trials have included these outcomes.^{13, 14} This suggests
7 that essential evidence of the impact of care from the survivors' perspective is currently
8 missing from clinical trials.

9
10 Adopting a consistent approach to outcome reporting for effectiveness trials has the potential
11 to reduce heterogeneity in reporting, improve transparency in outcome selection, reduce
12 reporting bias, and increase information available to pool for meta-analysis. Standardized
13 reporting frameworks have been developed for reporting the findings of observational studies
14 drawn from resuscitation registries.^{15, 16} These recommend 23 core data elements and 30
15 supplementary elements across the 5 domains of system, dispatch, patient, process, and
16 outcome.¹⁷ International guidelines exist for core outcomes to use in effectiveness trials in
17 patients with other conditions.¹⁸ Becker et al considered choices of primary outcomes across
18 a range of resuscitation science studies but concluded that no single primary outcome was
19 appropriate for all studies of cardiac arrest.¹⁹ However, no international guidelines exist to
20 define a focused core outcome set (COS) for use in effectiveness trials in patients with
21 cardiac arrest.

22
23 The Core Outcome Measures for Effectiveness Trials (COMET) initiative promotes the
24 development and application of agreed standardized sets of outcomes, known as *core*
25 *outcome sets*.²⁰

1 A COS is defined as a small, standardized group of outcomes that should be measured and
2 reported, *as a minimum*, in all effectiveness trials for a specific health area.^{20, 21} Effectiveness
3 trials should aim to capture the COS as part of their *a priori*-defined primary or secondary
4 outcomes.

5

6 The COSCA initiative, in collaboration with the International Liaison Committee on
7 Resuscitation (ILCOR), sought to develop a COS for cardiac arrest effectiveness trials
8 covering both in- and out-of-hospital cardiac arrest. This consensus paper draws on the views
9 and experiences of patients, the public, clinicians, policy makers, researchers, and the
10 international perspectives represented through the ILCOR collaborative network. The process
11 was informed by systematic reviews of the literature, as well as qualitative research involving
12 cardiac arrest survivors. A total of 168 participants used a Delphi process to draft a core
13 cardiac arrest outcome set, and a 2-day meeting was convened to develop consensus
14 recommendations.

15 **[h1]Methods**

16 The available evidence associated with the development of COSs^{18, 20} and the websites of key
17 COS development groups (COMET and Outcome Measures in Rheumatoid Arthritis Clinical
18 Trials [OMERACT], later renamed *Outcome Measures in Rheumatology*) informed our
19 approach. The project was registered with the COMET initiative ([www.comet-](http://www.comet-initiative.org/studies/details/284)
20 [initiative.org/studies/details/284](http://www.comet-initiative.org/studies/details/284)). Ethical approval was obtained from the National Health
21 Service Black Country Research Ethics Committee (13/WM/0464) to enable patients/partners
22 to participate.

23

1 Development of a COS involved 2 key steps: development of a core domain set (ie, what to
2 measure) followed by identification of appropriate measurement tools (ie, how to measure).^{18,}

3 ²⁰ A *core domain set* was defined as referring to the minimum number of health domains
4 (outcomes or aspects of health) that must be assessed. That is, it specifies *what* should be
5 measured. Importantly, this stage was driven by what is important and not how an outcome is
6 assessed. The second stage involved the establishment of a core outcome measurement set,
7 that is, the specific methods of assessment (ie, *how* to measure) for the domains identified in
8 step 1. The selection of measurement tools was informed by an appraisal of measurement
9 quality, relevance, and feasibility.

10

11 The OMERACT initiative suggests that a COS should seek to include at least 1 health
12 domain across each of 4 core areas of health (Figure 1): 3 core areas consider the impact of a
13 health condition (ie, survival, life impact, economic impact/resource use), and the fourth core
14 area reflects any pathophysiologic manifestations associated with the condition.¹⁸ Several
15 reviews^{11, 22, 23} suggest that these domains are relevant and encompass the large number of
16 outcomes assessed in cardiac arrest trials.

17

18 To develop the consensus outcome criteria, a 4-stage approach was used, which consisted of
19 the following steps, which are each explained in detail:

- 20 • Stage 1: Generation of an extensive list of potential outcomes across 4 core areas of
21 health
- 22 • Stage 2: International Delphi to refine and prioritize a list of potential outcomes
- 23 • Stage 3: International expert panel meeting
- 24 • Stage 4: Synthesis of findings and recommendations for measurement tools

25

1 ***[h2]Stage 1: Generation of an Extensive List of Potential Outcomes Across 4 Core Areas***
2 ***of Health***

3 This stage was informed by a systematic review of the literature and qualitative interviews
4 with cardiac arrest survivors and their partners. The systematic review focused on the
5 identification of outcomes reported from randomized controlled trials that enrolled adults
6 who had sustained a cardiac arrest.¹¹ The findings from the systematic review were
7 supplemented by conducting semi-structured interviews with adult cardiac arrest survivors
8 (and, if available, their partners) between 3 and 12 months after discharge from hospital
9 following their cardiac arrest. Interviews were conducted, recorded, and transcribed by using
10 NVivo (QSR International 2012) by L.W. Data were analyzed by using Interpretative
11 Phenomenological Analysis, which seeks to capture the individuals' experience of a
12 phenomenon and how they understand their experiences.²⁴ Findings from the systematic
13 review and qualitative research were synthesized to produce an extensive list of potential
14 outcomes. These were grouped under the OMERACT core area headings of survival, life
15 impact, resource use/economic, and pathophysiologic manifestations of cardiac arrest for
16 consideration in stage 2.

17

18 ***[h2]Stage 2: International Delphi to Refine and Prioritize List of Potential Outcomes***

19 The list of potential outcomes identified during stage 1 were placed into an online survey tool
20 (SurveyMonkey, Dublin, Ireland). Separate surveys were developed for healthcare
21 professionals and patients/patient advocates. The ILCOR network of 7 regional resuscitation
22 councils was used to solicit the views of healthcare professionals and patient and public
23 advocates. Each ILCOR member (n=27) was asked to invite 6 healthcare professionals and 3
24 patients to participate in the relevant surveys by email. The outcomes were prioritized in 2
25 rounds. Questions were structured to allow participants to rate the importance of each

1 outcome at 5 different time points across the patient journey: during cardiopulmonary
2 resuscitation (CPR), immediately after CPR, during hospitalization, at hospital discharge, and
3 within the first year after the cardiac arrest. In the first round, survey participants were also
4 given the opportunity to suggest additional outcomes they considered important if they were
5 not currently included in the survey. At the end of each round, outcomes rated as *critical*
6 *importance* by greater than 70% of respondents and rated as *limited importance* by less than
7 15% of respondents were advanced for additional consideration by the expert panel in stage
8 3. Similarly, those outcomes rated *of limited importance* by greater than 70% of respondents
9 and *of critical importance* by less than 15% of respondents were discarded. The findings
10 from the first round were summarized and presented for a second round of prioritization. Any
11 new suggestions were included in the second round. The second round of prioritization
12 differed by asking participants to rank outcomes according to importance. Outcomes that
13 received strong support (more than 70% agreement) were also advanced for consideration by
14 the expert panel in stage 3. Outcomes that received moderate support (60%–69% agreement)
15 were also presented to the expert panel in stage 3.

