



Utstein-style guidelines for uniform reporting of laboratory CPR research.

A Statement for Healthcare Professionals from a Task Force of the American Heart Association, the American College of Emergency Physicians, the American College of Cardiology, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Institute of Critical Care Medicine, the Safar Center for Resuscitation Research, and the Society for Academic Emergency Medicine

Ahamed H. Idris, Lance B. Becker, Joseph P. Ornato, Jerris R. Hedges, Nicholas G. Bircher, Nisha C. Chandra, Richard O. Cummins, Wolfgang Dick, Uwe Ebmeyer, Henry R. Halperin, Mary Fran Hazinski, Richard E. Kerber, Karl B. Kern, Peter Safar, Petter A. Steen, M. Michael Swindle, Joshua E. Tsitlik, Irene von Planta, Martin von Planta, Robert L. Wears, Max H. Weil

1. Introduction

Both laboratory and clinical investigators contribute to the multidisciplinary knowledge base of resuscitation science. While diversity can be a strength, it can also be a hindrance because of the lack of a common language and poor communication among investigators.

Modern cardiopulmonary resuscitation (CPR) research depends on the use of animal models that are designed to simulate cardiac arrest in humans [1,2]. Such models are used to explore important new treatments and to refine protocols used in standard interventions, including doses of drugs, chest compression techniques, defibrillation energies, and cerebral resuscitation, before they are applied to humans

[3]. When favorable results are reported in animal models, the new or refined techniques are often implemented soon afterward in human victims of cardiac arrest. Unfortunately, the results obtained in one laboratory may not be reproducible in another laboratory or in human trials. For example, high-dose epinephrine therapy significantly improves survival in most animal models of cardiac arrest but does not improve survival in humans [4–7]. In addition, some animal studies have documented the efficacy of administering bicarbonate during cardiac arrest, while others have shown it to be ineffective or deleterious [8]. Some of these differences are to be expected because an animal simulation is not a perfect model of cardiac arrest in humans. However, it is likely that some of these conflicting results are due to differences in experimental methods and laboratory model design. Variations in study design, such as the quality of chest compressions and ventilation, definitions of variables, or time intervals between an event and the beginning of therapy, are probably responsible for many of the inconsistencies and contradictions reported.

The lack of standardization and the use of nonuniform terminology in reports of studies of cardiac arrest in humans have been described as a ‘Tower of Babel’ [9]. To address these problems, par-

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ticipants at a June 1990 international resuscitation conference concerned with out-of-hospital cardiac arrest research, held at the Utstein Abbey in Norway, met to discuss the lack of standardized nomenclature and language in research reports. A second meeting, the Utstein Consensus Conference, was held in December 1990 in Surrey, England, to continue the discussion, and recommendations, including uniform definitions and terms ('Utstein Style') to assist clinical investigators in reporting results of resuscitation studies in humans [10], were developed and later published simultaneously in two American journals, in the journal of the European Resuscitation Council, and in major French and German journals.

In a recent review of the literature, Idris et al [11] examined four fundamental variables in animal resuscitation research: ventilation, the nonintervention interval (the duration of untreated cardiac arrest), measurement and production of blood flow during chest compressions, and the definition of return of spontaneous circulation. The investigators found a wide range of experimental methods and methods of reporting information and a conspicuous lack of uniformity in definitions of the four variables examined and other fundamental variables.

It is clear that uniform guidelines for reporting data would be useful to investigators and would enhance communication within the field of CPR research. In 1990 the European Academy of Anaesthesiology offered preliminary guidelines for issues related to such investigations [12]. That work provided the foundation for three international conferences organized to create guidelines for laboratory CPR research. At the first conference, held during the International Resuscitation Research Conference in Pittsburgh, Pa, in May 1994, participants identified issues related to experimental methods and methods of reporting laboratory CPR research and generated questions related to six main topics: (1) measurement and production of blood flow, (2) ventilation and acid-base conditions, (3) design of clinically appropriate protocols, (4) definitions and reporting, (5) defibrillation and induction of cardiac arrest, and (6) anesthetics and species differences. At the second conference, Utstein III: Setting Guidelines for Laboratory CPR Research, held in Chicago, Ill, in October 1994, workshops corresponding to the six fundamental areas of laboratory CPR research were organized to develop uniform definitions and guidelines for reporting. The guidelines developed in this second conference were presented and discussed several days later at the Second CPR Congress of the European Resuscitation Council, held in Mainz, Germany.

Participants at the three conferences represented 25 countries and the following eight organizations:

the American College of Cardiology; the American College of Emergency Physicians; the American Heart Association; the European Resuscitation Council; the Heart and Stroke Foundation of Canada; the Institute of Critical Care Medicine; the Safar Center for Resuscitation Research, University of Pittsburgh; and the Society for Academic Emergency Medicine. This statement is the final consensus of these investigators regarding laboratory CPR research. It includes a glossary of terms and a template of features to describe when reporting laboratory studies of CPR.

2. Glossary of key terms

2.1. Baseline conditions

Baseline conditions are the physiological conditions attained before induction of cardiac arrest, usually in an anesthetized, intubated, ventilated, and instrumented animal. They do not represent the normal physiological state of an animal subject. Researchers should describe how the baseline conditions were achieved and the duration of such conditions before the beginning of the experiment.

2.2. Induction of cardiac arrest

The method and time of *induction* of a hemodynamic condition of no blood flow is essential information and should be depicted graphically on a time line (Fig. 1). Although the time of induction of cardiac arrest is easily determined in models of ventricular fibrillation, this exact moment is less precise in studies using asphyxia or exsanguination. Asphyxia and exsanguination produce a gradual change in hemodynamic parameters over several minutes rather than an instantaneous change. Reports of studies using asphyxia or exsanguination should include a description of the time course of the induction period from baseline to a preselected critical value of blood pressure (e.g. to a blood pressure of < 25 mm Hg) or to a target change in cardiac rate or rhythm or ECG pattern.

