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Clinical paper

What change in outcomes after cardiac arrest is necessary to change practice? Results of an international survey☆

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ABSTRACT

Background: Efficient trials of interventions for patients with out-of-hospital cardiac arrest (OHCA) should have adequate but not excess power to detect a difference in outcomes. The minimum clinically important difference (MCID) is the threshold value in outcomes observed in a trial at which providers should choose to adopt a treatment. There has been limited assessment of MCID for outcomes after OHCA. Therefore, we conducted an international survey of individuals interested in cardiac resuscitation to define the MCID for a range of outcomes after OHCA.
Methods: A brief survey instrument was developed and modified by consensus. Included were open-ended responses. The survey included an illustrative example of a hypothetical randomized study with distributions of outcomes based on those in a public use datafile from a previous trial. Elicited information included the minimum significant difference required in an outcome to change clinical practice. The population of interest was emergency physicians or other practitioners of acute cardiovascular research.
Results: Usable responses were obtained from 160 respondents (50% of surveyed) in 46 countries (79% of surveyed). MCIDs tended to increase as baseline outcomes increased. For a population of patients with 25% survival to discharge and 20% favorable neurologic status at discharge, the MCID were median 5 (interquartile range [IQR] 3, 10) percent for survival to discharge; median 5 (IQR 2, 10) percent for favorable neurologic status at discharge, median 4 (IQR 2, 9) days of ICU-free survival and median 4 (IQR 2, 8) days of hospital-free survival.
Conclusion: Reported MCIDs for outcomes after OHCA vary according to the outcome considered as well as the baseline rate of achieving it. MCIDs of ICU-free survival or hospital-free survival may be useful to accelerate the rate of evidence-based change in resuscitation care.

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Introduction

There is a large variation in the process and outcome of care for patients with out of hospital cardiac arrest (OHCA).[1–3] Recently, several communities have reported that outcomes after OHCA have improved over time.[4–6] Now, many patients with cardiac arrest can return to a good quality of life if recognized and treated quickly. This variation in and improvement of outcomes emphasizes the need to conduct efficient randomized trials of interventions to accelerate evidence-based changes in resuscitation practices to improve outcomes for patients with OHCA.

Resources for clinical research are limited. Clinical research related to cardiac arrest is underfunded compared to other common clinical conditions.[7] There is heterogeneity in outcomes among randomized trials of interventions for patients with cardiac arrest.[8] The sample size for a trial depends in part on the magnitude of difference in outcomes sought. To optimize use of limited funds, efficient large simple trials of interventions for patients with OHCA should have adequate but not excess power to detect a difference in outcomes. The minimum clinically important difference (MCID) has been defined as the threshold value in outcomes observed in a trial at which patients or providers should choose to adopt a treatment.[9] If a trial reports a significant difference that is larger than the MCID for an outcome, then providers should likely use that intervention to treat patients. But if a trial reports a difference that is smaller than the MCID for an outcome, then rational providers may not use that intervention because the benefits may not be large enough to be important to patients or providers. To date, there has been limited descriptions of MCID for outcomes after OHCA.[10,11] Therefore, we conducted an international survey emergency physicians or other practitioners of acute cardiovascular research to define the MCID for a range of outcomes after OHCA, including novel outcomes for trials in patients with cardiac arrest, such as hospital-free survival and intensive care free survival. A secondary object was to estimate sample sizes of trials necessary to detect MCIDs.

Methods

Survey

A brief survey instrument was developed by several of the authors (GN, GP, FS, FK, MS, SB) and modified by consensus prior to distribution to probe for the minimum clinically important difference for outcomes in trials of interventions in patients with OHCA (see online appendix). Responses were open-ended rather than multiple-choice. The survey was prepared for online completion by using standard electronic data capture software.[12]

Survey questions were preceded by an illustrative example of a hypothetical randomized study to help focus the responses to the questions. MCID were sought for a range of outcomes intended to mimic the distribution of outcomes expected for all patients treated by emergency medical services (EMS) providers; those treated for pulseless electrical activity or asystole; those treated for ventricular fibrillation (VF); and those with VF and spontaneous circulation upon hospital arrival. These outcomes were patterned on those included in the Utstein template for standardized reporting of outcomes after OHCA.[13]

Two additional outcomes were included in the survey. Intensive care morbidity was defined as the number of days alive and permanently out of intensive care (ICU) during the first 30 days post arrest. 'Permanently' was defined as discharged from intensive care without any further readmission. Intensive care includes a ward capable of providing mechanical ventilation but not a ward capable of providing telemetry only. Patients who die before discharge from ICU would be assigned zero days out of intensive care. The day a subject was discharged from the ICU was counted as a full day in the ICU. Similarly, hospital morbidity was defined as the number of days alive and permanently out of hospital up to thirty days post arrest. Again patients who die before discharge will be assigned zero days out of hospital. The distribution of outcomes was estimated from the public use datafile of a previous large randomized trial of interventions in patients with OHCA.[14,15]

Respondents were asked to describe their general characteristics, including age, gender, years since medical school, years in practice and country of residence. No individually identifiable information was collated. The University of Washington Institutional Review Board reviewed this study and determined that it was exempt from human subjects research.