16

17 ***[h2]Stage 3: International Expert Panel Meeting***

18 The aim of the international expert panel was to consider the shortlist of outcomes identified
19 during stage 2 and select a COS comprising 4 to 8 outcomes and make recommendations of
20 measurement tools to capture those outcomes. A 2-day consensus meeting was convened in
21 Prague, Czech Republic, in October 2015. A group of experts uninformed in previous stages
22 was purposefully selected to capture those involved in clinical research (clinicians, clinical
23 trialists, methodologists), experts in the use of measurement tools for cardiac arrest,
24 healthcare providers involved in treating patients with cardiac arrest (physicians, nurses,

1 paramedics, allied health professionals), and survivors of cardiac arrests and patient
2 advocates.

3

4 Before the meeting, the participants were sent a written summary of the outcome selection
5 process described above. At the start of the meeting, an overview of steps undertaken and
6 findings from stages 1 and 2 were presented. The shortlisted outcomes were presented in a
7 matrix that covered the OMERACT core area headings of survival, life impact, resource
8 use/economic, and pathophysiologic manifestations of cardiac arrest during CPR,
9 immediately after CPR, during hospitalization, at hospital discharge, and within the first year
10 after the cardiac arrest. Initial presentations were followed by semi-structured, small-group
11 discussions that covered the 4 core areas. Each core area was assigned a facilitator who
12 supported 4 rounds of discussions on that topic. Each discussion group included a survivor of
13 cardiac arrest or patient advocate, as well as several researchers and clinicians who
14 participated in small-group discussion across each core area. Each group nominated a
15 recorder. The groups were tasked to consider the importance, relevance, acceptability, and
16 feasibility of the short-listed outcomes as potential core outcomes for cardiac arrest
17 effectiveness trials. The facilitator encouraged all group members to participate in
18 discussions and shared key findings from each group with the next. This enabled
19 consideration of and building upon what other participants discussed, facilitated the
20 identification of issues of agreement and disagreement, and supported a flow of new ideas or
21 key issues between groups. Participants, thereafter, reconvened in a whole-group discussion
22 session: facilitators and group recorders summarized feedback from the group discussion,
23 including areas of agreement and disagreement. The large-group discussion sought to
24 collectively explore agreement and refine issues or concerns raised within each core area. At
25 the end of the first day, expert panel members were invited to reflect on the day's discussions

1 and then vote for up to 7 outcomes they felt should be included as core outcomes. Secure
2 electronic votes were submitted by using Turningpoint Software and Responseware keypads
3 (Turning Technologies, Youngstown, Ohio, USA). The second day followed a similar model
4 of large- and small-group discussions designed to allow further discussion and reflection on
5 the optimal outcomes. A second round of voting was used to identify the final list of core
6 outcomes. Proceedings were captured in the form of detailed written records from discussion
7 groups, plenary sessions, and the outcome of voting.

8

9 *[h2]Stage 4: Synthesis of Findings and Recommendations for Measurement Tools*

10 A writing group was appointed by ILCOR and endorsed by the American Heart Association
11 Manuscript Oversight Committee after review for conflicts of interest. The charge to the
12 group was to draw together and summarize the findings from stages 1 through 3. The group
13 met by teleconference on 8 occasions and face-to-face on 1 occasion.

14

15 The writing group reviewed and summarized the findings from stages 1 through 3 presented
16 in this scientific statement. The group undertook further work with the intention of making
17 recommendations on relevant measurement tools for the outcome domains selected in stage
18 3. This was informed by considering existing measurement tools in cardiac arrest and other
19 relevant diseases or injuries and discussing their quality, acceptability, and feasibility for
20 application in clinical trials. Final recommendations were reached through discussion and
21 consensus among the writing group members.

22

23

1 [h1]Results

2 [h2]Stage 1: Generation of an Extensive List of Potential Outcomes Across 4 Core Areas 3 (OMERACT Framework)

4 The systematic review identified 61 randomized trials that reported 164 unique outcomes on
5 278 occasions.¹¹ The most frequently reported outcome was survival (85% of trials). This
6 included return of spontaneous circulation (ROSC) before hospital admission, in the
7 emergency department, or at any point during the resuscitation attempt. Survival was
8 reported at various time points from emergency department admission, hospital discharge,
9 and through to 3 years. There was a lack of consistency in definition and the time points at
10 which survival was assessed, although most studies (90%) reported survival up to, and
11 including, hospital discharge. Pathophysiologic outcomes (eg, coronary perfusion pressure,
12 arterial blood gas results) and life impact were frequently reported, although there was a lack
13 of consistency in outcomes, measurement tools, and the timings of assessments. Process of
14 care (eg, event timings), response to treatment (eg, temperature achieved in targeted
15 temperature management trials), quality of CPR, intervention success rates (eg, vascular
16 access) and adverse outcomes were reported in a quarter of studies. Writing group members
17 identified trials published more recently that reported outcomes in the domain of life
18 impact.^{13, 14, 25, 26}

19
20 Eleven interviews (8 patients, 3 partners) were conducted to provide a detailed understanding
21 of the lived experience of those surviving cardiac arrest. Five key themes were identified by
22 patients reflecting the disruption to normality caused by cardiac arrest (survival, physical
23 activities, emotional well-being, social well-being, and the impact on others; Table 1).

24

1 The findings from the systematic review and patient/partner interviews were used to produce
2 an extensive list of 53 potential outcomes, encompassing survival (5), life impact (24),
3 economic impact and resource use (10), and pathophysiologic manifestations (14), which
4 were used in the stage 2 Delphi process.

5

6 ***[h2]Stage 2: International Delphi to Refine and Prioritize Long List of Potential Outcomes***

7 Ninety-nine healthcare professionals, 62 cardiac arrest survivors and 7 relatives of cardiac
8 arrest victims from 15 countries participated in the Delphi survey. The clinician group
9 included: 46 physicians, 12 nurses, 20 allied health professionals and 6 academics. By the
10 end of the 2 Delphi rounds, 25 outcome domains were prioritized (Figure 2).

