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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 COSCA initiative (Core Outcome Set for Cardiac Arrest), 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 or 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 that led 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, neurological function, and health-related quality of life. This should be reported as survival status and modified Rankin scale score at hospital discharge, at 30 days, or both. Health-related quality of life should be measured with ≥1 tools from Health Utilities Index version 3, Short-Form 36-Item Health Survey, and EuroQol 5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources allow.
Sudden cardiac arrest is one of the leading causes of death in industrialized nations. In the United States, ≈360,000 cardiac arrests are attended by emergency services each year, with only 10.6% of patients surviving to hospital discharge. Similar statistics apply across Europe and all other industrialized areas worldwide. However, survival rates vary widely both globally and regionally, 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 efficacy 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. 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. Evaluated outcomes can 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.

Sometimes multiple trials might evaluate the same intervention in different settings. Reconciling disparate trial results can be challenging if each trial evaluated different outcomes at different time points. A systematic review of cardiac arrest trials published between 2000 and 2012 included 61 publications that identified >160 different trial outcomes. No single outcome was reported across all trials. The majority of outcomes reflected short-term clinical and clinician-reported outcomes, focusing on pathophysiological manifestations and process-based measures. Although survival was the most commonly reported outcome, 39 different definitions of survival were used. Patient-reported outcomes were rarely reported, although more recent trials have included these outcomes. 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. These frameworks recommend 23 core data elements and 30 supplementary elements across the 5 domains of system, dispatch, patient, process, and outcome. International guidelines exist for core outcomes to use in effectiveness trials in patients with other conditions. 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; however, no international guidelines exist to define a focused core outcome set (COS) for use in effectiveness trials in patients with cardiac arrest.

The COMET initiative (Core Outcome Measures for Effectiveness Trials) promotes the development and application of agreed standardized sets of outcomes known as COS. 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. Effectiveness trials should aim to capture the COS as part of their a priori–defined primary or secondary outcomes.

The COSCA initiative (Core Outcome Set for Cardiac Arrest), 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 article 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.

METHODS

The available evidence associated with the development of COS and the websites of key COS development groups (COMET and OMERACT [Outcome Measures in Rheumatoid Arthritis Clinical Trials], later renamed Outcome Measures in Rheumatology) informed our approach. The project was registered with the COMET initiative. Ethical approval was obtained from the National Health Service Black Country Research Ethics Committee (13/WM/0464) to enable patients and their 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 mea-
sure) 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 pathophysiological manifestations associated
with the condition.18 Several reviews11,23,24 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, each of which is explained in detail: (1) stage 1:
generation of an extensive list of potential outcomes
across 4 core areas of health; (2) stage 2: an interna-
tional Delphi approach to refine and prioritize a list of
potential outcomes; (3) stage 3: an international expert
panel meeting; and (4) 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 fo-
cused on the identification of outcomes reported from
randomized controlled trials that enrolled adults who
had sustained a cardiac arrest.11 The findings from the
systematic review were supplemented by conducting
semistructured interviews with adult cardiac arrest sur-
vivors (and, if available, their partners) between 3 and
12 months after discharge from the hospital after their
cardiac arrest. Interviews were conducted, recorded,
and transcribed with NVivo (QSR International, London,
United Kingdom) by Dr Whitehead. Data were analyzed
using interpretative phenomenological analysis, which
seeks to capture the individual’s experience of a phe-
nomenon and how they understand their experiences.25
Findings from the systematic review and qualitative re-
search 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 pathophysiological mani-
festations of cardiac arrest for consideration in stage 2.

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

The list of potential outcomes identified during stage
1 were placed into an online survey tool (SurveyMon-
key, Dublin, Ireland). Separate surveys were developed
for healthcare professionals and patients/patient advo-
cates. The ILCOR network of 7 regional resuscitation
councils was used to solicit the views of healthcare pro-
fessionals and patient and public advocates. Each ILCOR
member (n=27) was asked to invite 6 healthcare pro-
fessionals and 3 patients to participate in the relevant
surveys by E-mail. 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 cardio-
pulmonary resuscitation (CPR), immediately after CPR,
during hospitalization, at hospital discharge, and within