2.3. Cardiac arrest

Cardiac arrest can be defined more precisely in laboratory studies than in clinical studies. In the clinical setting, cardiac arrest is defined as the 'cessation of cardiac mechanical activity.... It is a clinical diagnosis, confirmed by unresponsiveness, the absence of a de-

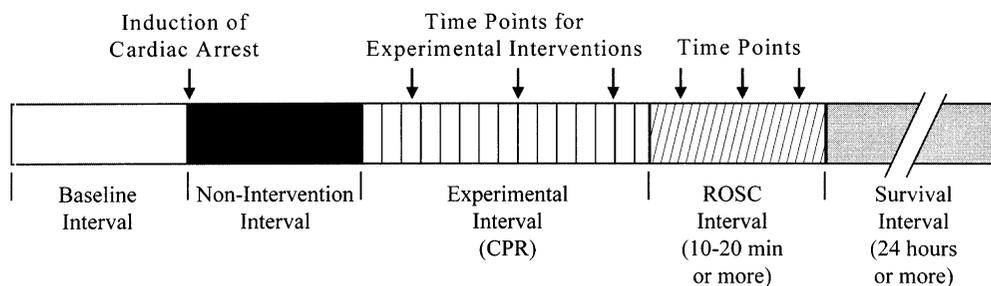


Fig. 1. Experimental time line. Arrows indicate time points for experimental interventions. CPR indicates cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

tectable pulse, and apnea (or agonal respirations)' [10]. Most laboratory studies produce cardiac arrest by electrically inducing ventricular fibrillation, which can be confirmed by electrocardiography. Blood flow stops quickly, and this can be identified by the sudden loss of arterial pulsations on intravascular pressure monitors and by a systolic aortic blood pressure of < 25 mm Hg (Fig. 2). With cardiac arrest secondary to asphyxia or exsanguination, the gradual decline in blood pressure is not usually accompanied by a sudden change in cardiac rhythm or ECG pattern. Regardless of which technique is used to induce cardiac arrest, it should be defined precisely enough to allow reproduction by other investigators.

2.4. Standard CPR

Standard CPR is a term commonly used in clinical studies to mean external chest compression and ventilation, but the term should be defined more precisely in laboratory studies. Researchers should include descriptions of both ventilation and chest compression. *Standard chest compression* refers to external closed chest compressions applied to an area of the chest approximately the size of the heel of an adult's hand (15 to 25 cm²). The frequency of compressions is usually 60 to 100 per min, with a 50% duty cycle and a downward compression force sufficient to produce 3.8 to 5 cm (1.5 to 2 in) of chest displacement in a large animal. Different displacements may be appropriate depending on the species and size of the animal. The techniques used to quantify and record the force or displacement should be specified, along with the method used to validate these techniques. The inaccuracies inherent in applying force without formal measurements, if unavoidable, should be discussed. Because *standard ventilation* does not exist for laboratory models of CPR, it is important for baseline and experimental ventilation parameters to be described in detail.

2.5. Ventilation

Ventilation refers to any movement of gas in and out of

the lungs. Ventilation does not necessarily result in alveolar-blood gas exchange, especially if the tidal volume is less than the dead-space volume. Ventilation includes spontaneous gasping (or *agonal respiration*), mechanical ventilation, and gas movement resulting from chest compressions. When positive pressure ventilation is given, it should be measured or controlled (e.g. with a volume-cycled ventilator). Pressure-cycled ventilators may deliver inconsistent tidal volumes during CPR because of changes in pulmonary compliance. *Alveolar ventilation* is the amount of inspired gas available for gas exchange (minute ventilation minus dead-space ventilation). At least two of the following three ventilation parameters should be measured and reported: minute ventilation, tidal volume, and respiratory rate.

2.6. Compression- and release-phase measurements

During spontaneous circulation, blood pressure is usually expressed as systolic, diastolic, and mean values. There are no conventional systolic and diastolic phases during external chest compressions (since, by definition, spontaneous cardiac contractions have ceased). Therefore, investigators should use the term *compression phase* for measurements obtained when applied force decreases the thoracic volume (analogous to the systolic phase in a beating heart) and the term *release phase* (analogous to the diastolic phase) for measurements made during the CPR cycle when little or no pressure is being applied to the thorax, allowing it to recoil [13].

2.7. Active decompression

During the release phase of standard chest compression, the chest is allowed to passively recoil without force being applied. The term *active decompression* is used when an outward force is applied to the external chest during the release phase. Since this requires the use of a decompression adjunct, describe the device used.

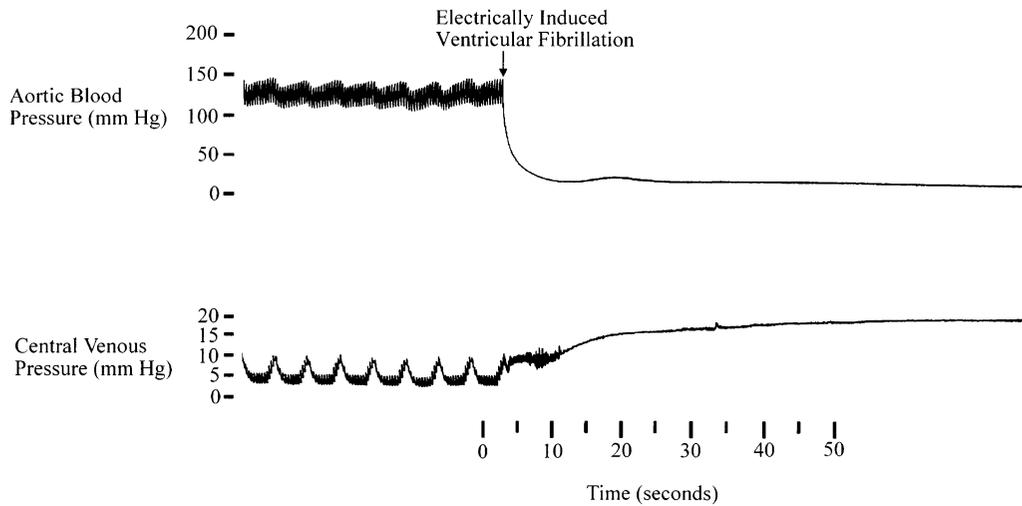


Fig. 2. Arterial and central venous pressure tracings showing electrical induction of ventricular fibrillation. After the onset of ventricular fibrillation, there is a loss of pulsatile waveforms and a rapid decline in the arterial and central venous pressures. The pressures do not fall to zero because vascular tone maintains some intravascular pressure.

2.8. Coronary or myocardial perfusion pressure

Coronary perfusion pressure has been used as a surrogate for the direct measurement of coronary blood flow during chest compression because it has been linked to return of spontaneous circulation in studies of cardiac arrest in animals and humans. It is therefore an important variable to measure and to control in laboratory studies. Several formulas for calculating coronary perfusion pressure are currently in use [11]. Most assess the simultaneous difference between the aortic and right atrial (or central venous) pressures during diastole or during the release phase of compression, when most coronary blood flow has been shown to occur [14]. Although differences between coronary perfusion pressures calculated with different formulas are usually minor, standardization of the calculation would make comparing results from different laboratories easier.

