Part 3: Evidence Evaluation Process

2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

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"There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we now know we don't know. But there are also unknown unknowns. These are things we do not know we don't know."
—United States Secretary of Defense Donald Rumsfeld (February 2002)

"Thought is the wind, knowledge the sail, and mankind the vessel."
—August Hare (1792–1834)

The international resuscitation community, under the auspices of the International Liaison Committee on Resuscitation (ILCOR), has performed an exhaustive review of the published literature related to resuscitation and emergency cardiovascular care (ECC). We had the opportunity to build on the detailed process developed over the past decade that facilitated the publication of the international consensus statement on therapeutic hypothermia[1] and the *Consensus on Cardiopulmonary Resuscitation (CPR) and ECC Science With Treatment Recommendations in 2005* (C2005).[2] The overall process has been informed by the increasing evidence base behind good, systematic literature reviews.[3,4] There are, however, many questions that have never been addressed in a randomized controlled trial, and much of the supporting scientific literature is at lower levels of evidence (LOEs). In total, 356 worksheet authors from 29 countries throughout the world completed 411 worksheets on 277 topics. The information from these worksheets, with additional iterations from the writing groups and editorial board, makes up the evidence base from which the *2010 International Consensus on CPR and ECC Science with Treatment Recommendations* (CoSTR) document is derived.

Worksheet Template

As has been the process since the evidence evaluation for Guidelines 2000,[5] volunteers from around the world were asked to perform systematic reviews of the literature. These reviews were conducted according to standardized instructions in completing the evidence worksheet template, and these worksheets were subsequently reviewed in a detailed iterative process (see www.ILCOR.org).[6] A revised worksheet template (based on that used for the C2005 process) was created and accompanied by detailed instruction documents and an example of a completed worksheet.

Identifying the Questions to Ask

As with the previous evidence evaluation processes, the specific questions to be asked were informed by priorities identified by task forces and individual councils/organizations, review of the research gaps analysis,[7] and a thorough systematic approach called "evidence mapping" based on the previous guidelines (http://www.evidencemap.org/about).[8]

The questions were allocated to worksheet authors by the relevant task forces, with 2 authors initially allocated to each worksheet. All potential reviewers completed a detailed conflict of interest disclosure form, and worksheet authors were selected to avoid significant conflicts whenever possible (see Part 4).[9] Authors also listed specific potential conflicts of interest on the individual worksheets, thus ensuring transparency of the review process.[9]

It was recognized that not every question could be incorporated, and some areas were therefore not reviewed in the 2010 consensus process. In the absence of a detailed review of all areas, there are, therefore, still some "unknown unknowns."

Formatting the Questions (PICO)

The questions for each worksheet topic were structured into a standardized format (PICO: Population/Patient, Intervention, Comparison, Outcome; http://www.cebm.net/?o=1036).[10] This process provided a clear statement about the components of the

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proposed topic, which facilitated the literature search, guided the accurate allocation of the LOEs, and identified areas of overlap (eg, in-hospital versus prehospital, during arrest versus after arrest, cardiac arrest versus hemodynamic instability, adult versus pediatric). Outcomes of relevance were documented, but in many cases these could be determined only after the initial review of the retrieved articles.

Clarifying the Search Strategy

Generic instructions were provided on the types of search strategy to be considered and databases to be searched. The initial search strategy was submitted electronically via the internet for initial review by one of the task force chairs and one of the worksheet experts. This was to ensure that the search appeared to be on track (eg, addressing the desired question, reasonable combination of search terms), and the search strategy was subsequently returned to the author with comments. The authors were expected to search multiple databases, including the Cochrane database for systematic reviews and the Central Register of Controlled Trials (http://www.cochrane.org/), MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed/), EMBASE (www.embase.com), and the master EndNote reference library collated by the American Heart Association (AHA). Many articles were not identified on the initial search but rather through a combination of additional strategies, including a review of the references from and forward searching on key articles.

Selecting Studies for Further Review

The authors were asked to review the titles and abstracts of all articles identified by their preliminary searches and assess the relevance of the articles to the question being asked. The worksheet author then retrieved the appropriate studies for further comparison with the previously developed inclusion and exclusion criteria. This allowed a reproducible final decision on articles to include in the worksheet.[3] Inclusion of all relevant evidence including animal and manikin/model studies, as well as human studies, was encouraged, unless substantive human data were available. Only manuscripts published in full (or accepted for publication) in a peer-reviewed journal were included. Unpublished data or manuscripts published only in abstract form were again excluded.