Figure 1. OMERACT framework 2.0 modified for cardiac arrest.
ICU indicates intensive care unit; OMERACT, Outcome Measures in Rheumatology; QOL, quality of life; and ROSC, return of
spontaneous circulation. Reprinted from Boers et al.18 Copyright © 2014, The Authors. https://creativecommons.org/licenses/
by-nc-nd/3.0/.
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 being of critical importance by >70% of respondents and rated as being of limited importance by <15% of respondents were advanced for additional consideration by the expert panel in stage 3. Similarly, those outcomes rated of limited importance by >70% of respondents and of critical importance by <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 (>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 pathophysiological 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 semistructured, 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 a 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 had discussed, facilitated the identification of issues of agreement and disagreement, and supported a flow of new ideas or key issues between groups. Thereafter, participants reconvened in a whole-group discussion session, in which facilitators and group recorders summarized feedback from the small-group discussions, 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 believed should be included as core outcomes. Secure electronic votes were submitted by use of TurningPoint software and ResponseWare keypads (Turning Technologies, Youngstown, Ohio). 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.
RESULTS

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.\(^1\) 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. Pathophysiological outcomes (e.g., 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 (e.g., event timings), response to treatment (e.g., temperature achieved in targeted temperature management trials), quality of CPR, intervention success rates (e.g., 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.\(^{13,14,26,27}\)

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 that reflected 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 pathophysiological manifestations (14), which were used in the stage 2 Delphi process.

Stage 2: International Delphi Approach 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 48 physicians, 12 nurses, 21 allied health professionals, 6 academics and 12 others. 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 (United Kingdom, the Netherlands, Finland, Germany, Belgium, Sweden, United States, Canada, Singapore, Australia, and New Zealand). The core outcome discussions and recommendations are summarized below.

Pathophysiological 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 pathophysiological measures to act as surrogate assessments for longer-term functional outcomes. For example, specific neuroimaging/electrophysiological tests might be a useful surrogate to reflect the impact of a cardiac arrest on brain function.\(^28\) The panel considered these outcomes might 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 pathophysiological manifestations as core outcomes

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

<table>
<thead>
<tr>
<th>Theme</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>Closeness to death, Gratitude to be alive</td>
</tr>
<tr>
<td>Impairment and impact on activities</td>
<td>Fatigue, Breathlessness, Vision, Muscle weakness, Pain (e.g., fractured ribs), Activities of daily living/increased dependence, Cognitive function</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>Anxiety, Confidence, Depression, Self-esteem, Personality changes, Frustration</td>
</tr>
<tr>
<td>Social well-being and participation</td>
<td>Participation (role: job, voluntary, career), Participation (leisure: hobbies, sports), Participation (social activities), Participation (family: relationships, intimacy)</td>
</tr>
<tr>
<td>Impact on others</td>
<td>Increased work/care, Impact to participation—hobbies, work, Strain on relationships, Worry</td>
</tr>
</tbody>
</table>
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 could include compression rate, preshock 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 can be initiated or completed before a study intervention is applied. Although CPR process could be an indicator of the quality of a resuscitation system of care or 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 COS categories. Where such data are reported, use of standardized definitions and time intervals could reduce variation in reporting.

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 the 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 can 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 among the most common and significant impacts of cardiac arrest are potential changes to cognition and neurological 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 multidomain approach, including assessing an individual’s HRQoL after arrest, was favored.

The panel reached consensus that neurological 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. Although economic evaluation was judged to be important, it was agreed that there was insufficient evidence to inform categorization currently. As a result, economic measures were not 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 information on 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 the hospital) and health system differences (efficiency of discharge processes; whether long-term care is provided in the hospital or in 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, can 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, 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.

**Neurological Function**

Five clinician-completed measures—the Cerebral Performance Category (CPC), 34 Structured CPC (assessment by semistructured interview), 35 CPC-Extended, 36 Glasgow Outcome Scale–Extended, 37 and modified Rankin Scale (mRS) 38—were considered. Moderate associations between the tools suggest that they measure similar constructs. 13,35,39-42 The CPC was not highly endorsed because of the lack of discrimination between scores and the potential for ceiling effects and overestimation of function. 14,43-46 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. 36 The mRS and Glasgow Outcome Scale–Extended appear to provide improved granularity. 41,43 The mRS has been used more extensively in cardiac arrest survivors 13,41,47-55 than the Glasgow Outcome Scale–Extended 44,56 or CPC-Extended. 37

The writing group reached unanimous agreement that the mRS should be the outcome measurement tool of choice for neurological function. The mRS is a brief, clinician-completed, ordinal hierarchical rating scale used to determine a summary score of global disability after a neurological 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. 58,59 There is evidence that it can discriminate between levels of mild and moderate disability. 58 It does not, however, provide detailed information of residual impairments and is unable to differentiate between whether effects are attributable to neurological or other sources of disability. 58,60

