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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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Abstract

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

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

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

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

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

Sometimes multiple trials may evaluate the same intervention in different settings. Reconciling disparate trial results can be challenging if each trial evaluated different outcomes at different timepoints. A systematic review of cardiac arrest trials published...
between 2000 and 2012 included 61 publications that identified more than 160 different trial outcomes.\(^\text{11}\) No single outcome was reported across all trials. The majority of outcomes reflected short-term clinical and clinician-reported outcomes, focusing on pathophysiologic manifestations and process-based measures. While survival was the most commonly reported outcome, 39 different definitions of survival were used. Patient-reported outcomes\(^\text{12}\) were rarely reported, although more recent trials have included these outcomes.\(^\text{13, 14}\) This suggests that essential evidence of the impact of care from the survivors’ perspective is currently missing from clinical trials.

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

The Core Outcome Measures for Effectiveness Trials (COMET) initiative promotes the development and application of agreed standardized sets of outcomes, known as core outcome sets.\(^\text{20}\)
A COS is defined as a small, standardized group of outcomes that should be measured and reported, as a minimum, in all effectiveness trials for a specific health area.\textsuperscript{20, 21} Effectiveness trials should aim to capture the COS as part of their \textit{a priori}–defined primary or secondary outcomes.

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

\section{Methods}

The available evidence associated with the development of COSs\textsuperscript{18, 20} and the websites of key COS development groups (COMET and Outcome Measures in Rheumatoid Arthritis Clinical Trials [OMERACT], later renamed \textit{Outcome Measures in Rheumatology}) informed our approach. The project was registered with the COMET initiative (\url{www.comet-initiative.org/studies/details/284}). Ethical approval was obtained from the National Health Service Black Country Research Ethics Committee (13/WM/0464) to enable patients/partners to participate.
Development of a COS involved 2 key steps: development of a core domain set (ie, what to measure) followed by identification of appropriate measurement tools (ie, how to measure). A core domain set was defined as referring to the minimum number of health domains (outcomes or aspects of health) that must be assessed. That is, it specifies what should be measured. Importantly, this stage was driven by what is important and not how an outcome is assessed. The second stage involved the establishment of a core outcome measurement set, that is, the specific methods of assessment (ie, how to measure) for the domains identified in step 1. The selection of measurement tools was informed by an appraisal of measurement quality, relevance, and feasibility.

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

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

- Stage 1: Generation of an extensive list of potential outcomes across 4 core areas of health
- Stage 2: International Delphi to refine and prioritize a list of potential outcomes
- Stage 3: International expert panel meeting
- Stage 4: Synthesis of findings and recommendations for measurement tools
Stage 1: Generation of an Extensive List of Potential Outcomes Across 4 Core Areas of Health

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

Stage 2: International Delphi to Refine and Prioritize List of Potential Outcomes

The list of potential outcomes identified during stage 1 were placed into an online survey tool (SurveyMonkey, Dublin, Ireland). Separate surveys were developed for healthcare professionals and patients/patient advocates. The ILCOR network of 7 regional resuscitation councils was used to solicit the views of healthcare professionals and patient and public advocates. Each ILCOR member (n=27) was asked to invite 6 healthcare professionals and 3 patients to participate in the relevant surveys by email. The outcomes were prioritized in 2 rounds. Questions were structured to allow participants to rate the importance of each
outcome at 5 different time points across the patient journey: during cardiopulmonary resuscitation (CPR), immediately after CPR, during hospitalization, at hospital discharge, and within the first year after the cardiac arrest. In the first round, survey participants were also given the opportunity to suggest additional outcomes they considered important if they were not currently included in the survey. At the end of each round, outcomes rated as critical importance by greater than 70% of respondents and rated as limited importance by less than 15% of respondents were advanced for additional consideration by the expert panel in stage 3. Similarly, those outcomes rated of limited importance by greater than 70% of respondents and of critical importance by less than 15% of respondents were discarded. The findings from the first round were summarized and presented for a second round of prioritization. Any new suggestions were included in the second round. The second round of prioritization differed by asking participants to rank outcomes according to importance. Outcomes that received strong support (more than 70% agreement) were also advanced for consideration by the expert panel in stage 3. Outcomes that received moderate support (60%–69% agreement) were also presented to the expert panel in stage 3.