Allocating Levels of Evidence

The LOEs used by any review process are a tool to create order and simplicity from the heterogeneity of published studies. There are many published classifications of LOEs. The international resuscitation community used 7 LOEs in the preparation of the 2005 CoSTR.[11,12] For the 2010 CoSTR, we reviewed the literature on available classifications (Evidence Report/Technology Assessment No. 47, Systems to Rate the Strength of Scientific Evidence; Agency for Healthcare Research and Quality [AHRQ] publication No. 02-E016, available at: http://www.ahrq.gov/clinic/epcsums/strengthsum.htm)[13,14] and created a simplified list of 5 LOEs.

Worksheet authors were educated about the LOEs, and instruction material was developed and made available on the internet (see www.ILCOR.org). Specific LOEs based on the likelihood for bias were developed for therapeutic interventions, diagnostic questions, and prognosis (Table 1). The principles of allocation for studies related to therapeutic interventions were based on the likelihood of eliminating bias in the control group (Figure 1): true randomization (LOE 1), concurrent (LOE 2) versus historic (LOE 3) controls, absence of controls (LOE 4), or studies that were related to the worksheet question but that did not directly answer it (LOE 5). LOE 5 studies include studies in related populations (eg, nonarrest), animal studies (designated in tables with an asterisk), and bench and mathematical models. Systematic reviews and meta-analyses were considered in addition to the original studies. If they added information beyond that of the studies they included, they were allocated the same LOE as that of the studies included in the review (http://www.cebm.net/index.aspx?o=1025;)[13]; otherwise, they were allocated LOE 5.

Table 1. Levels of Evidence

C2010 LOEs for studies of therapeutic interventions
LOE 1: RCTs (or meta-analyses of RCTs)
LOE 2: Studies using concurrent controls without true randomization (eg, "pseudo"-randomized)
LOE 3: Studies using retrospective controls
LOE 4: Studies without a control group (eg, case series)
LOE 5: Studies not directly related to the specific patient/population (eg, different patient/population, animal models, mechanical models)
C2010 LOEs for prognostic studies
LOE P1: Inception (prospective) cohort studies (or meta-analyses of inception cohort studies), or validation of CDR
LOE P2: Follow-up of untreated control groups in RCTs (or meta-analyses of follow-up studies), or derivation of CDR, or validated on split-sample only
LOE P3: Retrospective cohort studies
LOE P4: Case series
LOE P5: Studies not directly related to the specific patient/population (eg, different patient/population, animal models, mechanical models)
C2010 LOEs for diagnostic studies
LOE D1: Validating cohort studies (or meta-analyses of validating cohort studies), or validation of CDR
LOE D2: Exploratory cohort study (or meta-analyses of follow-up studies), or derivation of CDR, or a CDR validated on a split-sample only
LOE D3: Diagnostic case-control study
LOE D4: Study of diagnostic yield (no reference standard)
LOE D5: Studies not directly related to the specific patient/population (eg, different patient/population, animal models, mechanical models)

RCTs indicates randomized controlled trials; CDR, clinical decision rule.

Allocating Quality

The process for assessing methodological quality was also reviewed. Many different techniques had been proposed (Evidence Report/Technology Assessment No. 47, Systems to Rate the Strength of Scientific Evidence; AHRQ publication No. 02-E016, available at: http://www.ahrq.gov/clinic/epcsums/strengthsum.htm).[4,13] None of these approaches (largely involving checklists) are appropriate for all settings, and the use of different approaches could result in apparently conflicting results. Several independent factors have been reported to have an impact on the outcome of individual studies, and a modified version based on consensus was created for use.