**How to Complete**

mRS completion is preferably measured by direct interview with the patient and any relevant caregiver, either face-to-face or by telephone (Table 2). 57 Nonstandardized interview administration requires ≈5 minutes. 57 When 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—can be considered. However, proxy completion without the involvement of the patient is associated with suboptimal levels of reliability and validity. 57,61 Although some studies suggest that indirect mRS completion from hospital records is less accurate, 62 others suggest acceptable reliability after chart review by trained health professionals. 38,39

Substantial inter-rater reliability of the mRS has been described, 63 although this can be improved through...
digital training,\textsuperscript{63} use of a structured interview,\textsuperscript{59,64} or use of a web-based tool with 9 questions (mRS-9Q) and an mRS calculator.\textsuperscript{65} Use of trained raters and a structured approach to calculating the mRS score is recommended. Raters should 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 neurological function. Additional limitations of measuring neurological 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 the hospital longer. Additional challenges imposed by assessing neurological function at 30 days include the requirement for the research team to specifically follow up with the patient, because unlike mortality, these data often are not tracked routinely. Incomplete follow-up confers a risk of 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 was considered acceptable for reporting as a core outcome. Researchers can 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 an mRS cutoff of \(\leq 3\).\textsuperscript{17,66,67} However, in stroke trials, an mRS score of \(\leq 1\)\textsuperscript{68} or \(\leq 2\)\textsuperscript{69} has been used to represent the cut off between favorable and unfavorable outcomes.

To enable consistent reporting and comparisons between articles, the writing group advised that the core outcome be presented as the number and percentage of patients in each of the 6 categories rather than solely being categorized into favorable and unfavorable neurological outcome groups. This approach also provides greater granularity on clinically-relevant outcomes.\textsuperscript{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 the CPC score over the next 5 years, in addition to the mRS score. Useful information for calculating the mRS score can be found on the Internet.\textsuperscript{71}

The COSCA writing group suggested the use of the mRS version, where category 4 (moderate severe disability) includes dependency to attend to own bodily needs as separate from ability to walk unassisted (or instead of and). Outcome after cardiac arrest is less influenced by locomotor problems than after stroke, and this version will be more sensitive in identifying extensive dependency related to severe cognitive impairment in a patient still able to walk. This version is available online.\textsuperscript{71} The scoring is as follows: 0=no symptoms; 1=no significant disability—able to carry out all usual activities, despite some symptoms; 2=slight disability—able to look after own affairs without assistance but unable to carry out all previous activities; 3=moderate disability—requires some help but able to walk unassisted; 4=moderately severe disability—unable to attend to own bodily needs without assistance and/or unable to walk unassisted; 5=severe disability—requires constant nursing care and attention, bedridden, incontinent; and 6=dead.

**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 (eg, 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]\textsuperscript{72} and Short-Form 12-Item Health Survey [SF-12]\textsuperscript{73,74} and 4 preference-based, multiattribute utility measures (the 15-dimension Quality of Life questionnaire [15-D],\textsuperscript{75} the Health Utilities Index version 3 [HUI3],\textsuperscript{76} and both the original and revised versions of the EuroQol [EQ-5D-3L\textsuperscript{77} and EQ-5D-5L\textsuperscript{78} respectively]). All preference-based measures include both descriptive systems and a utility index and hence could be used in cost-utility evaluations.\textsuperscript{79}

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-36v2 (36 items). Although all measures are intended to be measures of health status or HRQoL, the number of items and HRQoL coverage vary (Table 3). The HUI3 and EQ-5D-5L have a preponderance of items that relate to physical health, whereas items within the SF-36v2 are equally distributed between physical and mental
Table 3. **Summary and Item Content of Short-listed Generic HRQoL Measures (n=3)**