**Stage 3: International Expert Panel Meeting**

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

Before the meeting, the participants were sent a written summary of the outcome selection process described above. At the start of the meeting, an overview of steps undertaken and findings from stages 1 and 2 were presented. The shortlisted outcomes were presented in a matrix that covered the OMERACT core area headings of survival, life impact, resource use/economic, and pathophysiologic manifestations of cardiac arrest during CPR, immediately after CPR, during hospitalization, at hospital discharge, and within the first year after the cardiac arrest. Initial presentations were followed by semi-structured, small-group discussions that covered the 4 core areas. Each core area was assigned a facilitator who supported 4 rounds of discussions on that topic. Each discussion group included a survivor of cardiac arrest or patient advocate, as well as several researchers and clinicians who participated in small-group discussion across each core area. Each group nominated a recorder. The groups were tasked to consider the importance, relevance, acceptability, and feasibility of the short-listed outcomes as potential core outcomes for cardiac arrest effectiveness trials. The facilitator encouraged all group members to participate in discussions and shared key findings from each group with the next. This enabled consideration of and building upon what other participants discussed, facilitated the identification of issues of agreement and disagreement, and supported a flow of new ideas or key issues between groups. Participants, thereafter, reconvened in a whole-group discussion session: facilitators and group recorders summarized feedback from the group discussion, including areas of agreement and disagreement. The large-group discussion sought to collectively explore agreement and refine issues or concerns raised within each core area. At the end of the first day, expert panel members were invited to reflect on the day’s discussions.
and then vote for up to 7 outcomes they felt should be included as core outcomes. Secure electronic votes were submitted by using Turningpoint Software and Responseware keypads (Turning Technologies, Youngstown, Ohio, USA). The second day followed a similar model of large- and small-group discussions designed to allow further discussion and reflection on the optimal outcomes. A second round of voting was used to identify the final list of core outcomes. Proceedings were captured in the form of detailed written records from discussion groups, plenary sessions, and the outcome of voting.

Stage 4: Synthesis of Findings and Recommendations for Measurement Tools

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

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

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

(OMERACT Framework)

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

Eleven interviews (8 patients, 3 partners) were conducted to provide a detailed understanding of the lived experience of those surviving cardiac arrest. Five key themes were identified by patients reflecting the disruption to normality caused by cardiac arrest (survival, physical activities, emotional well-being, social well-being, and the impact on others; Table 1).
The findings from the systematic review and patient/partner interviews were used to produce an extensive list of 53 potential outcomes, encompassing survival (5), life impact (24), economic impact and resource use (10), and pathophysiologic manifestations (14), which were used in the stage 2 Delphi process.

Stage 2: International Delphi to Refine and Prioritize Long List of Potential Outcomes

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

Stage 3: International Expert Panel Meeting

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

Pathophysiologic Manifestations

The expert panel considered circulatory function, respiratory function, and brain function as potential core outcomes. There was general agreement that the assessment of these outcomes is of high importance during and immediately after cardiac arrest. They become less important once ROSC has been achieved. Consideration was given to the potential for pathophysiologic measures to act as surrogate assessments for longer-term functional outcomes. For example, specific neuroimaging/electrophysiologic tests might be a useful surrogate to reflect the impact of a cardiac arrest on brain function. The panel considered
these outcomes may be valuable during the validation of new interventions and advancing
discovery, for example, in efficacy trials. However, there was general agreement that the
assessment of specific pathophysiologic manifestations as core outcomes across the wide
range of effectiveness trials in this field is of limited value.

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

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

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

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

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

**Life Impact**

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

### Economic Evaluation

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

### Stage 4: Recommendations for Measurement Tools and Timing of Measurement

#### Survival

Survival to discharge and survival to 30 days were considered to be better indicators of patient recovery than shorter-term survival, such as survival to admission or 4 to 6 hours after emergency department arrival. Discussion highlighted international variation in the feasibility of collecting survival at discharge and survival at 30 days. Both time points have limitations: survival to discharge is limited by cultural differences (whether patients are discharged home to die or die predominantly in hospital) and health system differences (efficiency of discharge processes; whether long-term care is provided in hospital or home care settings). This can limit comparisons across different health systems. Survival to specific intervals (eg, 30 days)
after arrest can avoid some of these limitations, but in some settings requires consent, which,
as noted elsewhere, may introduce bias through higher rates of loss to follow-up.