11

12 ***[h2]Stage 3: International Expert Panel Meeting***

13 A total of 23 expert panel members (including 2 survivors, 1 partner, and 1 patient advocate)
14 participated from 11 countries (UK, the Netherlands, Finland, Germany, Belgium, Sweden,
15 United States, Canada, Singapore, Australia, and New Zealand). The core outcome
16 discussions and recommendations are summarized below.

17

18 ***[h3]Pathophysiologic Manifestations***

19 The expert panel considered circulatory function, respiratory function, and brain function as
20 potential core outcomes. There was general agreement that the assessment of these outcomes
21 is of high importance during and immediately after cardiac arrest. They become less
22 important once ROSC has been achieved. Consideration was given to the potential for
23 pathophysiologic measures to act as surrogate assessments for longer-term functional
24 outcomes. For example, specific neuroimaging/electrophysiologic tests might be a useful
25 surrogate to reflect the impact of a cardiac arrest on brain function.²⁷ The panel considered

1 these outcomes may be valuable during the validation of new interventions and advancing
2 discovery, for example, in efficacy trials. However, there was general agreement that the
3 assessment of specific pathophysiologic manifestations as core outcomes across the wide
4 range of effectiveness trials in this field is of limited value.

5

6 The importance of reporting adverse events was discussed at length. There was general
7 agreement that the reporting of adverse events should occur in accordance with Good Clinical
8 Practice guidelines, which are relevant to all clinical trials, rather than as a core outcome
9 specific for cardiac arrest.

10

11 Although not introduced during the Delphi survey, participants discussed the importance of
12 the quality of CPR (ie, CPR process) and its potential use as a core outcome. Such measures
13 may include compression rate, pre-shock pause duration, compression depth, or time to
14 intervention. There was unanimous consensus that the processes of CPR are important
15 contributors to outcome after cardiac arrest. Participants recognized that CPR may be
16 initiated or completed before a study intervention is applied. While CPR process may be an
17 indicator of the quality of a resuscitation system of care or as a potential modifier of the
18 effect of a study intervention, it was concluded that CPR process should not be a core
19 outcome for effectiveness trials. This should not limit researchers from reporting CPR
20 quality matrices to enable the assessment of associations between CPR performance and Core
21 Outcome Set categories. Where such data are reported, use of standardised definitions²⁸ and
22 time intervals may reduce variation in reporting.²⁹

23

24 *[h3]Survival*

1 The expert panel discussed the relative importance of short-term survival, such as ROSC. The
2 outcome was thought to be important in efficacy studies, which seek to advance discovery in
3 this field, but contributed less toward understanding longer-term aspects of survival.

4
5 Hospital-free survival (number of days alive and permanently outside a hospital in the first 30
6 days after cardiac arrest) was introduced during discussions. It was recently used in a large
7 pragmatic cardiac arrest trial³⁰ and offers potential statistical efficiencies over dichotomous
8 outcomes.^{31, 32} Challenges can exist around the interpretation of a composite outcome, which
9 combines survival with length of hospital stay.

10

11 The panel concluded that longer-term survival (alive/dead) should be the core survival
12 outcome.

13

14 *[h3]Life Impact*

15 Patient/partner participants voiced a number of potentially overlapping domains that may be
16 affected after a cardiac arrest, which included cognition and consciousness, physical
17 symptoms, activities of daily living, health-related quality of life (HRQoL), emotional well-
18 being, family impact, participation, and fatigue. It was agreed that one of the most common
19 and significant impacts of cardiac arrest are potential changes to cognition and neurologic
20 functioning. Other contributors to daily life such as physical, social, and emotional changes
21 after returning home were discussed and considered important. To capture these important
22 domains of health, a multi-domain approach, including assessing an individual's HRQoL
23 after arrest, was favored.

24

1 The panel reached consensus that neurologic function and HRQoL should be included as core
2 outcomes.

3

4 *[h3]Economic Evaluation*

5

6 Although domains reflective of this core area were not prioritized by participants in the
7 Delphi survey, the importance attributed to this core area in the OMERACT initiative
8 suggested that further discussion of the relative importance of this core area and possible
9 domains was required. Group discussion highlighted the complexities of capturing sufficient
10 information to allow for a full economic analysis of costs related to cardiac arrest. While
11 economic evaluation was judged to be important, it was agreed that there was insufficient
12 evidence to inform categorization currently. As a result, economic measures are not being
13 suggested as a core outcome.

14

15 *[h2]Stage 4: Recommendations for Measurement Tools and Timing of Measurement*

16 *[h3]Survival*

17 Survival to discharge and survival to 30 days were considered to be better indicators of
18 patient recovery than shorter-term survival, such as survival to admission or 4 to 6 hours after
19 emergency department arrival. Discussion highlighted international variation in the feasibility
20 of collecting survival at discharge and survival at 30 days. Both time points have limitations:
21 survival to discharge is limited by cultural differences (whether patients are discharged home
22 to die or die predominantly in hospital) and health system differences (efficiency of discharge
23 processes; whether long-term care is provided in hospital or home care settings). This can
24 limit comparisons across different health systems. Survival to specific intervals (eg, 30 days)

1 after arrest can avoid some of these limitations, but in some settings requires consent, which,
2 as noted elsewhere, may introduce bias through higher rates of loss to follow-up.

3
4 The writing group concluded that neither time point is perfect, and, for consistency with the
5 Utstein recommendations,¹⁷ it was agreed either survival to hospital discharge or survival to
6 30 days would be acceptable to report as core outcomes. Researchers are encouraged to
7 report both measures if feasible, but should avoid reporting these as a composite outcome
8 (survival to discharge or survival to 30 days) because this impairs pooling results in a meta-
9 analysis.

10

11 *[h3]Neurologic Function*

12 Five clinician-completed measures—the Cerebral Performance Category (CPC),³³ Structured
13 CPC (assessment by semi-structured interview),³⁴ CPC-Extended,³⁵ the Glasgow Outcome
14 Scale–Extended (GOS-E),³⁶ and modified Rankin Scale (mRS)³⁷—were considered.