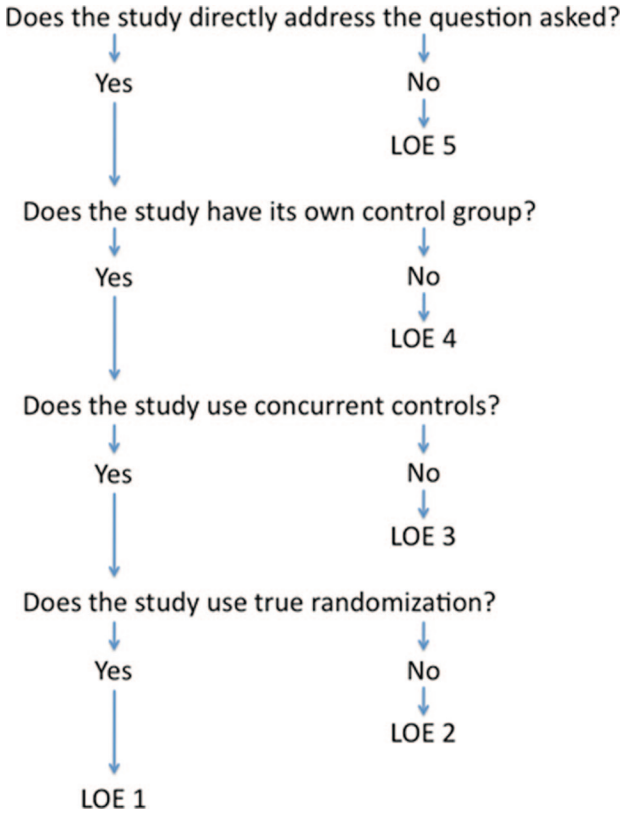

Figure 1. Decision tree for allocation of LOE (LOE) to therapeutic intervention studies.

A list of quality factors was provided for each LOE (1 through 5, including systematic reviews) and for the different types of LOEs (intervention, diagnostic, and prognostic). Three quality terms were defined on the basis of these lists: good, fair, and poor. Studies were designated as "good" if they had most or all of the relevant quality items, "fair" if they had some of the relevant quality items, and "poor" if they had only a few of the relevant quality items but sufficient quality to include for further review (Table 2). Worksheet authors were also asked to comment on the sources of funding for the individual studies, given the concerns about conflict of interest and the association between funding and outcome.[15]

Tabulating the Evidence

All of the evidence identified and evaluated was displayed in standardized evidence tables. In each of 3 tables (supporting evidence, neutral evidence, and opposing evidence), studies were displayed according to LOE, methodological quality, and outcomes identified (Figure 2).

Interpreting the Evidence

The worksheet authors were asked to consider the internal and external validity of each study included and then to summarize the information they reviewed under the section entitled "Reviewer's Final Comments." This is where authors, who had the most intricate understanding of the literature, could succinctly describe the results of their review, start to synthesize the information, tease out the contradictions, make observations, and propose solutions. To facilitate interpretation of the results of the studies identified, the authors were asked to include the magnitude of any differences in the outcomes with an expression of their precision (ie, 95% confidence interval) whenever possible. Absolute as well as relative changes in proportions were also requested.

Table 2. Quality Factors for LOE 1, LOE P1, and LOE D1

The 7 factors that were included as the relevant quality items for RCTs (LOE 1):

- Was the assignment of patients to treatment randomized?
- Was the randomization list concealed?
- Were all patients who entered the trial accounted for at its conclusion?
- Were the patients analyzed in the groups to which they were randomized?
- Were patients and clinicians "blinded" to which treatment was being received?
- Aside from the experimental treatment, were the groups treated equally?
- Were the groups similar at the start of the trial?

Good studies=have most/all of the relevant quality items. Fair studies=have some of the relevant quality items. Poor studies=have few of the relevant quality items (but sufficient value to include for further review).

The 4 factors that were included as the relevant quality items for studies of LOE P1 (as well as P2 and P3):

- Were comparison groups clearly defined?
- Were outcomes measured in the same (preferably blinded) objective way in both groups?
- Were known confounders identified and appropriately controlled for?
- Was follow-up of patients sufficiently long and complete (eg, >80%)?

For these studies it would be reasonable to consider the presence of all 4 factors=Good, only 3 factors=Fair, and only 2 factors=Poor. A study with only 1 factor would be considered of insufficient quality to include in the next step of the review.

The 3 factors that were included as the relevant quality items for studies of LOE D1 (as well as D2 and D3):

- Was the diagnostic test evaluated in an appropriate spectrum of patients (eg, in those in whom it would be used in practice)? (Minimizing "spectrum bias")?
- Was there an independent, blind comparison with a reference ("gold") standard of diagnosis? (Minimizing "review bias")
- Was the reference standard applied regardless of the test result? (Minimizing "verification bias")

For these studies it would be reasonable to consider the presence of all 3 factors=Good, only 2 factors=Fair, and only 1 factor=either Poor or of insufficient quality to include in the next step of the review.