Respondents

The population of interest was emergency physicians or other practitioners of acute cardiovascular research. Individuals invited to participate had previously published at least one peer-reviewed article related to OHCA. These were supplemented as needed by recommendation of peers to achieve at least two responses from each country. Repeat invitations were sent by electronic mail to non-respondents until at least two responses were obtained from any individual country.

Countries

We sought participation from individuals in as many countries as possible with the purpose of representing a diversity of medical practices. After we achieved responses from 50% of individuals, we determined that we had a broad enough set of responses to allow meaningful inferences.

Analysis

Responses were summarized descriptively (R 3.2.1, R Development Core Team available at www.r-project.org; and SAS JMP 11.2.0, SAS Institute, Cary, NC). The median absolute increase in each outcome across the range of baseline rates was used to estimate the number of patients required to detect the MCID in a hypothetical superiority trial. These estimates assumed a single analysis with 90% power, and two-sided alpha = 0.05.

Results

Survey responses

Participation was sought from 321 individuals in 58 countries. Responses were obtained from 161 (50% of sample) individuals in 46 countries (79% of sample) that included India, China, Kenya, Nigeria, and South Africa, many of the European Union countries, as well as North and South American countries including Canada, USA, Mexico, and Brazil (Fig. 1). One response was not usable. The total census population represented by respondents was about 4.5 billion people. Responses were reported overall and then by the subgroup of countries in North America (3 countries; 36 responses) vs. Europe (21 countries; 67 responses) vs. the rest of the world (22 countries; 54 responses).

Table 1 describes the characteristics of the respondents. The majority were male ($n = 129$, 81%). Most of the respondents were physicians ($n = 131$, 82%). Years in practice were mean 15.9 ± 12.3.

Table 2 summarizes the responses to the elicitations of MCID overall and grouped by region. The majority of reported MCIDs were clustered together (i.e. had narrow interquartile range). MCID were not significantly different among North American respondents as compared to those from Europe or the rest of the world.

Fig. 1. Participating countries.

Fig. 2 describes the MCID for an absolute increase in favorable neurologic status at discharge as a function of the baseline distribution of favorable neurologic status at discharge. As the baseline outcomes increased, the MCID tended to increase. MCIDs for other outcomes are available (See Supplementary Appendix).

The sample size required to detect an MCID varies according to the population of patients considered (Table 3). Fig. 3 describes the overall number of patients to be enrolled in a trial with 90% power and two-sided alpha = 0.05 to detect the MCID for ICU-free days, hospital-free days, survival to discharge and favorable neurologic status at discharge across the baseline distribution of each outcome. Significantly fewer patients were required to detect the MCID for ICU-free days or hospital-free days as compared to survival to discharge or favorable neurologic status at discharge (p value < 0.001).

In post hoc subgroup analyses of the MCID for survival to discharge in a population with a baseline survival to discharge proportion of 25%, there was no heterogeneity in MCID grouped by male vs. female gender (p for interaction = 0.14; mean (SD) MCID of 7.9 (7.9) for males and 5.8 (6.5) for females). However, there was heterogeneity by physician vs. non-physician respondents (p for interaction = 0.004; mean (SD) MCID of 8.0 (8.2) for physicians and 4.9 (3.7) for others).

Discussion

We have defined the MCID by emergency physicians or other practitioners of acute cardiovascular research. These differences vary according to the outcome considered as well as the baseline rate of achieving it.

Future trials can be designed to be large enough to be able to detect the MCID in an outcome. Enrolling too few patients to detect the MCID for an outcome is not sufficient to change clinical practice. Enrolling too many to detect the MCID for an outcome uses resources that can be efficiently reallocated to investigate other interventions. If a significant difference is observed, then the intervention would likely be adopted by rational providers. Conversely,

Table 1
Characteristics of respondents.