15 Moderate associations between the tools suggest that they measure related, but not identical,
16 constructs.^{13, 34, 38-41} The CPC was not highly endorsed because of the lack of discrimination
17 between scores and the potential for ceiling effects and overestimation of function.^{14, 42-45} The
18 CPC-Extended was considered to show good evidence of content validity, reliability,
19 acceptability, and feasibility, although its use in cardiac arrest survivors was limited at this
20 time.³⁵ The mRS and GOS-E appear to provide improved granularity.^{40, 42} The mRS has been
21 used more extensively in cardiac arrest survivors^{13, 40, 46-54} than the GOS-E^{43, 55} or CPC-
22 Extended have.³⁶

23

24 The writing group reached unanimous agreement that the mRS should be the outcome
25 measurement tool of choice for neurologic function. The mRS is a brief, clinician-completed,

1 ordinal hierarchical rating scale used to determine a summary score of global disability^{56, 57}
2 after a neurologic event or condition. The mRS captures impairment of physical and
3 cognitive abilities. Questions primarily focus on limitations in basic, instrumental, and more
4 advanced daily activities and restrictions in ability to participate in normal social roles.^{57, 58}
5 There is evidence that it can discriminate between levels of mild and moderate disability.⁵⁷ It
6 does not, however, provide detailed information of residual impairments and is unable to
7 differentiate between whether effects are due to neurologic or other sources of disability.^{57, 59}

8

9 *[h3]How to Complete (Table 2)*

10 mRS completion is preferably measured by direct interview with the patient and any relevant
11 caregiver—face-to-face or, optionally, by telephone.⁵⁶ Non-standardized interview
12 administration requires approximately 5 minutes.⁵⁶ Where patients are unable to participate in
13 interviews because of physical, language, or cognitive impairment, proxy completion—that
14 is, completion by informants, such as family members, caregivers, or health professionals
15 who know the patient well—may be considered. However, proxy completion without
16 involving the patient is associated with suboptimal levels of reliability and validity.^{56, 60}
17 Although some studies suggest that indirect mRS completion from hospital records is less
18 accurate,⁶¹ others suggest acceptable reliability following chart review by trained health
19 professionals.^{35, 38}

20

21 Substantial inter-rater reliability of the mRS has been described,⁶² although this can be
22 improved through digital training,⁶² use of a structured interview,^{58, 63} or use of a Web-based
23 tool with 9 questions (mRS-9Q) and an mRS calculator.⁶⁴ Use of trained raters as well as a
24 structured approach to calculating the mRS score are recommended. Raters should optionally
25 also be familiar with problems common after cardiac arrest.

1

2 *[h3]Timing*

3 The advantages and disadvantages outlined above for reporting survival status at discharge or
4 at 30 days apply similarly to the reporting of favorable neurologic function. Additional
5 limitations of measuring neurologic function at discharge are that the patient will not have
6 been exposed to normal/their previous activities to allow accurate determination of the
7 relevant mRS category. The time of discharge is also likely to be influenced by the degree
8 and speed of recovery, with those having the greatest disabilities remaining in hospital for
9 longer. Additional challenges imposed by assessing neurologic function at 30 days is the
10 requirement for the research team to specifically follow up with the patient because, unlike
11 mortality, these data are not usually tracked routinely. Incomplete follow-up risks introducing
12 attrition bias. Whichever time-point is selected, the outcome should be reported as measured
13 on the day of the assessment and not the best ever achieved.

14

15

16 The writing group accepted that there were advantages and disadvantages to both time points,
17 and similar to our suggestion for assessing survival status, mRS score at discharge or 30 days
18 is considered acceptable for reporting as a core outcome. Researchers may report both time
19 points if feasible but should avoid reporting as a composite outcome (mRS score at discharge
20 or 30 days) because this impairs pooling results in a meta-analysis.

21

22 *[h3]What to report*

23

24 Historically cardiac arrest trials have dichotomized neurological outcomes into favorable or
25 unfavorable categories based on a mRS cut off of ≤ 3 .⁶⁵⁻⁶⁷ However in stroke trials a mRS of

1 $\leq 1^{68}$ or $\leq 2^{69}$ has been used to represent the cut off between favorable and unfavorable
2 outcomes.

3

4 To enable consistent reporting and comparisons between papers, the writing group advised
5 that the core outcome is presented as the number and percentages of patients in each of the 6
6 categories rather than solely categorizing into favorable and unfavorable neurological
7 outcome groups. This approach also provides greater granularity on clinically relevant
8 outcomes.⁷⁰

9

10 To facilitate the transition to mRS as the core outcome measurement tool and to support
11 backward comparability, the writing group was also supportive of continued reporting of
12 CPC score over the next 5 years, in addition to mRS score.

13

14 Useful information for calculating the mRS score can be found at www.modifiedrankin.com.

15

16 The COSCA writing group suggested the use of the mRS version, where category 4
17 (moderate severe disability) is scored when the patient is either unable to attend to own
18 bodily needs without assistance and/or unable to walk unassisted. This better captures the
19 level of disability for a patient with severe cognitive impairment, but still able to walk.

20 Outcome after cardiac arrest is less influenced by locomotor problems when compared with
21 stroke, and this version will be more sensitive to identify extensive dependency related
22 to severe cognitive impairment in a patient still able to walk. This version is available at
23 www.modifiedrankin.com.

24 • 0 = No symptoms

- 1 • 1 = No significant disability. Able to carry out all usual activities, despite some
- 2 symptoms
- 3 • 2 = Slight disability. Able to look after own affairs without assistance but unable to
- 4 carry out all previous activities
- 5 • 3 = Moderate disability. Requires some help but able to walk unassisted
- 6 • 4 = Moderately severe disability. Unable to attend to own bodily needs without
- 7 assistance and/or unable to walk unassisted
- 8 • 5 = Severe disability. Requires constant nursing care and attention, bedridden,
- 9 incontinent
- 10 • 6 = Dead

11

12 *[h3]Health-Related Quality of Life*

13 The writing group spent considerable time deliberating which tools should be used to capture
14 HRQoL after cardiac arrest. Key considerations were the relevance or acceptability to cardiac
15 arrest survivors, feasibility (eg, ease of use, information collection methods), the
16 measurement properties and their previous use in the cardiac arrest patient population, and
17 cost. The writing group prioritized 6 generic measures of HRQoL for detailed consideration:
18 2 multi-item profile measures (the Short-Form 36-Item Health Survey [SF-36]⁷¹ and Short
19 Form 12-Item Health Survey [SF-12]^{72, 73}) and 4 preference-based, multi-attribute utility
20 measures (the 15-dimension Quality of Life questionnaire [15-D],⁷⁴ the Health Utilities Index
21 version 3 [HUI3],⁷⁵ and both the original and revised versions of the EuroQol [EQ-5D-3L⁷⁶
22 and EQ-5D-5L,⁷⁷ respectively]). All preference-based measures include both descriptive
23 systems and a utility index, and hence, could be used in cost-utility evaluations.⁷⁸

24

1 The group was unable to reach consensus and recommend a single tool among these
2 measures. Patient and public partners highlighted that none of the tools comprehensively
3 captured their experiences of the aftermath of a cardiac arrest. In online voting, the HUI3,
4 followed by the SF-36 and EQ-5D-5L, received the most support (Table 3). The briefest
5 measures are the EQ-5D-5L (5 items) and HUI3 (8 items); the longest is the SF-36 (v2) (36
6 items). While all measures are intended to be measures of health status or HRQoL, the
7 number of items and HRQoL coverage is varied (Table 3). The HUI3 and EQ-5D-5L have a
8 preponderance of items that relate to physical health, whereas items within the SF-36(v2) are
9 equally distributed between physical and mental health.⁷⁸ However, only the HUI3 includes
10 items that measure cognition, speech, and dexterity, which are concerns relevant to cardiac
11 arrest survivors. Only the SF-36(v2) includes an assessment of fatigue.