The method of calculating coronary perfusion pressure should be reported in the 'Materials and methods' section of your report. Since the precise point for the mid-diastolic (release-phase) aortic pressure may be difficult to ascertain, it is suggested that the point just before compression be used as the reference release-phase pressure because this point is likely to be more consistent among investigators than the midpoint. The reference points used to calculate coronary perfusion pressure should be illustrated with aortic and central venous or right atrial pressure tracings (Fig. 3).

2.9. Blood flow

Blood flow is the volume of blood flowing in a given direction per unit of time. *Region-specific blood*

flow is the blood flow per unit mass of tissue. Because these measurements are difficult to obtain, precise descriptions of the methods used to quantify blood flow, as well as how these methods were validated, should be included.

2.10. Defibrillation attempt or rescue shock

Electrical shock used specifically to defibrillate an experimentally induced episode of ventricular fibrillation is called *defibrillation attempt* or *rescue shock*. These shocks are performed to keep the animal alive so that the study can continue. The number, timing, and strength of the shocks should be reported.

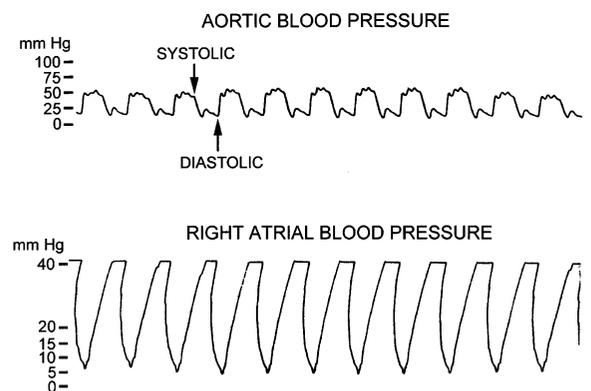


Fig. 3. Arterial and central venous pressure waveforms during external closed chest compression. The arrows indicate the points at which arterial systolic (compression phase) and diastolic (release phase) pressures were selected for calculating coronary perfusion pressure. Reproduced from Idris AH, Wenzel V, Becker LB, Banner MJ, Orban DJ. Does hypercarbia or hypoxia independently affect resuscitation from cardiac arrest? *Chest*. 1995;108:522–528.

2.11. Return of spontaneous circulation

The principal means of assessing circulation in laboratory CPR research is by measurement of arterial pressure. During cardiac arrest, a nonpulsatile arterial pressure of approximately 10 to 20 mm Hg may be maintained, reflecting vascular tone, not cardiac contractile activity or blood flow (Fig. 2). In a review of 42 laboratory studies, 29 widely discrepant definitions of *return of spontaneous circulation* were found [11]. The return of spontaneous cardiac contractile activity is indicated by the return of pulsations in the arterial pressure waveform.

It is important that investigators define return of spontaneous circulation prospectively in terms of the minimum aortic blood pressure to be maintained for a specified minimum time. It must also be stated clearly whether vasoactive drugs were administered during this time and whether such drugs were allowed to wash out. We recommend that return of spontaneous circulation be defined as maintenance of a systolic aortic blood pressure of at least 60 mm Hg for at least 10 consecutive minutes. This definition is consistent with those used in cardiac arrest studies in humans [10]. We also recommend reporting the mean, median, and confidence intervals for blood pressure and the duration of the return of spontaneous circulation.

2.12. Intensive care

Some protocols include postarrest interventions and *intensive care* such as additional defibrillation or cardioversions, vasopressors, and antiarrhythmic drugs. These should be delineated clearly in the 'Materials and methods' section and further described in the 'Results' section (e.g. report the dose of epinephrine given, the number of times it was given, and the dosing interval).

2.13. Survival

Survival should be used to refer to existence beyond return of spontaneous circulation and the immediate postarrest period. Some studies have reported 96-hour survival rates, but studies that measure survival 24 h after resuscitation can be reasonably called survival studies. Such studies allow determination of neurological status, detection of multisystem failure, and assessment of cardiovascular physiology following withdrawal of pharmacocirculatory support. Studies that use the term survival should extend to at least 24 h and should explain the rationale for using the term.

2.14. Intervals and time points

An *interval* is the period of time between two events. In reports, the two anchor events, including the specific

beginning and ending times, should be explicitly defined. *Time point* refers to one point (i.e. event) in time.

2.15. Experimental events and intervals

The beginning and end of an experimental intervention should be described clearly for all significant components of an experiment. This allows precise definition of the experimental intervals.

2.16. Nonintervention interval

The *nonintervention interval*, the interval of untreated cardiac arrest without chest compression, is one of the most important factors related to outcome. Therefore, investigators must clearly define and describe the treatment time points and intervals used in each protocol. Jargon, such as 'downtime,' is unacceptably imprecise, and its use should be avoided. The lack of agreement regarding the definition of downtime can be attributed to the complex protocols used in laboratory research. For example, in many protocols, the nonintervention interval begins with cardiac arrest and ends with the start of closed chest compression. In some protocols, however, treatment such as drug therapy is given before the initiation of circulatory support. In these cases, there is no precise nonintervention interval. The reasons for using a particular nonintervention interval should also be stated in reports.

2.17. Experimental time line

A graphic *experimental time line* should be included in each report to indicate the critical times, events, and intervals (e.g. induction of cardiac arrest, the nonintervention interval, treatment intervals, defibrillation attempts, the experimental interval, and duration of an outcome). Fig. 1 is an example of an experimental time line.

3. Reporting template: features to describe when reporting laboratory studies of CPR

A template was developed to assist investigators in reporting their methods and results. Fig. 4 is an illustration of the reporting template; specific items to be reported in each section are listed in Tables 1–9. **Essential data** (which appear in **boldface type** in the tables) are necessary for reproduction, analysis, and comparison of studies and should be included in all reports; *desirable data* (which appear in *italic type*) would be useful and are recommended for inclusion in your report.

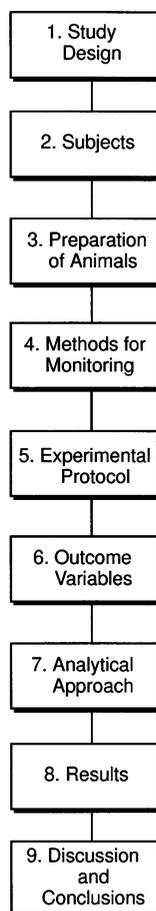


Fig. 4. Reporting template listing features to describe when reporting laboratory studies of CPR. Essential and desirable data to include in each section are listed in Tables 1 through 9.