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

\textbf{[h3]Neurologic Function}

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

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

The writing group reached unanimous agreement that the mRS should be the outcome
measurement tool of choice for neurologic function. The mRS is a brief, clinician-completed,
ordinal hierarchical rating scale used to determine a summary score of global disability.\textsuperscript{56, 57} After a neurologic event or condition, the mRS captures impairment of physical and cognitive abilities. Questions primarily focus on limitations in basic, instrumental, and more advanced daily activities and restrictions in ability to participate in normal social roles.\textsuperscript{57, 58} There is evidence that it can discriminate between levels of mild and moderate disability.\textsuperscript{57} It does not, however, provide detailed information of residual impairments and is unable to differentiate between whether effects are due to neurologic or other sources of disability.\textsuperscript{57, 59}

**How to Complete (Table 2)**

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

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

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

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

### What to report

Historically cardiac arrest trials have dichotomized neurological outcomes into favorable or unfavorable categories based on a mRS cut off of $\leq 3$.\cite{65,66} However in stroke trials a mRS of
<1.68 or ≤ 2.69 has been used to represent the cut off between favorable and unfavorable outcomes.

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

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

Useful information for calculating the mRS score can be found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The COSCA writing group suggested the use of the mRS version, where category 4 (moderate severe disability) is scored when the patient is either unable to attend to own bodily needs without assistance and/or unable to walk unassisted. This better captures the level of disability for a patient with severe cognitive impairment, but still able to walk. Outcome after cardiac arrest is less influenced by locomotor problems when compared with stroke, and this version will be more sensitive to identify extensive dependency related to severe cognitive impairment in a patient still able to walk. This version is available at [www.modifiedrankin.com](http://www.modifiedrankin.com).

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

[h3]Health-Related Quality of Life

The writing group spent considerable time deliberating which tools should be used to capture HRQoL after cardiac arrest. Key considerations were the relevance or acceptability to cardiac arrest survivors, feasibility (e.g., ease of use, information collection methods), the measurement properties and their previous use in the cardiac arrest patient population, and cost. The writing group prioritized 6 generic measures of HRQoL for detailed consideration: 2 multi-item profile measures (the Short-Form 36-Item Health Survey [SF-36]\(^{71}\) and Short Form 12-Item Health Survey [SF-12]\(^{72,73}\)) and 4 preference-based, multi-attribute utility measures (the 15-dimension Quality of Life questionnaire [15-D]\(^{74}\), the Health Utilities Index version 3 [HUI3]\(^{75}\) and both the original and revised versions of the EuroQol [EQ-5D-3L\(^{76}\) and EQ-5D-5L\(^{77}\) respectively]). All preference-based measures include both descriptive systems and a utility index, and hence, could be used in cost-utility evaluations.\(^{78}\)
The group was unable to reach consensus and recommend a single tool among these measures. Patient and public partners highlighted that none of the tools comprehensively captured their experiences of the aftermath of a cardiac arrest. In online voting, the HUI3, followed by the SF-36 and EQ-5D-5L, received the most support (Table 3). The briefest measures are the EQ-5D-5L (5 items) and HUI3 (8 items); the longest is the SF-36 (v2) (36 items). While all measures are intended to be measures of health status or HRQoL, the number of items and HRQoL coverage is varied (Table 3). The HUI3 and EQ-5D-5L have a preponderance of items that relate to physical health, whereas items within the SF-36(v2) are equally distributed between physical and mental health. However, only the HUI3 includes items that measure cognition, speech, and dexterity, which are concerns relevant to cardiac arrest survivors. Only the SF-36(v2) includes an assessment of fatigue.