12
13 Preference-based utility scores can be calculated for HUI3, EQ-5D-5L, and SF-36(v2) (in the
14 form of the SF-6D⁷⁹), supporting their use in cost-utility evaluation. The SF-36(v2) provides
15 the most detailed profile score—that is, separate scores are calculated across the 8 health
16 domains, providing a more detailed assessment of health status than is otherwise afforded by
17 the 2 summary scores. More limited descriptive profile scores can also be reported for both
18 the HUI3 and EQ-5D across their 8 and 5 attributes, respectively. Normative population data
19 are available for all measures, supporting data interpretation, and between-group
20 comparisons. Estimates of meaningful change have been calculated for all measures
21 following completion by the general population and specific patient groups, further
22 supporting data interpretation. License requests are required for all measures, but only the
23 EQ-5D-5L is free to use.

24

1 A review of published evidence on the reliability and validity of these measures following
2 completion by survivors of cardiac arrest demonstrated that the strongest evidence was
3 available for the HUI3, followed by the SF-36(v2).⁸⁰ The EQ-5D-5L has not been evaluated
4 in this population; however, evaluations in comparable populations suggest improved data
5 quality and psychometric performance when compared with the original EQ-5D-3L.⁷⁷

6
7 In summary, multiple measures of HRQoL, including the SF-12(v2), SF-36(v2), EQ-5D-5L,
8 and HUI3, are acceptable for measurement of outcomes in trials enrolling patients with
9 cardiac arrest. Each of these has strengths and weaknesses compared with other measures
10 available. HUI3 has been applied frequently to patients with cardiac arrest and directly
11 measures cognition. The other measures are also acceptable.

12 13 *[h3]How to Complete*

14 Although all the above HRQoL measures were developed to be self-completed, all have been
15 successfully interview-administered in person,^{39, 41} via the telephone,^{13, 55, 81, 82} or both¹⁴ in the
16 cardiac arrest population. Postal self-completion, although possible has been only used
17 infrequently. However, the ability to self-complete a questionnaire after a cardiac arrest can
18 be severely impaired by cognitive impairment (which may result in an overestimation of
19 ability),⁸³ fatigue, or general poor health. Although proxy ratings of non-observable
20 constructs such as emotional well-being and cognition may underestimate limitations,^{84, 85}
21 agreement is generally greater for more physical attributes.^{84, 86, 87} Cronberg et al described
22 interview-based proxy completion of the SF-36(v2) with 8% of survivors at 6-month follow-
23 up.¹⁴ Where possible, proxy completion by appropriate, well-informed assessors is suggested
24 to ensure that the views of survivors who are unable to self-report are included in trials and
25 the results do not underestimate the impact of cardiac arrest on HRQoL.⁸⁷

1

2 *[h3]Timing*

3 There was consensus that HRQoL should be measured after the patient's discharge from the
4 hospital. Patient recovery often continues to 6 months and beyond. Three-quarters of patients
5 of a working age return to work after cardiac arrest at a median interval of 4 months.⁸⁸ The
6 optimal time points and frequency of follow-up need to be considered in the context of study
7 resources and overall study design. If sufficient resources are available to measure post-
8 discharge outcomes, the group recommends—as a minimum—assessment at 90 days. The
9 group considered that this best balanced the trade-off between costs and other implications
10 associated with longer-term follow-up with the positive effect of the value and stability of the
11 data and is consistent with the review of primary outcomes by Becker et al.¹⁹ However, it is
12 recognized that health status may continue to change in the subsequent months and that
13 capturing this change is important.^{40, 88, 89} Therefore, the group agreed that HRQoL could also
14 be assessed at 180 days and/or 1 year. However, the longer duration of follow-up would be
15 associated with increased logistic challenges and may be influenced by factors external to
16 surviving a cardiac arrest.

17

18 **[h1]Discussion**

19 The COSCA Writing Group identified that survival, neurologic function, and HRQoL should
20 be reported as core outcomes in cardiac arrest effectiveness trials. Survival status should be
21 reported at hospital discharge and / or at 30 days. Neurologic function (measured by using the
22 mRS) should be reported at hospital discharge and / or 30 days. HRQoL should be measured
23 by using 1 or more tools from the HUI3, SF-36(v2), or EQ-5D-5L at 90 days and at periodic
24 intervals up to 1 year after cardiac arrest, if resources allow.

25

1 Core outcome sets are intended to enhance standardization of the outcomes, which are
2 reported for effectiveness trials. As such, future cardiac arrest effectiveness trials should
3 include the core outcomes identified by COSCA as part of the *a priori*-designated primary or
4 secondary trial outcomes. The COSs are intended to be complimentary to other outcome
5 measures relevant to the particular intervention under evaluation. The COS recommendations
6 sit alongside, rather than replace, tools designed to enhance the quality and transparency of
7 health research, such as the Standard Protocol Items: Recommendations for Interventional
8 Trials (SPIRIT)⁹⁰ and Consolidated Standards of Reporting Trials⁹¹ (Figure 3). Earlier phase
9 trials will typically focus primarily on measures of efficacy, such as biomarkers, ROSC, or
10 immediate survival, although selected core outcomes could also be considered.

11
12 Traditionally, outcome assessment of patients experiencing cardiac arrest has focused on
13 survival rates and clinician-based assessments of outcome.¹¹ However, the growth in patient-
14 centered care and recognition of the importance of seeking to understand the impact of
15 cardiac arrest from the perspective of the survivor demand a shift in the way in which
16 outcomes—in particular, over the longer-term—are assessed in clinical trials. The use of
17 well-developed questionnaires, which provide an assessment of how patients feel, function,
18 and live their lives because of their health and health care, can provide essential patient-
19 derived information to enhance outcome reporting in clinical trials.⁹² Such questionnaires or
20 patient-reported outcome measures may be simply categorized as *generic* or *specific* (to a
21 condition [eg, diabetes], a problem [eg, cognition], a function [eg, activities of daily life], or a
22 population [eg, children]).