3.1. Template section 1: study design

3.1.1. Control groups

The consensus conference participants recognized that the design of control groups deserved special consideration and that a quality ‘hierarchy’ exists. A prospective study with a concurrent control group is the optimal method for testing hypotheses. Concur-

Table 1

Template section 1: Study design. Features to describe when reporting laboratory studies of CPR

Control groups (hierarchy)
Concurrent control groups
Sample control groups (verify consistency of model and note limitations)
Historical control groups (note limitations)
Blinding
Crossover
Dose escalation
Randomization method (intact animal, ex vivo preparation)

Essential data are indicated in **boldface type**; desirable data are indicated in *italic type*.

Table 2

Template section 2: Subjects. Features to describe when reporting laboratory studies of CPR

Species
Gender
Age range
Weight range
<i>Breeding</i>
<i>Supplier</i>
<i>Living conditions</i>
<i>Fasting vs nonfasting</i>
<i>Caged vs noncaged</i>

Essential data are indicated in **boldface type**; desirable data are indicated in *italic type*.

rent control groups make it possible to blind investigators to some interventions, to control bias in animal selection, and to control experimental variation. Use of sample control groups (independent subsamples in which some concurrent control experiments are performed but with a control group that is smaller than the experimental group) can be acceptable, but the consistency of the model should be verified and the limitations should be noted. The rationale for use of strictly historical control groups, along with the limitations of not having concurrent control experiments, must be stated clearly.

3.1.2. Blinding

Blinding should be considered when an experiment is designed. True blinding is often impossible since investigators are usually aware of the data collected. One possible solution is to have a separate (blind) investigator analyze the data independently. Describe who was blinded to what (i.e. treatment assignment, treatment, or outcome).

3.2. Template section 2: subjects [15–26]

Reporting of husbandry conditions is important, especially for the rodent species. Rodents have substantial

Table 3

Template Section 3: Preparation of animals. Features to describe when reporting laboratory studies of CPR

Inclusion, exclusion, and dropout criteria (prospective definition)
Preanesthesia
Assessment of baseline status
<i>Description of animal's handling before experiment</i>
<i>Validation that inclusion and exclusion criteria were met</i>
Sedation, analgesia, and anesthesia
Detailed description of dose, sequence, route, and method for judging level of anesthesia, and titration to effect
Stabilization period

Essential data are indicated in **boldface type**; desirable data are indicated in *italic type*.

Table 4

Template Section 4: Methods for monitoring. Features to describe when reporting laboratory studies of CPR

Equipment used
Name of equipment
Model number
Manufacturer (city, state, country)
Variables monitored (observed) and controlled
Temperature
Heart rate
Systemic and mean blood pressures
Coronary or myocardial perfusion pressure
End-tidal CO ₂
Cardiac output
Blood flow (myocardial, cerebral, other organ)
Vascular resistance
Central venous parameters
<i>Measurements</i>
<i>Who performed them?</i>
Were any blinded?

Essential data are indicated in **boldface type**; desirable data are indicated in *italic type*.

physiological alterations associated with disturbances in their circadian rhythms and changes in environmental conditions. Furthermore, temperature, humidity, and air-flow parameters have a direct effect on the pulmonary physiology of these species. The terms *viral-antibody-free* and *pathogen-free* have specific connotations in rodents. Various viruses, as well as bacterial pathogens such as *Mycoplasma* spp., have adverse effects on physiological measurements in rodents, even in the absence of clinical signs.

Regardless of the source of swine and dogs or of the species used, the 'Materials and methods' section of your report should state that the animals are clinically normal and free of diseases that could affect results. Examples of such diseases are heartworm infestation or respiratory infection in dogs and clinical pneumonia or consolidation and fibrosis of the lungs in swine. Environmental standards are less important in swine and dogs, but basic husbandry standards should still be followed to ensure that the animals receive proper care. Reporting that the facility is accredited by the American Association for the Accreditation of Laboratory Animal Care or a similar national agency would provide such assurance.

Specifying the source of animals is important. In rodents, the strain or stock designation and the name of the supplier are desirable because of the variations associated with genetic background in these species. For large animals, the use of random suppliers, such as municipal shelters for dogs or farm auctions for swine, suggests that the animals are from an unknown background and have an unknown health status. The term *conditioned* for these species indicates that the animals are free of clinical disease and have been vaccinated and treated for

parasites. In swine, the term *specific-pathogen-free* indicates that swine are from a herd accredited by a national agency. In dogs, the term *purpose-bred* indicates that the animals were bred specifically for research in a regulated facility.

Anatomic and physiological characteristics should be considered when selecting an animal species or breed for an experimental procedure. Species differ in response to anesthetics and drugs, and different species may require different doses to produce the same physiological response. Interpretation of results from pharmacological interventions in CPR research must consider these differences. There are also differences in metabolism, physiological function, response to ischemia, hypoxia, and hypercarbia, and difficulty

Table 5

Template Section 5: Experimental Protocol. Features to Describe When Reporting Laboratory Studies of CPR

Experimental time sequence (link to hypothesis)
Washout interval for drugs
Time of onset of experiment (event)
Time of onset of cardiac arrest
Asphyxia time interval
Nonintervention time interval
No-flow time interval
CPR (low-flow) time interval
Exsanguination time interval
Ventilatory support
Instrumentation
Volume
Rate
<i>Peak and/or mean inspiratory pressure</i>
Mode of ventilation
Time-cycled
Volume-cycled
Pressure-cycled
Peak end-expiratory pressure, intermittent mandatory ventilation, etc.
Duty cycle (inspiration, expiration, ventilatory pauses)
Changes made in ventilation during experiment
Methods to assess quality of ventilation
Arterial blood gas levels
End-tidal CO ₂
Arterial or tissue oxygenation
Circulatory support
Instrumentation
Rate of chest compressions
Applied force, generated pressure, chest wall excursion, etc.
Duty cycle (duration of compression phase and release phase or decompression phase)
Changes made in ventilation during experiment
Methods used to assess quality of circulation
Blood pressure
Blood flow
Care provided to animals following return of spontaneous circulation
Euthanasia technique
Necropsy studies performed and methods used

Essential data are indicated in **boldface type**; desirable data are indicated in *italic type*.