RCTs indicates randomized controlled trials.

The authors formulated draft Consensus on Science (CoS) statements and Treatment Recommendations (TRs) using standard formats.[13,16] Within the treatment recommendations, authors were asked to consider the magnitude of the effect, the outcome affected, the generalizability from the specific population studied, and the potential barriers to implementation (including cost, education, and logistics).[13] The recommended generic format for the CoS statement was:

Evidence from X# type of study in adults [*insert study design and highest-quality design*] *and X# additional studies* [*insert range of LOE*] *document consistent improvement in* [*insert relevant clinical outcome*] *when* [*insert treatment*] *is administered by* [*insert provider*] *to patients with* [*insert clinical condition*] *in the* [*insert prehospital, hospital, etc*] *setting.*[16]

The generic format for the treatment recommendation statement was:

Summary of evidence

Evidence Supporting Clinical Question

Good	Arrich 2009 CD# Hypothermia After Cardiac Arrest Study Group, 2002 CD* Tiainen, 2003 E*		Bernard, 1997 C, D	Hovdenes, 2007 CD Wolff, 2009 DE Nielsen, 2009 CD	
Fair	Holzer, 2005 CD#	Bernard, 2002 D Holzer, 2006 CD	Knafelj, 2007 CD Busch, 2006 C Belliard, 2007 CD Oddo, 2006 D Sunde, 2007 CD Storm, 2008 CDE Don, 2009 CD Bro-Jeppesen, 2009 D	Oksanen, 2007 C Sagalyn, 2009 #	
Poor	Hachimi-Idrissi, 2001 E Cheung, 2006 CD#	Arrich, 2007 CD	Castrejon, 2009 D	Williams, 1958 D	
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
* = overlapping patients
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
# = meta-analysis

Figure 2. Example of supportive evidence grid for therapeutic hypothermia worksheet.

Therefore, administration of [*therapy*] *for patients with* [*condition, setting by personnel*] *is recommended/should be considered.*

Identifying the Gaps

Worksheet authors were also asked to identify critical gaps in the literature, which were then incorporated into the final CoSTR document.

Iterative Review Process

Each worksheet was submitted electronically and underwent a rigorous iterative evaluation process. The layers of review before final acceptance of the worksheet included the task force chair and task force (in addition to a "domain leader" in the advanced life support task force), a worksheet expert, and the evidence evaluation expert. When the worksheet was finalized, it was posted on the Internet for public comment (www.americanheart.org/ILCOR; Figure 3).

In general, multiple worksheets were prepared for each topic, but the authors were encouraged to submit a combined final worksheet whenever possible. The CoS statements and TRs drafted by the worksheet authors were also iteratively reviewed by the relevant task force(s) and writing groups in face-to-face meetings or by Web conferences ("Webinars"). These versions of the CoS and TRs were used to create the draft of the CoSTR document, which was then reviewed by the international councils and the editorial board to create the final manuscript (members of the editorial board are writing group members of Part 1: Executive Summary[17,18]).

Controversies in the Evidence Evaluation Process

Four main issues arose from the evidence evaluation process. First, a recurrent theme was the allocation of an LOE based on study type rather than whether the study addressed the specific PICO question. Randomized controlled trials involving a therapeutic intervention in patients who were not in cardiac arrest were often initially allocated an incorrect LOE. If the worksheet PICO question specified the population as patients who were in cardiac arrest, then all randomized controlled studies in nonarrest patients were allocated as "Good LOE 5" rather than LOE 1. Second, there was confusion about the classification of studies that looked retrospectively at data (eg, registry studies). If the population was appropriate for the worksheet (PICO) question, and the appropriate intervention was compared with a control group from the same time period, these studies were classified as having concurrent controls (LOE 2). The methodological quality