23
24 Generic measure of HRQoL, such as those short-listed in the COSCA recommendations
25 (HUI3, SF-36(v2), EQ-5D-5L), includes multidimensional concepts (physical, social,

1 emotional, and mental functioning) that provide a general assessment of HRQoL of relevance
2 to patients and the general population, facilitating between-group comparisons and ensuring
3 that the patient perspective is captured in clinical trials. Although the generic measures
4 supported by COSCA start to move the focus toward patient-centered outcomes, the current
5 tools still fail to comprehensively capture the breadth of outcomes and experiences that
6 matter most to cardiac arrest survivors.⁹³⁻⁹⁵ As consequence, the impact of cardiac arrest and
7 associated healthcare may be incompletely assessed. Although a condition-specific measure
8 for survivors of cardiac arrest does not currently exist, measures specific to problems of
9 relevance to cardiac arrest survivors (eg, cognition, fatigue, anxiety, social participation) are
10 available and have been increasingly used in this population.^{13, 14, 25, 26, 96-98} Even though the
11 COSCA recommendations do not currently include guidance for 1 or more problems or
12 function-specific measures, per good practice guidance for outcome assessment,^{84, 85} where
13 possible, we encourage their inclusion. Although not yet evaluated in the cardiac arrest
14 population, the PROMIS initiative (Patient Reported Outcome Measures Information System
15 <http://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis>)
16 describes a range of fixed or dynamic (computer adaptive tests) self-report measures of
17 physical, mental and social health appropriate for use with the general population and those
18 with chronic conditions, and hence suitable for comparing the burden of illness and treatment
19 impact. The paucity of evidence to suggest which tools are best suited highlights the need for
20 further research in this area.

21

22 Collecting health-related quality-of-life measures as an outcome of a clinical trial can be
23 challenging and expensive. Sometimes, such data are missing from patients with the poorest
24 outcomes, which may result in systematic bias, which cannot be ignored.^{99, 100} To maximize
25 the quality and timeliness of quality-of-life measures and reduce the risk of systematic bias

1 due to missing data, standardized administration and routine screening for avoidable missing
2 data are advised.¹⁰⁰⁻¹⁰² The approaches used and handling of missing data should be detailed
3 in the study protocol and standard operating procedures.^{99, 101}

4
5 The writing group was cognizant of the balance that needs to be struck between the
6 requirements of collecting the core outcomes identified by the COSCA initiative at a time of
7 constrained research resources and the need to accelerate the pace of evidence-based change
8 in resuscitation practices. The overall efficiency of the research pathway may be improved
9 through a better understanding of the pathophysiology and effects of therapeutic interventions
10 from animal and laboratory studies. By establishing proof of concept with evidence from
11 early efficacy trials, internal pilots may reduce redundancy in effectiveness trials.¹⁰³⁻¹⁰⁵
12 Improving the efficiency of the conduct of trials¹⁰⁶ and making use, where possible, of
13 registry data¹⁰⁷ may reduce costs and shorten the time to complete trials. The use of fixed
14 dichotomous analysis of ordered categorical outcomes is rarely the most statistically efficient
15 approach and usually requires a larger sample size to demonstrate efficacy than other
16 approaches.⁶⁸ Alternative analytical approaches such as shift analysis, ordinal logistic
17 regression, used widely in stroke research,^{68, 70} require further evaluation in the cardiac arrest
18 population. A better understanding of measurement properties of continuous outcomes, such
19 as hospital-free survival,³¹ may also aid reductions in sample size and trial costs.

20

21 **[h1]Conclusion**

22 Through a partnership between patients, partners, clinicians, and researchers and endorsed by
23 ILCOR, consensus emerged that a core outcome set for reporting on effectiveness studies of
24 cardiac arrest (COSCA) should include survival, neurologic function, and health-related
25 quality of life (HRQoL). To facilitate meaningful comparisons across studies over time,

- 1 survival status and modified Rankin scale at hospital discharge and / or 30 days should be
- 2 reported. HRQoL should be measured by using 1 or more tools from the HUI3, SF-36(v2), or
- 3 EQ-5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources
- 4 allow.
- 5
- 6

1 Acknowledgments

2 This scientific statement is dedicated to the memory of Dr Ian Jacobs, who inspired,
3 supported, and contributed to the COSCA initiative. Dr Jacobs was a lifelong volunteer of the
4 Australian Resuscitation Council and co-chair of ILCOR at the time of his death. His legacy
5 and contributions to the science of resuscitation and compassionate cardiac arrest care will
6 live on through COSCA's focus on patient-centered outcomes.

7

8 We acknowledge the support and guidance from ILCOR and its member councils, including
9 American Heart Association, European Resuscitation Council, Heart and Stroke Foundation
10 of Canada, Australia and New Zealand Committee on Resuscitation, Resuscitation Council of
11 Southern Africa, Inter-American Heart Foundation, and Resuscitation Council of Asia.

12

13 Sources of Funding

14 None

15

16 Disclosures

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1 **Table 1. Themes From Patient and Partner Interviews Relating to Disruption to**
 2 **Normality**

Theme	Examples
Survival	Closeness to death Gratitude to be alive
Impairment and impact to activities	Fatigue Breathlessness Vision Muscle weakness Pain (eg, fractured ribs) Activities of daily living/increased dependence Cognitive function
Emotional well-being	Anxiety Confidence Depression Self-esteem Personality changes Frustration
Social well-being and participation	Participation (role: job, voluntary, career) Participation (leisure: hobbies, sports) Participation (social activities) Participation (family: relationships, intimacy)
Impact on others	Increased work/care Impact to participation—hobbies, work

	Strain on relationships Worry
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Table 2. Core outcomes, time-point and preferred methods for collection

Outcome	Time-point	Preferred method	Alternative method
Survival	30 days and / or discharge	Ambulance / Hospital records Death registry	
Neurological function (mRS)	30 days and / or discharge	Face to face interview by trained raters using mRS-9Q	Informant interview Telephone assessment Review of hospital records
Quality of Life	90 days	Face-to-face (proxy completion where respondents are unable to participate)	Telephone interviews Postal questionnaire

Table 3. Summary and Item Content of Short-listed Generic HRQoL Measures (n=3)

PROM Developer Website Cost (License) Completion Time	Conceptual Focus, Response Options/Recall Period, Completion Format, Language Versions	HRQoL Domains (Ferrans et al, 2005) (Items Per Domain)						How to Score
		Symptom Status Symptoms	Functional Status				General Health Perception	
			Physical	Cognitive	Psychological	Social/Role		
Preferences based (2)								
Health Utilities Index 3 (HUI3) www.healthutilities.com License for use per project; minimum fee \$3000 (US) [Horsman, 2003] Completion time: Approximately 8 minutes self-completion	Preference-based, comprehensive system for measuring health status and HRQoL and for producing utility scores. Applicable for all persons aged 5 years and older. HUI3 classification system: describes the comprehensive health state of an individual across 8 attributes of general health (6/8 items reflect physical functional status) Response options: Between 4 and 6 descriptive response options (ability/disability)	Pain—severity (1)	Ambulation: Ability to walk (distances) Dexterity: Ability to use hands and fingers Senses: Vision	Cognition: ability to solve day-to-day problems (1)	Emotion: happiness and interest in life (1)		2 ways of presenting the data: 1. HUI3 utility index: scored by using single- and multiattribute utility functions HUI-specific coding	