Table 6

Template Section 6: Outcome Variables. Features to Describe When Reporting Laboratory Studies of CPR*

Methodological issues to address

Which variables were controlled and which were only observed?

What was measured?

How was it measured?

How often was it measured?

How was it validated?

What are the relevant limitations of the measurement technique?

Did the measurement itself alter the physiology of the animal?

Cardiovascular and respiratory function variables

Cardiac rhythm and ECG pattern

Detectable pulse

Spontaneous respiration

Blood pressure (systolic, diastolic, mean)

Blood flow (heart, brain, vital organ)

Ventricular function

Intracardiac and intravascular pressures

Coronary or myocardial perfusion pressure

End-tidal CO₂

Arterial and central venous oxygen saturation

Tissue oxygen saturation

Arterial and central venous blood gas levels and AV differences

Tissue electrolyte and high-energy phosphate levels

Return of spontaneous circulation

Cerebral function variables

Glasgow-Pittsburgh coma score

Overall performance score

Neurological deficit score

Histopathologic damage score (total, regional)

Electroencephalogram

Survival over time (short and long term)

ECG indicates electrocardiographic; AV, arterial-venous

Essential data are indicated in **boldface type**; desirable data are indicated in *italic type*. (Note that desirable data could be essential data depending on the objectives of the study).

in achieving return of spontaneous circulation among mammalian species such as rats, dogs, and swine. These are due to anatomic differences in the cardiovascular system, including myocardial blood supply, preexisting

Table 7

Template Section 7: Analytical approach. Features to describe when reporting laboratory studies of CPR

Describe statistical methods and why they were used

State null hypothesis for each statistical test and report exact *P* values

Report which study units are included in denominators

Explain when the sample size for a table, graph, or text differs from that for the study as a whole

Use tables and figures to explain the argument of the paper

Do not duplicate data in figures and tables

Rely less on hypothesis testing and more on effect magnitude (define the magnitude of the effect seen instead of simply stating whether the data support the hypothesis); include confidence intervals

Discuss sample size limitations and power calculations

State willingness to supply a detailed protocol on request

Essential data are indicated in **boldface type**; desirable data are indicated in *italic type*.

Table 8

Template Section 8: Results. Features to describe when reporting laboratory studies of CPR

Present results in a logical sequence in the text, tables, and figures
Emphasize or summarize only important observations; do not repeat in the text all data in the tables and figures

State number of animals screened, excluded, dropped out, analyzed, and reported

Describe statistical methods used

Describe analytical techniques used

Comment on observer variability

Provide original data for studies with a small sample size to allow meta-analysis

Report scatter plots and confidence intervals

Essential data are indicated in **boldface type**; desirable data are indicated in *italic type*.

collateral circulation, sensitivity to arrhythmias, and differences in the compliance and shape of the chest, which can influence the effectiveness of external chest compression. Metabolic differences in rodents and in younger animals may make them more resistant to the effects of hypoxia and hypercarbia.

Regardless of the species used, a clear description of the condition of the animals before the experiment should be provided. Outcome can be affected by age, gender, weight, health status, physiology, temperature, food, and light cycle. As a general rule, animals used in CPR studies should be free of disease, and the various anatomic and physiological differences should be considered in selecting the model. Recommendations should not be limited to certain species. Ethical considerations in animal experimentation include approval of the protocol by the animal use committee of the research facility, use of adequate anesthesia during the experiment, and study designs that minimize the number of animals used.

3.2.1. Rats

There are many advantages to the use of certain species in specific situations. For instance, small animals such as the rat can be used in screening and

Table 9

Template Section 9: Discussion and conclusions. Features to describe when reporting laboratory studies of CPR

Discuss principal findings, emphasizing new and important aspects

Discuss limitations and implications of the findings, including possible clinical implications and implications for future research

Comment on and compare the statistical and biological significance of results

Cite pertinent literature, discussing similarities and differences in findings and the reasons for these

State new hypotheses, clearly labeling them as such

Discuss economic, social, and political considerations

Essential data are indicated in **boldface type**; desirable data are indicated in *italic type*.

confirmatory tests requiring large numbers of animals. Data from these studies can then be used to design more clinically relevant research using larger animals such as swine or dogs. Rats have been particularly useful in neurological models and in studies incorporating behavioral techniques to assess neurological outcome. Because rats and other small animals defibrillate themselves spontaneously, they have not been used in studies that require electrically induced ventricular fibrillation. However, reliable cardiac arrest models using rats have been developed recently [27]. There are differences between inbred and outbred stocks of rats, so the type and source of rats used in a study should be defined.

3.2.2. Dogs

Dogs have been used for more than 100 years as general mammalian models, so extensive data exist for this species. Cardiovascular function in dogs is similar to that in humans, except that the existence of extensive collateral circulation in the heart and differences in myocardial blood flow may require additional interpretation of data. There is a substantial difference in size and shape of the chest, heart, and brain between breeds of dogs that may affect the results and outcome. Preexisting conditions to be avoided include heartworm infestation and chronic myocarditis secondary to parvovirus infection.

3.2.3. Swine

There is less background information available on the use of swine in research than there is on the dog, but the information that is available is current and uses recent technology [25,28,29]. Swine have the advantage of being uniform in size and shape between breeds at similar ages and weights (although there are differences in size between miniature pigs and domestic farm breeds). There are many similarities in metabolic and cardiovascular function between swine and humans [28,29]. Swine also have similar coronary anatomy (with the exception of the left azygous vein, which enters the coronary sinus rather than the precava). Most experienced investigators believe it is best to use swine in the weight range of 20 to 25 kg or larger for adult studies and 4 to 5 kg for pediatric studies. Preexisting conditions to be avoided include susceptibility to malignant hyperthermia.

3.3. Template section 3: preparation of animals

3.3.1. Perioperative conditions

Conditions present prior to the beginning of the experiment (e.g. uncorrected acidemia, dehydration, hyper- and hypothermia, and minor differences in anesthesia and analgesia) may have an important im-

pact on many outcome variables, possibly even return of spontaneous circulation and long-term outcome. Therefore, the environment of the animal prior to the experiment should be described. Was the animal acclimatized to the laboratory? Were handling, environment, and other preanesthesia conditions consistent for each subject? The duration of time at the institution and in the laboratory before anesthesia should be reported. Nutrition, fasting, and fluid administration before and during the experiment should be described.