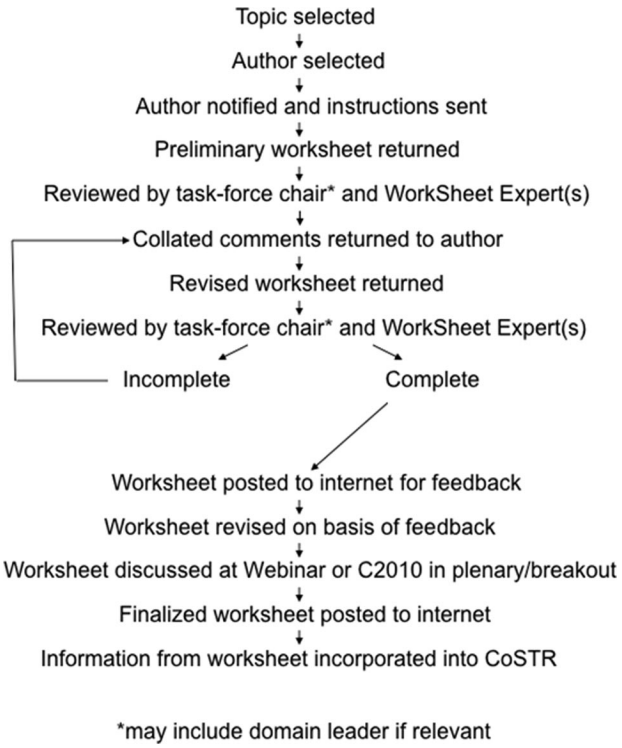

Figure 3. Worksheet flow for C2010 process.

allocation was based on the quality items for LOE 2. The third issue related to the choice of LOEs (intervention, diagnosis, or prognosis). The precise wording of the PICO question for the worksheet determined the correct LOE allocation. The comparison of techniques with the outcome to diagnose or predict was graded using diagnostic or prognostic LOEs, respectively (refer, again, to Table 1). If instead the question related to a diagnostic or prognostic tool compared with another tool or standard therapy, and its effect on an outcome (eg, return of spontaneous circulation) was evaluated, it was considered an intervention and was graded with intervention LOEs.

The final issue relates to the definition of outcomes for educational interventions. For the purposes of the worksheets, the worksheet authors customized outcomes (eg, E1=improved score on written test, E2=skill retention at 6 months). There is a clear need to use a well-defined hierarchy of educational outcomes.

Summary

The C2010 evidence evaluation process used the best evidence on critical appraisal to develop a unique process to incorporate all the peer-reviewed, published science underpinning resuscitation and emergency cardiovascular care. A detailed systematic, multilayered, iterative review of the individual topics (worksheets) has informed the final product: the 2010 CoSTR.

Disclosures

CoSTR Part 3: Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Peter T. Morley	Royal Melbourne Hospital: Director of Medical Education; University of Melbourne–Clinical Dean, Royal Melbourne Hospital; AHA–Evidence Evaluation Expert	None	None	None	None	None	None
Dianne L. Atkins	University of Iowa: University and Medical School—Professor. Compensated worsksheet editor for the Guidelines 2010 Process. Money is paid approximately 2/3 to my institution and 1/3 to directly me. My salary from my institution is not changed by this reimbursement	None	None	None	None	None	*Serving as defense expert witness in a case involving a cardiac arrest in a young child who had ventricular fibrillation. Money is paid directly to me. Law firm is Buckly and Theroux in Princeton, NJ
John E. Billi	University of Michigan: Medical School–Professor	None	None	None	None	None	None
Leo Bossaert	University of Antwerp; Professor	None	None	None	None	None	None
Clifton W. Callaway	University of Pittsburgh: Associate Professor, UPMC; Evidence evaluation expert for AHA	†Grants to University of Pittsburgh: NHLBI-Resuscitation Outcomes Consortium HRSA-Development and Dissemination of Program Tools for Uncontrolled Donation After Cardiac Death (UDCD)	†Loan of an Arctic Sun cooling device (without disposables) to human physiology laboratory for experiments on hypothermia by Medivance, Inc.	None	†Co-inventor on patent about ventricular fibrillation waveform analysis, licensed by University of Pittsburgh to Medtronic ERS, Inc.	None	None
Allan R. de Caen	Self employed: Pediatric Intensivist	None	None	None	None	None	*Expert witness for the Canadian Medical Protective Association
Charles D. Deakin	South Hampton University Hospital	None	None	None	None	None	None
Brian Eigel	American Heart Association Director of Science, ECC Programs	None	None	None	None	None	None
Mary Fran Hazinski	Vanderbilt University School of Nursing. Professor. †AHA consultant compensated to co-edit the international consensus on CPR and ECC Science with Treatment and to co-edit the AHA Guidelines on CPR and ECC	None	None	None	None	None	None

(*Continued*)