<p>Approximately 3 minutes interview completion (not reported in cardiac arrest population)</p> <p>User guide: Available once HUI3 is purchased</p> <p>Country of origin: Canada</p>	<p>Recall period: “Current” or “Usual” —“Usual” recommended for clinical studies. Choice of 1-week, 2-week, or 4-week recall available. (Horsman et al, 2003)</p> <p>Completion: Self, interview (in person; telephone), or proxy (proxy version available) supported</p> <p>Language: 16 versions, including English, Chinese, Dutch, French, German, Italian, Japanese, Portuguese, Russian, Spanish, Swedish</p>		<p>Senses:</p> <p>Hearing</p> <p>Speech:</p> <p>Ability to be understood</p> <p>(5)</p>					<p>algorithms to support calculation of single-attribute Utility Score (Index)</p> <p>Index range – 0.36 to 1.00, where 1.00 is perfect health, 0 is dead, and <0 is a health state worse than death</p> <p>Population-based norms available</p> <p>2. Multiattribute descriptive</p>
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								system— “Classification system”— reflects individual item scores
<p>EuroQol EQ-5D-5L</p> <p>(EQ-5D-5L)</p> <p>www.euroqol.org/home.html</p> <p>License: For use per project; free, but use must be registered on EuroQol website: www.euroqol.org/register-to-use-eq-5d.html</p> <p>Completion time: Less than 5 minutes (not reported in cardiac arrest population)</p>	<p>Standardized, preference-based measure of health status for use in clinical and economic appraisal</p> <p>EQ-5D descriptive system: 5 items across “5 domains” (2/5 reflects physical functional status)</p> <p>(EQ VAS: self-rated health on a 20 cm vertical visual analogue scale)</p> <p>Response options: 5-level categorical response options per item (no problems [1] to extreme problems [5])</p> <p>Completion of all items will produce a 5-digit number describing the respondent’s health state (but the numerals 1–5 have no inherent arithmetic properties and should not be used as a cardinal score)</p>	<p>Pain/discomfort (1)</p>	<p>Mobility Self-care (2)</p>	<p>–</p>	<p>Anxiety/depression (1)</p>	<p>Usual activities (including work, study, housework, and family or leisure activities) (1)</p>	<p>–</p>	<p>2 ways of presenting the data:</p> <p>1. EQ-5D-5L Index value EuroQol-specific coding algorithms to support calculation of Utility Score (Index):</p> <p>Crosswalk value sets from EQ-5D-</p>

<p>User guide: Free at following link: www.euroqol.org/about-eq-5d/publications/user-guide.html</p> <p>Country of origin: Multiple</p>	<p>Recall period: Today</p> <p>Completion: Self, interview (in person, telephone), or proxy (2 proxy versions) supported: www.euroqol.org/about-eq-5d/modes-of-administration.html</p> <p>Formats: PDA, pen and paper, proxy paper, tablet, telephone, Web: www.euroqol.org/eq-5d-products/eq-5d-5l.html</p> <p>Language: >120 language versions (see www.euroqol.org)</p>							<p>3L support calculation of EQ-5D-5L utility score</p> <p>Index range – 0.59 to 1.00, where 1.00 is perfect quality of life, 0 is death, and <0 is a health state worse than death</p> <p>Country-specific value sets and population-based norms available</p> <p>Report both measure of</p>
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								<p>central tendency and a measure of dispersion, eg, mean and SD; median and percentiles</p> <p>2. EQ-5D-5L descriptive system as a health profile: reflects individual item scores.</p> <p>2.1 Report as the frequency or proportion of reported problems for each level for each dimension</p>
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								2.2 Dichotomize into “No problems” (1) and “Problems” (2–5), report frequencies of reported problems
Profile measures (1)								
Short Form 36-Item Health Survey, version 2 (SF-36v2) https://campaign.optum.com/optum-outcomes/what-we-do/health-surveys/sf-36v2-health-survey.html	<p>Functional health and well-being from the patient’s perspective—underpinned by 8 health domains across both physical (4) and mental (4) aspects of health</p> <p>Total 35 items plus 1 health transition item</p> <p>Response options: Between 3- and 6-level categorical response options per item</p>	<p>Bodily pain (BP) (2)</p> <p>Vitality (VT): fatigue/tiredness (2)</p>	<p>Physical functioning (PF) (10)</p> <p>Role limitation (RP) (4)</p>	–	<p>Mental health (MH) (5)</p> <p>Role limitation (RE) (3)</p>	<p>Social functioning (SF) (2)</p>	<p>General health (GH) (5): perceived well-being</p>	<p>2 ways of presenting the data:</p> <p>2.1 Eight-domain profile</p> <p>2.2 Two component</p>

<p>License For use per project; minimum fee \$US</p> <p>Survey license request: via above URL</p> <p>Completion time: Range 5 to 30 minutes (not reported in cardiac arrest population)</p> <p>User guide: Available once SF-36v2 is purchased</p> <p>Country of origin: United States</p>	<p>Recall period: Standard recall 4 weeks; acute recall 1 week</p> <p>Completion: Self, interview (in person; telephone), or proxy supported</p> <p>Language: >170 language versions: See website</p> <p>The IQOLA project supported the development of conceptually equivalent and culturally appropriate translations (see www.iqola.org)</p> <p>Note: utility values A preference-based utility index, the SF-6D can be calculated after completion of the SF-36 to inform economic analyses: https://www.shef.ac.uk/scharr/sections/heds/mvh/sf-6d</p>						<p>summary scales: PCS, MCS</p> <p>Scoring requires SF-36-specific algorithm.</p> <p>Norm-based scoring: score transformed to 0–100 (mean 50 [SD 10])</p> <p>Population-based norms available</p>
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EQ VAS indicates EuroQol visual analogue scale; HRQoL, health-related quality of life; IQOLA, International Quality of Life Assessment; MCS, mental component summary; PCS, physical component summary; PROM, patient-reported outcome measure; SD, standard deviation; VAS, visual analogue scale.