| PROM Details, Developer, Website, Cost (License), Completion Time | Conceptual Focus, Response Options/Recall Period, Completion Format, Language Versions | HRQoL Domains(1) (Number of Items Per Domain) | Symptom Status: Symptoms | Functional Status: Physical | Functional Status: Cognitive | Functional Status: Psychological | Social/ Role | General Health Perception | How to Score |
|---|---|---|---|---|---|---|---|---|---|---|
| Preferences based (2) | | | | | | | | | | |
| HUI3 | Website: www.healthutilities.com | Preference-based, comprehensive system for measuring health status and HRQoL and for producing utility scores. Applicable for all people aged ≥5 y. | 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 data: 1. HUI3 utility index: scored using single-attribute and multi-attribute utility functions HUI3 classification system: describes the comprehensive health state of an individual across 8 attributes of general health (6 of 8 items reflect physical functional status) Response options: Between 4 and 6 descriptive response options (ability/disability) Recall period: “Current” or “Usual”; “Usual” recommended for clinical studies. Choice of 1-, 2-, or 4-wk recall available Completion: Self, interview (in person, telephone), or proxy (proxy version available) supported Language: 16 versions, including English, Chinese, Dutch, French, German, Italian, Japanese, Portuguese, Russian, Spanish, Swedish |
| EuroQol EQ-5D-5L (EQ-5D-5L) | Website: https://www.euroqol.org/ | Standardized, preference-based measure of health status for use in clinical and economic appraisal EQ-5D descriptive system: 5 items across “5 domains” (2 of 5 reflect physical functional status) (EQ VAS: self-rated health functional status) EQ-5D utility score. Applicable for all people aged ≥5 y. | Pain—discomfort (1) | Mobility: Self-care (2) | – | Anxiety/ depression (1) | Usual activities (including work, study, housework, and family or leisure activities) (1) | – | 2 ways of presenting data: 1. EQ-5D-5L index value: scored using single-attribute and multi-attribute utility functions EuroQol-specific coding algorithms to support calculation of Utility Score (Index): Crosswalk value sets from EQ-5D-3L support calculation of EQ-5D-5L utility score. Index range –0.59 to 1.00, where 1.00 is perfect health, 0 is dead, 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 2.2 Dichotomize into “No problems” (1) and “Problems” (2–5), report frequencies of reported problems |

(Continued)
health. Only the HUI3 includes items that measure cognition, speech, and dexterity, which are concerns relevant to cardiac arrest survivors. Only the SF-36v2 includes an assessment of fatigue.

Preference-based utility scores can be calculated for HUI3, EQ-5D-5L, and SF-36v2 (in the form of the SF-6D86), which supports their use in cost-utility evaluation. The SF-36v2 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, which supports data interpretation and between-group comparisons. Estimates of meaningful change have been calculated for all measures after completion by the general population and specific patient groups, which further supports 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 after completion by survivors of cardiac arrest demonstrated that the strongest evidence was available for the HUI3, followed by the SF-36v2.87 The EQ-5D-5L has not been evaluated in this population; however, evaluations in comparable populations suggest improved data quality and psychometric performance compared with the original EQ-5D-3L.78

In summary, multiple measures of HRQoL, including the SF-36v2, 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 of the HRQoL measures discussed here were developed to be self-completed, all have been successfully administered by interview in person.40,42

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**Table 3. Continued**

<table>
<thead>
<tr>
<th>PROM Details, Developer, Website, Cost</th>
<th>Conceptual Focus, Response Options/Recall Period, Completion Format, Language Versions</th>
<th>HRQoL Domains85 (Number of Items Per Domain)</th>
<th>How to Score</th>
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<tr>
<td>Profile measures (1)</td>
<td></td>
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<tr>
<td>Short Form 36-Item Health Survey, version 2 (SF-36v2)</td>
<td>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</td>
<td>Bodily pain (2)</td>
<td>2 ways of presenting the data:</td>
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<td></td>
<td>Total 35 items plus 1 health transition item</td>
<td>Vitality: fatigued/tiredness (2)</td>
<td>2.1 Eight-domain profile</td>
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<tr>
<td></td>
<td>Response options: Between 3- and 6-level categorical response options per item</td>
<td>Physical functioning (10)</td>
<td>2.2 Two component summary scales: PCS, MCS</td>
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<td></td>
<td>Recall period: Standard recall 4 wk; acute recall 1 wk</td>
<td>Role limitation (4)</td>
<td>Scoring requires SF-36–specific algorithm.</td>
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<tr>
<td></td>
<td>Completion: Self, interview (in person; telephone), or proxy supported</td>
<td>–</td>
<td>Norm-based scoring: score transformed to 0–100 (mean 50 (SD 10))</td>
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<td></td>
<td>Language: &gt;170 language versions</td>
<td>Mental health (5)</td>
<td>Population-based norms available</td>
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<td></td>
<td>See website</td>
<td>Role limitation (3)</td>
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<tr>
<td></td>
<td>The IQOLA project supported the development of conceptually equivalent and culturally appropriate translations86</td>
<td>Social functioning (2)</td>
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<td>Note: utility values</td>
<td>General health (5): perceived well-being</td>
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<td>A preference-based utility index, the SF-6D, can be calculated after completion of the SF-36 to inform economic analyses85</td>
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EQ VAS indicates EuroQol visual analogue scale; HRQoL, health-related quality of life; HUI3, Health Utilities Index 3; IQOLA, International Quality of Life Assessment; MCS, mental component summary; PCS, physical component summary; FDA, personal digital assistant; and PROM, patient-reported outcome measure.