Preference-based utility scores can be calculated for HUI3, EQ-5D-5L, and SF-36(v2) (in the form of the SF-6D), supporting their use in cost-utility evaluation. The SF-36(v2) provides the most detailed profile score—that is, separate scores are calculated across the 8 health domains, providing a more detailed assessment of health status than is otherwise afforded by the 2 summary scores. More limited descriptive profile scores can also be reported for both the HUI3 and EQ-5D across their 8 and 5 attributes, respectively. Normative population data are available for all measures, supporting data interpretation, and between-group comparisons. Estimates of meaningful change have been calculated for all measures following completion by the general population and specific patient groups, further supporting data interpretation. License requests are required for all measures, but only the EQ-5D-5L is free to use.
A review of published evidence on the reliability and validity of these measures following completion by survivors of cardiac arrest demonstrated that the strongest evidence was available for the HUI3, followed by the SF-36(v2). The EQ-5D-5L has not been evaluated in this population; however, evaluations in comparable populations suggest improved data quality and psychometric performance when compared with the original EQ-5D-3L.

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

How to Complete

Although all the above HRQoL measures were developed to be self-completed, all have been successfully interview-administered in person, via the telephone, or both in the cardiac arrest population. Postal self-completion, although possible has been only used infrequently. However, the ability to self-complete a questionnaire after a cardiac arrest can be severely impaired by cognitive impairment (which may result in an overestimation of ability), fatigue, or general poor health. Although proxy ratings of non-observable constructs such as emotional well-being and cognition may underestimate limitations, agreement is generally greater for more physical attributes. Cronberg et al described interview-based proxy completion of the SF-36(v2) with 8% of survivors at 6-month follow-up. Where possible, proxy completion by appropriate, well-informed assessors is suggested to ensure that the views of survivors who are unable to self-report are included in trials and the results do not underestimate the impact of cardiac arrest on HRQoL.
Timing
There was consensus that HRQoL should be measured after the patient’s discharge from the hospital. Patient recovery often continues to 6 months and beyond. Three-quarters of patients of a working age return to work after cardiac arrest at a median interval of 4 months.\textsuperscript{88} The optimal time points and frequency of follow-up need to be considered in the context of study resources and overall study design. If sufficient resources are available to measure post-discharge outcomes, the group recommends—as a minimum—assessment at 90 days. The group considered that this best balanced the trade-off between costs and other implications associated with longer-term follow-up with the positive effect of the value and stability of the data and is consistent with the review of primary outcomes by Becker et al.\textsuperscript{19} However, it is recognized that health status may continue to change in the subsequent months and that capturing this change is important.\textsuperscript{40, 88, 89} Therefore, the group agreed that HRQoL could also be assessed at 180 days and/or 1 year. However, the longer duration of follow-up would be associated with increased logistic challenges and may be influenced by factors external to surviving a cardiac arrest.

Discussion
The COSCA Writing Group identified that survival, neurologic function, and HRQoL should be reported as core outcomes in cardiac arrest effectiveness trials. Survival status should be reported at hospital discharge and / or at 30 days. Neurologic function (measured by using the mRS) should be reported at hospital discharge and / or 30 days. HRQoL should be measured by using 1 or more tools from the HUI3, SF-36(v2), or EQ-5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources allow.
Core outcome sets are intended to enhance standardization of the outcomes, which are reported for effectiveness trials. As such, future cardiac arrest effectiveness trials should include the core outcomes identified by COSCA as part of the \textit{a priori}–designated primary or secondary trial outcomes. The COSs are intended to be complimentary to other outcome measures relevant to the particular intervention under evaluation. The COS recommendations sit alongside, rather than replace, tools designed to enhance the quality and transparency of health research, such as the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)\textsuperscript{90} and Consolidated Standards of Reporting Trials\textsuperscript{91} (Figure 3). Earlier phase trials will typically focus primarily on measures of efficacy, such as biomarkers, ROSC, or immediate survival, although selected core outcomes could also be considered.