3.3.2. Anesthesia

A wide variety of anesthetic and analgesic drugs are used in laboratory models of CPR [30,31]. These agents may produce a variety of hemodynamic effects [30,31]. In addition, different species may have different neurological and cardiovascular responses to ischemia and anesthesia. The physiological (including cardiovascular and neurological) effects of anesthetic agents should be considered during the selection process. The rationale for use of specific agents should be summarized in the report. The dose/weight ratio of the anesthetic, the inspiratory and expiratory gas concentrations, and whether a titration-to-effect approach was used should be described. Consultation with a veterinary anesthesiologist can be helpful in choosing appropriate anesthetics and doses.

Animals must be properly anesthetized unless they are unconscious for other reasons, such as cerebral ischemia, postischemic coma, or deep hypothermia. Loss of consciousness secondary to cardiac arrest and postischemic coma should be considered to be anesthetic in nature. Anesthetic agents should be discontinued immediately prior to induction of cardiac arrest to reduce or eliminate the cardiovascular and cerebral effects that they may have on outcome.

Adequate anesthesia is given not only for humane reasons but also because the stress of being paralyzed and awake, even without pain, greatly increases the cerebral metabolic rate secondary to catecholamine release [32], and could affect the outcome of CPR. Depth of anesthesia should be monitored during the study with standard veterinary methods, including examination for absence of muscular reflexes (such as leg withdrawal following a toe pinch), loss of mandibular jaw tone or ocular reflexes, and change in pupil size. Heart rate and blood pressure, as well as other cardiovascular parameters, should also be monitored. An increase in heart rate or blood pressure above baseline values after surgical manipulation should be considered a possible indication of pain and a need for additional anesthetic agent. If neuromuscular blockers are used, the animals must be insensitive to pain and unconscious.

3.4. Template section 4: methods for monitoring

All variables known to affect end points and outcome should be monitored and controlled. Some baseline measurements important in CPR research are pulse rate, cardiac output, coronary perfusion pressure, blood pressure (mean and cyclical arterial, central venous, and/or right atrial pressure), vascular resistance, end-tidal CO₂, arterial and central venous blood gas levels, and electrolyte levels. Some indicator of core temperature, such as esophageal, pulmonary artery, vena cava, rectal, or bladder temperature, should be monitored continuously. Tympanic membrane temperature may also be useful.

3.5. Template section 5: experimental protocol

The experimental period begins with the induction of cardiac arrest or the administration of the experimental intervention and ends with the assessment of final outcome variables, such as return of spontaneous circulation, 24-hour survival rate, or 48-hour or longer neurological outcome. The time interval between the beginning and end of an experiment is the duration of the experimental protocol. In designing protocols for cardiac arrest resuscitation studies, investigators should consider the following elements: the nonintervention interval, duration of CPR, production of blood flow, ventilation, attempted defibrillation, use of drug and other interventions, and postresuscitation care. This sequence of events can become complicated, but the general procedures that are used to keep animals alive should be described.

One of the greatest challenges facing the investigator is to create a clinically relevant protocol. The nonintervention interval should be viewed as an important experimental variable that affects outcome. The duration of untreated ventricular fibrillation has a striking effect on the success of defibrillation and return of spontaneous circulation [33–36]. In cardiac arrest in humans, for each minute that ventricular fibrillation persists, the survival rate declines by an estimated 5 to 10% [34]. Most of the animal studies reviewed did not present a clear rationale for the use of a specific nonintervention interval [11]. In these studies, the nonintervention interval varied from 0 to 15 min; 50% used an interval of 3 min or less. A potential problem with short nonintervention intervals is that they may not show the effect of a treatment that might be significant with a longer interval. Other important aspects of the experimental protocol are presented below.

3.5.1. Ventilation

Ventilation is an important variable during cardiac arrest because it can affect tissue oxygenation, CO₂-

mediated acid-base conditions, and cardiac output [37–45]. Unfortunately, minute ventilation has been measured and controlled in few published laboratory resuscitation studies. The most frequently used device for providing ventilation in these studies was a pressure-cycled ventilator. With such a device, tidal volume is markedly altered by changes in thoracic and pulmonary compliance during constant pressure ventilation. Since lung compliance decreases during CPR, minute ventilation may decrease during an experiment if a pressure-cycled ventilator is used [46,47]. A time-cycled, volume-controlled ventilator can provide constant minute ventilation under these conditions.

The inspired O₂ concentration, method of airway control, and ventilation mode (spontaneous or controlled) are essential information. When spontaneous ventilation is allowed, it should be measured, and the method of measurement should be reported. Ventilation changes made during the prearrest, CPR, and postarrest phases, as well as how these adjustments are made (e.g. by changing the rate, tidal volume, or gas mixture) should be reported as essential information. During CPR, two of three variables (tidal volume, minute ventilation, or frequency) are sufficient for reporting. Whether ventilation is synchronized or unsynchronized with chest compressions is also essential information. Measurement of dead-space and airway pressures provides valuable additional information.

During normal circulation, arterial blood gas analysis is probably the most meaningful tool for monitoring pulmonary ventilation. End-tidal CO₂ can be monitored continuously and used during normal spontaneous circulation to reduce the number of arterial blood gas samples needed. Pulse oximetry can also be used during normal hemodynamics but not during CPR because pulsatile blood flow through a tissue bed is necessary for accurate estimation of hemoglobin oxygen saturation.

If monitoring oxygenation and acid-base status during low blood flow states is desirable, pulmonary artery, right atrial, central venous, and arterial blood gas levels should be measured. Venous blood gases more closely reflect tissue oxygenation and acid-base conditions than arterial blood gases. Arteriovenous differences are also very useful for understanding the physiological alterations that occur during low flow states and may permit calculation of cardiac output using the Fick technique. Great cardiac vein, coronary artery, and tissue or organ pH, PCO₂, and PO₂ can also provide important information.

3.5.2. Induction of cardiac arrest and defibrillation

The methods used to induce ventricular fibrillation and cardiac arrest should be described. Factors to be described include use of KCl, electrical voltage and

current (amplitude and duration), whether an intravascular wire or other electrical method was used to deliver a fibrillatory shock, and the number of attempts required to induce cardiac arrest. If asphyxia, hypoxia, or exsanguination was involved, the technique, as well as whether asphyxia was initiated during inspiration or expiration, should be described in detail.