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via the telephone, \textsuperscript{13,56,88,89} or both\textsuperscript{14} in the cardiac arrest population. Postal self-completion, although possible, has been used infrequently. However, the ability to self-complete a questionnaire after a cardiac arrest can be severely impaired by cognitive impairment (which can result in an overestimation of ability),\textsuperscript{90} fatigue, or general poor health. Although proxy ratings of nonobservable constructs such as emotional well-being and cognition can underestimate limitations,\textsuperscript{91,92} agreement is generally greater for more physical attributes.\textsuperscript{91,93,94} Cronberg et al\textsuperscript{14} described interview-based proxy completion of the SF-36v2 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.\textsuperscript{94}

**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{95} 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 postdischarge 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 can continue to change in the subsequent months and that capturing this change is important.\textsuperscript{41,95,96} Therefore, the group agreed that HRQoL could also be assessed at 180 days or 1 year, or both. However, the longer duration of follow-up would be associated with increased logistic challenges and could be influenced by factors external to surviving a cardiac arrest.

**DISCUSSION**

The COSCA writing group identified that survival, neurological function, and HRQoL should be reported as core outcomes in cardiac arrest effectiveness trials. Survival status should be reported at hospital discharge, at 30 days, or both. Neurological function (measured with the mRS) should be reported at hospital discharge, 30 days, or both. HRQoL should be measured with ≥1 tools from the HUI3, SF-36v2, or EQ-5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources allow.

COS are intended to enhance standardization of outcomes that are reported for effectiveness trials. As such, future cardiac arrest effectiveness trials should include the core outcomes identified by COSCA as part of the a priori–designated primary or secondary trial outcomes. The COS are intended to be complementary 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 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)\textsuperscript{97} and CONSORT (Consolidated Standards of Reporting Trials)\textsuperscript{98} (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.

![Figure 3. Core outcome sets as part of Good Clinical Practice.](http://circ.ahajournals.org/Downloadedfromhttp://circ.ahajournals.org/)

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. CONSORT indicates Consolidated Standards of Reporting Trials; EQ-5D-5L, 5-level EQ-5D; HUI3, Health Utilities Index version 3; mRS, modified Rankin scale; QoL, quality of life; SF-36, 36-item Short Form Survey; and SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.
Traditionally, outcome assessment of patients experiencing cardiac arrest has focused on survival rates and clinician-based assessments of outcome. 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 that outcomes (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 outcomes reporting in clinical trials. Such questionnaires or patient-reported outcome measures can be simply categorized as generic or specific (to a condition [e.g., diabetes mellitus], a problem [e.g., cognition], a function [e.g., activities of daily life], or a population [e.g., children]).

Generic measure of HRQoL, such as those short-listed in the COSCA recommendations (HUI3, SF-36v2, 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 a consequence, the impact of cardiac arrest and associated health care might 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 (e.g., cognition, fatigue, anxiety, social participation) are available and have been used increasingly in this population. Although the COSCA recommendations do not currently include guidance for ≥1 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) 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 HRQoL 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 can 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 caused by missing data, standardized administration and routine screening for avoidable missing data are advised. The approaches used and handling of missing data should be detailed in the study protocol and standard operating procedures.

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 can 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 pilot studies could reduce redundancy in effectiveness trials. Improving the efficiency of the conduction of trials and making use of registry data, where possible, could 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. Alternative analytical approaches such as shift analysis and ordinal logistic regression, used widely in stroke research, require further evaluation in the cardiac arrest population. A better understanding of measurement properties of continuous outcomes, such as hospital-free survival, might also aid reductions in sample size and trial costs.

**CONCLUSIONS**

Through a partnership between patients, partners, clinicians, and researchers and endorsed by ILCOR, consensus emerged that a COS for reporting on effectiveness studies of cardiac arrest (COSCA) should include survival, neurological function, and HRQoL. To facilitate meaningful comparisons across studies over time, survival status and mRS at hospital discharge, 30 days, or both should be reported. HRQoL should be measured with ≥1 tools from the HUI3, SF-36v2, or EQ-5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if resources allow.

**ARTICLE INFORMATION**

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This ILCOR Advisory Statement was approved by the American Heart Association Science Advisory and Coordinating Committee on November 2,
Disclosures

Writing Group Disclosures

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*Significant.
†Modest.

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**REFERENCES**


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On behalf of the COSCA Collaborators

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