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

Generic measure of HRQoL, such as those short-listed in the COSCA recommendations (HUI3, SF-36(v2), EQ-5D-5L), includes multidimensional concepts (physical, social,
emotional, and mental functioning) that provide a general assessment of HRQoL of relevance
to patients and the general population, facilitating between-group comparisons and ensuring
that the patient perspective is captured in clinical trials. Although the generic measures
supported by COSCA start to move the focus toward patient-centered outcomes, the current
tools still fail to comprehensively capture the breadth of outcomes and experiences that
matter most to cardiac arrest survivors. As consequence, the impact of cardiac arrest and
associated healthcare may be incompletely assessed. Although a condition-specific measure
for survivors of cardiac arrest does not currently exist, measures specific to problems of
relevance to cardiac arrest survivors (eg, cognition, fatigue, anxiety, social participation) are
available and have been increasingly used in this population. Even though the
COSCA recommendations do not currently include guidance for 1 or more problems or
function-specific measures, per good practice guidance for outcome assessment, where
possible, we encourage their inclusion. Although not yet evaluated in the cardiac arrest
population, the PROMIS initiative (Patient Reported Outcome Measures Information System
http://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis) describes a range of fixed or dynamic (computer adaptive tests) self-report measures of
physical, mental and social health appropriate for use with the general population and those
with chronic conditions, and hence suitable for comparing the burden of illness and treatment
impact. The paucity of evidence to suggest which tools are best suited highlights the need for
further research in this area.

Collecting health-related quality-of-life measures as an outcome of a clinical trial can be
challenging and expensive. Sometimes, such data are missing from patients with the poorest
outcomes, which may result in systematic bias, which cannot be ignored. To maximize
the quality and timeliness of quality-of-life measures and reduce the risk of systematic bias
due to missing data, standardized administration and routine screening for avoidable missing
data are advised.\textsuperscript{100-102} The approaches used and handling of missing data should be detailed
in the study protocol and standard operating procedures.\textsuperscript{99, 101}

The writing group was cognizant of the balance that needs to be struck between the
requirements of collecting the core outcomes identified by the COSCA initiative at a time of
constrained research resources and the need to accelerate the pace of evidence-based change
in resuscitation practices. The overall efficiency of the research pathway may be improved
through a better understanding of the pathophysiology and effects of therapeutic interventions
from animal and laboratory studies. By establishing proof of concept with evidence from
early efficacy trials, internal pilots may reduce redundancy in effectiveness trials.\textsuperscript{103-105}

Improving the efficiency of the conduct of trials\textsuperscript{106} and making use, where possible, of
registry data\textsuperscript{107} may reduce costs and shorten the time to complete trials. The use of fixed
dichotomous analysis of ordered categorical outcomes is rarely the most statistically efficient
approach and usually requires a larger sample size to demonstrate efficacy than other
approaches.\textsuperscript{68} Alternative analytical approaches such as shift analysis, ordinal logistic
regression, used widely in stroke research,\textsuperscript{68, 70} require further evaluation in the cardiac arrest
population. A better understanding of measurement properties of continuous outcomes, such
as hospital-free survival,\textsuperscript{31} may also aid reductions in sample size and trial costs.

[h1]Conclusion

Through a partnership between patients, partners, clinicians, and researchers and endorsed by
ILCOR, consensus emerged that a core outcome set for reporting on effectiveness studies of
cardiac arrest (COSCA) should include survival, neurologic function, and health-related
quality of life (HRQoL). To facilitate meaningful comparisons across studies over time,
survival status and modified Rankin scale at hospital discharge and / or 30 days should be reported. HRQoL should be measured by using 1 or more tools from the HUI3, SF-36(v2), or EQ-5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources allow.
Acknowledgments

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

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

Sources of Funding

None

Disclosures
References


the elderly after target temperature management for out-of-hospital cardiac arrest.


94. Pietersma S, de Vries M and van den Akker-van Marle ME. Domains of quality of life: results of a three-stage Delphi consensus procedure among patients, family of patients,


<table>
<thead>
<tr>
<th>Theme</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Survival</td>
<td>Closeness to death</td>
</tr>
<tr>
<td></td>
<td>Gratitude to be alive</td>
</tr>
<tr>
<td>Impairment and impact to activities</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Breathlessness</td>
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<td></td>
<td>Vision</td>
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<td></td>
<td>Muscle weakness</td>
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<td></td>
<td>Pain (eg, fractured ribs)</td>
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<td></td>
<td>Activities of daily living/increased dependence</td>
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<td>Cognitive function</td>
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<td>Emotional well-being</td>
<td>Anxiety</td>
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<td>Confidence</td>
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<td>Depression</td>
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<td>Self-esteem</td>
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<td>Personality changes</td>
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<td>Frustration</td>
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<td>Social well-being and participation</td>
<td>Participation (role: job, voluntary, career)</td>
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<td>Participation (leisure: hobbies, sports)</td>
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<td>Participation (social activities)</td>
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<td>Participation (family: relationships, intimacy)</td>
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<tr>
<td>Impact on others</td>
<td>Increased work/care</td>
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<td>Impact to participation—hobbies, work</td>
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<td>Strain on relationships</td>
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<tr>
<td>1</td>
<td>Worry</td>
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Table 2. Core outcomes, time-point and preferred methods for collection