For defibrillation, the timing and amount of selected or delivered energy, voltage, current, impedance, the amount of energy (joules) applied per kilogram of body weight, and the timing and number of rescue shocks used for each subject should be described. The cardiac rhythm following rescue shocks should also be reported. The defibrillator used, specifically the manufacturer and model, should be reported, as should details of defibrillator maintenance, calibration, and waveform. This is especially important in protocols that use low-energy defibrillation. A number of studies have shown that defibrillator electrodes influence the success of rescue shocks [48]. The size, type, and position of the electrodes, the pressure applied to the electrodes during defibrillation attempts, and the electrical couplant used on electrodes should be stated. If electrode patches are applied with gel, the manufacturer and lot number of the gel should be specified. Also, any antiarrhythmic drugs administered, the dose, and the site of administration should be noted.

3.5.3. Production of blood flow

The technique used to produce blood flow during CPR should be described in sufficient detail to be reproduced. Examples of important waveforms should be part of the reported results. There should be some comment on the variable or end point that flow production was intended to achieve. The method of calibration should also be mentioned (e.g. the amount of force used or the way the force was titrated to produce an effect). The depth and rate of compressions and the duty cycle should be reported as well.

3.5.4. Measurement of blood flow

Measuring vascular, myocardial, and/or cerebral blood flow or a validated indicator of blood flow is essential to many studies. Blood flow and coronary perfusion pressure produced during chest compressions are known to be important predictors of return of spontaneous circulation [49–52]. Under most experimental conditions, blood flow produced by chest compression is difficult to control because an identical force of compression can result in different blood flows in different animals. In addition, vascular tone may alter the distribution of flow between the heart, brain, and periphery. Despite this difficulty, consistency of chest compression or blood flow is desirable to ensure that animals do not live or die simply be-

cause they receive 'good' or 'bad' chest compression or blood flow.

Coronary perfusion pressure should be consistent in the control and experimental groups unless it is a variable under investigation. For example, when two methods of defibrillation are tested, the coronary perfusion pressure should be similar for the two groups during CPR. Control of coronary perfusion pressure is especially important because most laboratory studies use relatively few animals and a difference in coronary perfusion pressure can have a profound effect on outcome.

Measuring devices must be capable of detecting the low pressures and flow rates produced during CPR. However, measuring blood pressure or blood flow during CPR is particularly problematic because closed chest compressions produce vigorous motion of the chest and structures within the chest and neck. This movement can impose a great deal of 'background noise' on measurements made with flow probes, and some devices may lose acoustic or electromagnetic contact, making any measurement impossible. Despite these problems, a number of technologies have been used successfully to measure blood pressure or flow during CPR. Aortic pressure may be measured with fluid-filled catheters or with microtransducer-tipped catheters (e.g. Millar catheters). The latter are preferred because they are not subject to the resonance effects of fluid-filled catheters, which can cause substantial ringing artifacts in the pressure tracings during closed chest compression. Blood flow may be quantified with microspheres (colored or radioactive), thermodilution, or saline dilution techniques that use the Fick principle [53–56]. Electromagnetic and ultrasonic flow probes, guided imaging, bioimpedance, end-tidal CO₂, and certain metabolic markers such as myocardial acetate and potassium arteriovenous gradients have also been used to measure or estimate blood flow [13]. Because all methods have unique advantages and disadvantages, any method of measuring blood flow should be tested and validated. It is difficult to recommend one particular method since the research protocol and the objectives of the study will influence the method used.

3.5.5. Baseline flow

It is extremely important to measure or calculate prearrest baseline flows since these values are extensively reported for various animal models, and baseline values should be within published ranges. Measurement of baseline blood flow will provide added validation of the flow-measuring technique and of the integrity of the animal model.

3.5.6. Bilateral organ flow

For techniques that use such instruments as microspheres, it is best to have independent measurements of bilateral organ flow, including measurements of flow at the two microsphere withdrawal sites [56]. The left withdrawal catheter would be used to determine flow to organs on the left side, and the right catheter would be used to determine flow to organs on the right side. Because flow to paired organs should be identical, major discrepancies in flow between sides would indicate significant inaccuracies in the flow-measuring technique.

3.5.7. Changes in flow

It is preferable to report the absolute magnitude of the flow rather than simply report changes in flow. If only changes in flow are reported, misleading conclusions can easily be made. For instance, if CPR intervention A produces a flow of 1 mL/min per 100 g of tissue and intervention B produces a flow of 2 mL/min per 100 g, the increase in flow would be 100%. The significance of the change is misleading when compared with a situation in which intervention A produces a flow of 10 mL/min per 100 g and intervention B produces a flow of 15 mL/min per 100 g, an increase of only 50%. The absolute increase of 5 mL/min per 100 g in the latter example may actually be much more significant than the increase of 1 mL/min per 100 g. If the absolute level of flow is reported, a number of different analyses can be presented, and clear conclusions can be made.

3.5.8. Implantable flow probes

Loss of contact between the probe and the vessel being studied is most likely to occur in acute preparations in which the experiment begins immediately after surgery. This loss of contact can often be avoided if the flow probe is allowed to 'scar in' for a few days so that it is firmly attached to the vessel being studied.

3.5.9. Microsphere-based techniques

Use of radioactive microspheres for measurement of the low blood flow states found during CPR has been studied extensively [56]. These validation studies have included verification of washout of the spheres from injection sites, adequate mixing, and correlation of flows with those measured by non-particle-based techniques.

3.5.10. Catheter-based techniques

There is no way to ensure that the position of a catheter is stable during chest compressions because there is usually substantial motion of the internal organs. Therefore, observing the catheter in the correct position at the end of an experiment does not indicate that the catheter remained in the correct position during the experiment. If variations in the position of the

tip of the catheter across the lumen of the vessel can produce substantial errors in measurement, then the particular catheter-based technique should not be used.

3.5.11. Quality control

Some form of quality control should be used to ensure the validity of blood flow measurements. For example, catheter position and calibration should be verified at the beginning and end of an experiment. Because of the problem of motion artifact, quality control is particularly important when blood flow is measured during external chest compression. Measured flows should be validated against known flows for each flow technique used. These validations are necessary because subtle variations in some techniques, such as when withdrawal pumps are started in relation to injection of the microsphere, can cause major variations in measured values. Adequate quality assurance, which includes periodic review of data and techniques, is necessary to ensure reproducibility as well as adherence to good laboratory practice.