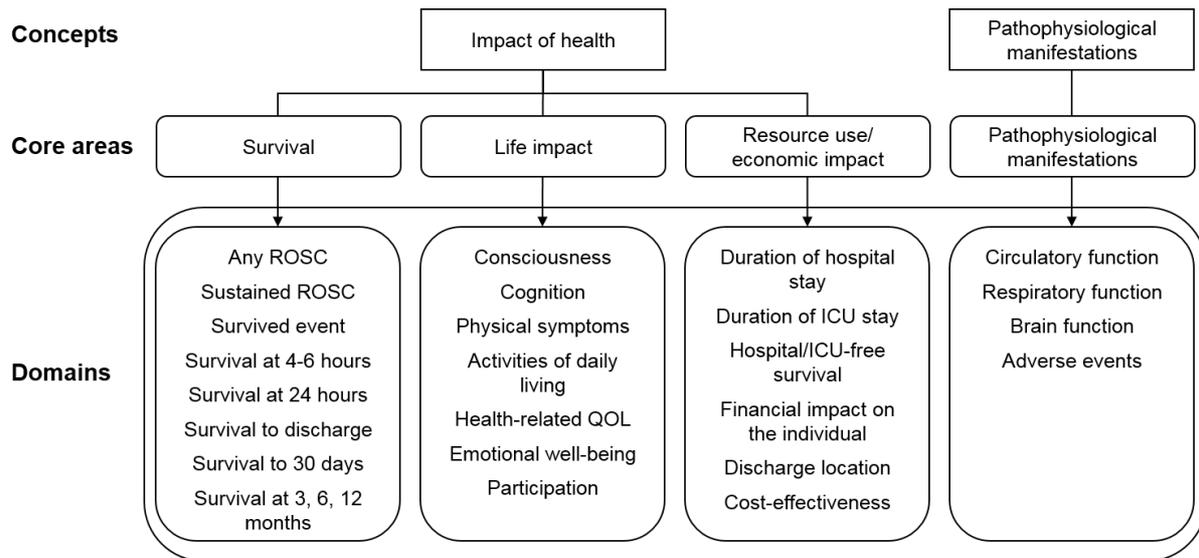


Figure 1. OMERACT framework 2.0 modified for cardiac arrest.

ICU indicates intensive care unit; QoL, quality of life; and ROSC, return of spontaneous circulation.

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Core Area	Outcome Domain	Timing of Measurement				
		<i>During CPR</i>	<i>Immediately after CPR</i>	<i>During hospital stay</i>	<i>At hospital discharge</i>	<i>Within 1 year</i>
Pathophysiologic manifestations	Circulatory function	○	●	●▲		
	Respiratory function			▲		
	Renal function					
	Brain function (neurologic markers)		○	○▲		
	Adverse events					▲
	CPR process measures*					
Survival	Survival	●	●	●▲	●▲	●▲
Life impact	Consciousness and cognition		○	○▲	●▲	●▲
	Physical symptoms				●	●▲
	Activities of daily living				●	●▲
	Health-related quality of life				○	●▲
	Emotional well-being					▲
	Family impact					▲
	Participation				△	●▲

	Fatigue					▲
Economic impact and resource use	Cost-effectiveness					
	Hospital-free survival*					

Figure 2: Outcome domains presented for discussion at COSCA meeting.

Symbol key: Circles indicate healthcare professionals and researchers. Triangles indicate patients and partners. Gray fill indicates strong consensus (<70%); white fill indicates moderate support. Gray boxes were not rated or ranked on their importance.

*Hospital-free survival and CPR process measures were introduced during expert panel meeting.

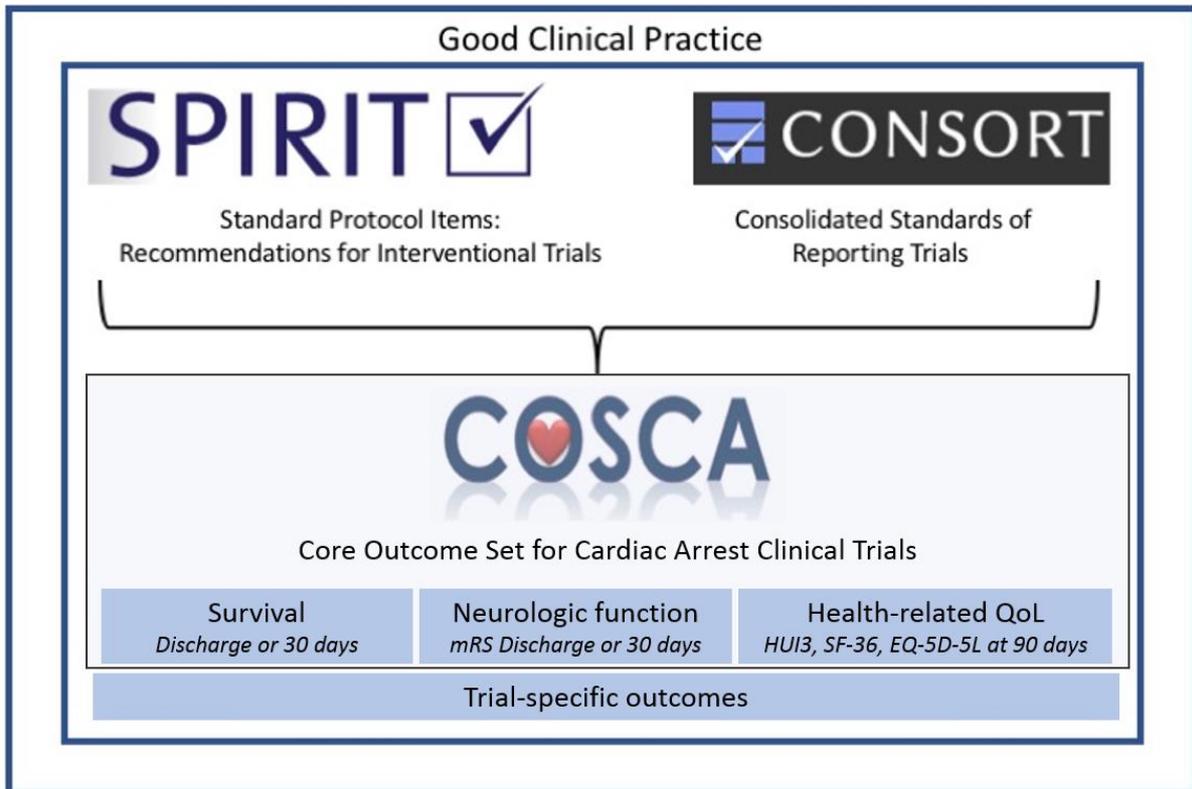


Figure 3. Clinical trials are conducted within the overall framework of good clinical practice, which supports clear and transparent reporting. Core outcome sets are suggested for inclusion as part of the *a priori*-designated primary or secondary end points of effectiveness trials. They enhance the quality and transparency of health research promoted by SPIRIT and CONSORT.

QoL indicates quality of life.