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<thead>
<tr>
<th>Outcome</th>
<th>Time-point</th>
<th>Preferred method</th>
<th>Alternative method</th>
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</thead>
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<td>Survival</td>
<td>30 days and / or discharge</td>
<td>Ambulance / Hospital records</td>
<td>Death registry</td>
</tr>
<tr>
<td>Neurological function (mRS)</td>
<td>30 days and / or discharge</td>
<td>Face to face interview by trained raters using mRS-9Q</td>
<td>Informant interview</td>
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<tr>
<td></td>
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<td></td>
<td>Telephone assessment</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Review of hospital records</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>90 days</td>
<td>Face-to-face (proxy completion where respondents are unable to participate)</td>
<td>Telephone interviews</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Postal questionnaire</td>
</tr>
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<td>Table 3. Summary and Item Content of Short-listed Generic HRQoL Measures (n=3)</td>
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<td>Completion Time:</td>
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<td>Preferences based (2)</td>
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<tr>
<td><strong>Health Utilities Index 3 (HUI3)</strong></td>
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<td>Completion time:</td>
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<td></td>
<td><strong>HRQoL Domains (Ferrans et al, 2005) (Items Per Domain)</strong></td>
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<tr>
<td>Pain—severity (1)</td>
<td>Ambulation: Ability to walk (distances)</td>
<td>Cognition: ability to solve day-to-day problems (1)</td>
<td>Emotion: happiness and interest in life (1)</td>
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<td>Symptom Status</td>
<td>Symptom Status</td>
<td>Functional Status</td>
<td>General Health Perception</td>
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<tr>
<td>Physical</td>
<td>Cognitive</td>
<td>Psychological</td>
<td>Social/Role</td>
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<tr>
<td>Symptoms</td>
<td></td>
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<tr>
<td>Preference-based, comprehensive system for measuring health status and HRQoL and for producing utility scores. Applicable for all persons aged 5 years and older.</td>
<td>HUI3 classification system: describes the comprehensive health state of an individual across 8 attributes of general health (68 items reflect physical functional status)</td>
<td>Response options: Between 4 and 6 descriptive response options (ability/disability)</td>
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<td>Response options: Between 4 and 6 descriptive response options (ability/disability)</td>
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</tr>
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</table>
| **Approximately 3 minutes interview completion** (not reported in cardiac arrest population) | **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) | **Completion:** Self, interview (in person; telephone), or proxy (proxy version available) supported | **Senses:**  
- Hearing  
- Speech:  
  - Ability to be understood (5) | **algorithms to support calculation of single-attribute Utility Score (Index)**  
  - 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  
  - Population-based norms available  
  - 2. Multiattribute descriptive |
**EuroQol EQ-5D-5L**

**EuroQol website:**
[www.euroqol.org/home.html](http://www.euroqol.org/home.html)

**License:** For use per project; free, but use must be registered on EuroQol website:
[www.euroqol.org/register-to-use-eq-5d.html](http://www.euroqol.org/register-to-use-eq-5d.html)

**Completion time:**
Less than 5 minutes
(not reported in cardiac arrest population)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
<th>Response options</th>
<th>Data presentation</th>
</tr>
</thead>
</table>
| Pain/discomfort | 1 | 5-level categorical response options per item (no problems [1] to extreme problems [5]) | 1. EQ-5D-5L Index value 
2. EQ-5D-5L specific coding algorithms to support calculation of Utility Score (Index): Crosswalk value sets from EQ-5D-5L 
| Mobility | 2 | Self-care | 1. EQ-5D-5L Index value 
2. EQ-5D-5L specific coding algorithms to support calculation of Utility Score (Index): Crosswalk value sets from EQ-5D-5L 
| Anxiety/depression | 1 |  | 1. EQ-5D-5L Index value 
2. EQ-5D-5L specific coding algorithms to support calculation of Utility Score (Index): Crosswalk value sets from EQ-5D-5L 
| Usual activities (including work, study, housework, and family or leisure activities) | 1 |  | 1. EQ-5D-5L Index value 
2. EQ-5D-5L specific coding algorithms to support calculation of Utility Score (Index): Crosswalk value sets from EQ-5D-5L 