3.6. Template section 6: outcome variables

Measures of outcome are essential evidence to support the hypothesis. These include such physiological variables as cardiac rhythm; intracardiac and intravascular pressures; blood flow; ventricular function; end-tidal CO₂; the presence of spontaneous respiration; arterial and central venous pH, PO₂, PCO₂, and HCO₃; tissue electrolytes and high-energy phosphates; and return of spontaneous circulation. Most studies have focused on the above 'process variables' such as return of spontaneous circulation and short-term survival. However, long-term survival and cerebral function following resuscitation are the most important measures of outcome in CPR research because these are the most relevant to outcome in humans. Such measures as the Glasgow-Pittsburgh coma score, the overall performance score, the neurological deficit score, the histopathologic damage score (total and regional), and the electroencephalogram have all been used to assess neurological outcome. It is important to understand and to describe the relevant limitations of the measurement technique and to recognize whether the measurement itself altered the physiology of the animal.

3.6.1. Assessment of cerebral outcome

Long-term intensive care after cardiac arrest and return of spontaneous circulation are essential for evaluation of the effects of new cerebral resuscitation measures on outcome [57,58]. Intensive care is necessary to prevent extracerebral complications and to control variables that are known to influence cerebral outcome, such as postarrest arterial pressure, core temperature, blood osmolality and viscosity, acid-base conditions,

blood glucose levels, and sedation and other drug treatments. In particular, cardiopulmonary failure following cardiac arrest worsens cerebral outcome [58]. It is important to include assessment of long-term survival in cerebral outcome models because cerebral dysfunction and morphological changes do not stabilize until 3 days after cardiac arrest and reperfusion.

Long-term outcome models have been developed and used since the 1970s for the evaluation of cerebral resuscitation, with events ranging from temporary complete global brain ischemia to cardiac arrest secondary to ventricular fibrillation, asphyxia, or exsanguination [57–59]. Such models have used standard CPR, open-chest CPR, and cardiopulmonary bypass as experimental tools to maintain perfusion during cardiac arrest [60–66].

Cerebral outcome should be measured in terms of brain morphology (with such tools as the histopathologic damage score) and function (with such tools as the overall performance and neurological damage scores). Electroencephalogram patterns of early postarrest recovery in animals are quite consistent but do not correlate well with functional and morphological outcome scores [65,67].

3.7. *Template section 7: analytical approach*

This and the remaining two sections contain recommendations from the International Committee of Medical Journal Editors (the Vancouver Group) [68,69], on content and style of manuscripts submitted to medical journals. This section presents the recommendations related to statistical reporting [70].

Statistical methods should be described in enough detail to enable a knowledgeable reader with access to the data to verify results. Explain why the particular methods were used. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). State each null hypothesis clearly for each statistical test of data and report exact P values rather than make statements like ' $P < 0.05$.' Rely less on hypothesis testing and more on effect magnitude, i.e. define the magnitude of the effect seen instead of simply stating whether the data support the hypothesis. For example, report the size of an effect (e.g. 'treatment A was associated with a 20% absolute increase in survival') rather than a direction (e.g. 'treatment A had better survival, $P < 0.05$ '). Confidence intervals, which give information about the size of the difference and variability, should also be used in addition to statistical hypothesis testing.

Report the number of observations made and specify which study units are included in denominators, especially when reporting ratios, proportions, and percentages. Report and explain reasons for losses to

observation or dropouts from a trial and treatment complications. When the sample size for a table, graph, or text statement differs from that for the study as a whole, explain the difference. Discuss sample size limitations and power calculations. Be prepared to supply a detailed protocol on request.

Place general descriptions of statistical methods in the 'Materials and methods' section. When data are summarized in the 'Results' section, specify the statistical methods used to analyze them. Use tables and figures to explain the argument of the paper and to assess its support. Do not duplicate data in illustrations and tables.

3.8. *Template section 8: results [68,69]*

Present results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all data in the tables and illustrations. Emphasize or summarize only important observations.

3.9. *Template section 9: discussion and conclusions [68,69]*

Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat data given in the 'Introduction' or the 'Results' section. Include in the 'Discussion' section the implications of the findings, including implications for future research, and their limitations. Relate the observations to other relevant studies. Link the conclusions with the goals of the study, but avoid unqualified statements not supported by your data. Avoid claiming priority and alluding to work not yet completed. State new hypotheses, and clearly label them as such. Recommendations may be included when appropriate (Table 9).

4. Concluding remarks

This statement presents the consensus of a group of international investigators who met to establish guidelines for reporting data from laboratory studies of CPR. The consensus process consisted of formal discussions at three international meetings, expert review, endorsements from multiple organizations, and the invitation for additional recommendations from interested parties. The concept of using consensus workshops to formulate guidelines is not new; similar consensus guidelines for reporting research have been developed for adult out-of-hospital cardiac arrest [10], and for pediatric cardiac arrest [71]. Guidelines for in-hospital cardiac arrest were developed at a conference held at Utstein Abbey in Norway in June 1995. Recent publications have cited the 'Utstein guidelines,' suggesting that au-

thors are referring to the recommendations for more consistent reporting and terminology [72–74].

The purpose of these guidelines is to achieve a similar positive effect on reports of laboratory studies of CPR. Some investigators have expressed a prudent concern that these guidelines might have the unintended effect of restricting creativity or inhibiting laboratory experimentation. It should be clearly understood, however, that the consensus task force realized this would be an undesirable outcome and that these guidelines were drafted with the intention of promoting creative experimental research, not inhibiting it. The guidelines are offered only to improve communication among investigators by suggesting vital data and terminology to share when reporting results to colleagues; they do not recommend protocols, conditions, hypotheses, or other factors that are important in designing experiments. Furthermore, if a particular experiment does not lend itself to these guidelines, we advise the authors to simply explain so in the report.

Use of these guidelines will enhance communication within the field of CPR research. One limitation of the guidelines, however, is that they do not specify or address many important methodological issues. In addition, as new laboratory methods to study cardiac arrest evolve, new reporting dilemmas will arise. For example, intramyocardial fluorescence techniques, nuclear magnetic resonance measurements, and molecular biology assays may provide important insights for future studies. They are powerful tools for investigators but are currently beyond the scope of these guidelines. We invite your comments and questions on evolving issues for consideration in the future.

Comments and questions about these guidelines and letters from organizations that wish to be represented at future conferences may be sent to Ahmed Idris, MD, Associate Professor of Surgery, Anesthesiology, and Medicine, Division of Emergency Medicine, P.O. Box 100392, Division of Emergency Medicine, University of Florida College of Medicine, Gainesville, FL 326109-0392, E-mail aidris2@aol.com, or to Lance Becker, MD, Emergency Medicine, MC5068, University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637. Requests for reprints should be sent to the address given on the first page of this statement.

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