CoSTR Part 3: Writing Group Disclosures, *Continued*

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Robert W. Hickey	CHP	NIH	None	None	None	None	Expert witness 1–2 year
Ian Jacobs	University of Western Australia: Discipline of Emergency Medicine Teaching/Research academic—Professor; American Heart Association–Work Sheet Expert	†Chief investigator on numerous grants awarded by: a) National Health and Medical Research Council b) The Department of Health-Western Australia c) The National Heart Foundation of Australia These funds are awarded to the University of Western Australia and none are used to provide any direct or indirect salary or other financial support	†Funds are received into the Discipline of Emergency Medicine-University of Western Australia from the Ambulance Service-Western Australia and Laerdal (Australia) to maintain the Cardiac Arrest Registry for Western Australia. Our role is to independently maintain, anlayse and report outcomes of cardiac arrest in Western Australia. I oversee the operation of the registry and reporting of outcomes. These funds are not used in any way to provide any direct or indirect salary or other financial support	None	None	None	None
Monica E. Kleinman	Children's Hospital Anesthesia Foundation: Senior Associate in Critical Care Medicine	None	None	None	None	None	None
Rudolph W. Koster	Academic Medical Center: Staff cardiologist-Full time employee	None	†Jolife covers cost of CT scans, autopsy and a 50 Euro per patient contribution to the institution (times 120 patients) Zoll covers cost of CT scans, autopsy and a 50 Euro per patient contribution to the institution (times 120 patients); *Jolife: Lucas chest compression device on loan to institution for research purposes. Zoll: Autopulse chest compression device on loan to institution for research purposes. Philps: chest compression feedback device on loan to institution for research purposes	None	None	None	None
Mary E. Mancini	University of Texas at Arlington University: Professor	None	None	None	None	None	None
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Laurie J. Morrison	St. Michaels; clinician scientist	*Laerdal Foundation Centre Grant-infrastructure support without salary support	None	None	None	None	None
Vinay M. Nadkarni	University of Pennsylvania School of Medicine; attending physician	†Laerdal Foundation for Acute Care Medicine: Pediatric Cardiac Arrest Learning Laboratory PI *NIH: THAPCA (Therapeutic Hypothermia After Pediatric Cardiac Arrest) *NIH: NHTSA: Thoracic Compliance in Pediatric Cardiac Arrest and Car Crashes	None	None	None	None	Expert Witness: Cardiac Arrest Facts
Jerry P. Nolan	Royal United Hospital NHS Trust: Consultant in Anaesthesia and Critical Care	None	None	None	None	None	None
Robert E. O'Connor	University of Virginia Health System: Professor and Chair of Emergency Medicine	None	None	None	None	None	None
Jeffrey M. Perlman	Weill Cornell: Professor of Pediatrics	†NIH-Improving antimicrobial prescribing practices in the NICU	None	None	None	None	None
Michael R. Sayre	The Ohio State University: Associate Professor	None	None	None	None	None	None

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CoSTR Part 3: Writing Group Disclosures, *Continued*

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
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Michael Shuster	Self employed physician	None	None	None	None	None	None
Jasmeet Soar	North Bristol NHS Trust: Government Hospital in UK–Consultant in Anaesthetics & Intensive Care Medicine	None	None	None	None	None	None
Jonathan Wyllie	South Tees Foundation NHS Trust Health Service Provider NHS UK Consultant Neonatologist and Clinical Director of Neonatology	None	None	*Spoke for "Trouble Up North" sponsored by Chiesi Other invited lectures for no cost. *Will receive small honorarium for speaking at the Middlesbrough Neonatal meeting Honorarium as above from Chiesi	None	*European Resuscitation Council Board Member and ICC co-chair. Voluntary expenses only *Resuscitation Council (UK) Executive mamber and Chair of Newborn Life Support Working group. Voluntary expenses only *HEMS Clinical Governance Group. Voluntary expenses only *North east Ambulance Clinical Governance Group. Voluntary expenses only	*Occasional Case. Nothing recent but one pending report in the UK now
David Zideman	Imperial College NHS Trust: United Kingdom Healthcare provider–Consultant Anaesthetist; London Organising Committee of the Olympic Games: Lead Clinician for EMS	None	None	None	None	None	*Expert witness reviews for Her Majesty's Coroner for Surrey

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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Part 3: Evidence Evaluation Process: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

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