Standardized, preference-based measure of health status for use in clinical and economic appraisal

EQ-5D descriptive system: 5 items across “5 domains” (2/5 reflects physical functional status)

(EQ VAS: self-rated health on a 20 cm vertical visual analogue scale)

**Response options:** 5-level categorical response options per item (no problems [1] to extreme problems [5])

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)

“Classification system” — reflects individual item scores

www.euroqol.org/home.html

Completion time:
Less than 5 minutes
(not reported in cardiac arrest population)
<table>
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<tr>
<th>User guide: Free at following link:</th>
<th>Recall period: Today</th>
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<tr>
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<tr>
<td>Language: &gt;120 language versions (see <a href="http://www.euroqol.org">www.euroqol.org</a>)</td>
<td></td>
</tr>
</tbody>
</table>

3L support calculation of EQ-5D-5L utility score

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

Country-specific value sets and population-based norms available

Report both measure of
central
tendency and
a measure of
dispersion, eg,
mean and SD;
median and
percentiles

2. EQ-5D-5L
descriptive
system as a
health profile:
reflects
individual
item scores.

2.1 Report as
the frequency
or proportion
of reported
problems for
each level for
each
dimension
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)**


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.

Total 35 items plus 1 health transition item.

**Response options:** Between 3- and 6-level categorical response options per item.

<table>
<thead>
<tr>
<th>Bodily pain (BP) (2)</th>
<th>Physical functioning (PF) (10)</th>
<th>–</th>
<th>Mental health (MH) (5)</th>
<th>Social functioning (SF) (2)</th>
<th>General health (GH) (5): perceived well-being</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitality (VT): fatigue/tiredness (2)</td>
<td>Role limitation (RP) (4)</td>
<td></td>
<td>Role limitation (RE) (3)</td>
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<td></td>
</tr>
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2 ways of presenting the data:

2.1 Eight-domain profile

2.2 Two component
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</tr>
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<td><strong>Completion time:</strong></td>
<td>Range 5 to 30 minutes (not reported in cardiac arrest population)</td>
</tr>
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<td><strong>Recall period:</strong></td>
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<td><strong>Completion:</strong></td>
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<td><strong>Language:</strong></td>
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<tr>
<td><strong>User guide:</strong></td>
<td>Available once SF-36v2 is purchased</td>
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<tr>
<td><strong>Country of origin:</strong></td>
<td>United States</td>
</tr>
</tbody>
</table>

The IQOLA project supported the development of conceptually equivalent and culturally appropriate translations (see [www.iqola.org](http://www.iqola.org)).

**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

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.

<table>
<thead>
<tr>
<th>Core Area</th>
<th>Outcome Domain</th>
<th>Timing of Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>During CPR</td>
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<tr>
<td>Pathophysiologic manifestations</td>
<td>Circulatory function</td>
<td>O</td>
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<tr>
<td></td>
<td>Respiratory function</td>
<td>●</td>
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<td></td>
<td>Renal function</td>
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<td></td>
<td>Brain function (neurologic markers)</td>
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<tr>
<td></td>
<td>Adverse events</td>
<td>●</td>
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<tr>
<td></td>
<td>CPR process measures*</td>
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</tr>
<tr>
<td>Survival</td>
<td>Survival</td>
<td>●</td>
</tr>
<tr>
<td>Life impact</td>
<td>Consciousness and cognition</td>
<td>○</td>
</tr>
<tr>
<td></td>
<td>Physical symptoms</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>Activities of daily living</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>Health-related quality of life</td>
<td>○</td>
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<td></td>
<td>Emotional well-being</td>
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<td></td>
<td>Family impact</td>
<td>●</td>
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<tr>
<td></td>
<td>Participation</td>
<td>△</td>
</tr>
</tbody>
</table>
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.