	North America $N = 36$	Europe $N = 67$	Other $N = 54$	Overall $N = 160$
Age in years, mean (SD), median (Q1, Q3) [$N = 36; 67; 54; 159$]	49.0 (11.0) 49 (39, 57)	46.9 (11.4) 48 (39, 55)	46.3 (10.4) 45 (39, 53)	47.0 (11.0) 47 (39, 55)
Male gender, no. (%)	29 (81)	50 (75)	46 (85)	129 (81)
Primary profession, no. (%)				
MD	25 (69)	59 (88)	45 (83)	131 (82)
EMS provider	6 (17)	1 (1)	2 (4)	10 (6)
Nurse	0	(0)	2 (4)	2 (1)
Researcher	4 (11)	6 (9)	5 (7)	14 (9)
Other	1 (3)	1 (1)	1 (2)	3 (2)
Clinical experience				
Years in practice, mean (SD)	15.0 (13.5)	17.3 (11.7)	15.1 (12.3)	15.9 (12.3)
median (Q1, Q3) [$N = 36; 65; 53; 156$]	12 (1, 27)	15 (8, 25)	14 (4, 24)	15 (6, 25)
Patients with OHCA treated annually, mean (SD) [$N = 36; 66; 52; 156$]	33.7 (53.5)	30.8 (44.0)	63.3 (155.0)	42.0 (97.9)
Enrolled patients in trial, no. (%)l [$N = 36; 66; 54; 159$]	20 (56)	41 (61)	22 (41)	83 (52)
Led trial, no. (%) [$N = 36; 66; 54; 159$]	11 (31)	18 (27)	14 (26)	43 (27)
Location, no. (%) [$N = 157$]				
North America	–	–	–	37 (23)
Europe	–	–	–	69 (43)
Other	–	–	–	54 (34)

Table 2
Reported minimum clinically important differences.

Subgroup	Outcome [baseline value]	North America median (Q1, Q3)	Europe median (Q1, Q3)	Other median (Q1, Q3)	Overall median (Q1, Q3)
EMS-treated OHCA	ROSC at ED Arrival [27%]	10(5,15)	10(5,10)	10(5,20)	10(5,14)
	Survive 3 days post-arrest [15%]	6(3,10)	5(3,10)	5(5,15)	5(3,10)
	Survive to discharge [9%]	3(2,6)	4(2,5)	5(2,15)	4(2,10)
	Good neuro at discharge [6%]	2(1,5)	3(2,5)	4(2,10)	3(2,7)
	ICU-free days [1.7 ± 6.1]	2(1,6)	3(1,5)	4(1,7)	3(1,7)
	Hospital-free days [1.2 ± 4.8]	2(1,6)	3(1,7)	3(1,10)	3(1,8)
Non-shockable OHCA	ROSC at ED arrival [22%]	10(5,12)	10(5,15)	10(5,20)	10(5,15)
	Survive 3 days post-arrest [9%]	5(3,10)	5(3,10)	5(3,10)	5(3,10)
	Survive to discharge [3%]	3(1,8)	4(2,5)	3(2,8)	3(2,5)
	Good neuro at discharge [2%]	2(1,6)	3(1,5)	3(2,10)	3(1,5)
	ICU-free days [0.7 ± 4.1]	2(1,6)	3(1,7)	3(1,10)	3(1,6)
	Hospital-free days [0.5 ± 3.2]	2(1,5)	3(1,10)	3(1,10)	3(1,7)
Shockable OHCA	ROSC at ED arrival [43%]	10(5,15)	10(5,13)	10(5,19)	10(5,15)
	Survive 3 days post-arrest [36%]	7(4,13)	7(4,10)	8(4,15)	7(4,12)
	Survive to discharge [25%]	5(3,6)	5(3,7)	6(2,13)	5(3,10)
	Good neuro at discharge [20%]	4(2,6)	5(2,10)	5(2,11)	5(2,10)
	ICU-free days [4.9 ± 9.3]	3(2,5)	4(2,6)	5(2,10)	4(2,9)
	Hospital-free days [3.5 ± 7.4]	3(2,5)	4(2,8)	5(1,10)	4(2,8)
OHCA VF, pulse at ED arrival	Survive 3 days post-arrest [74%]	10(4,15)	9(5,15)	10(5,17)	10(5,15)
	Survive to discharge [53%]	5(3,10)	7(5,10)	10(4,15)	6(4,10)
	Good neuro at discharge [43%]	5(3,10)	5(4,10)	10(3,15)	5(3,10)
	ICU-free days [10.5 ± 11.4]	5(2,7)	5(2,10)	8(2,10)	5(2,10)
	Hospital-free days [7.5 ± 9.3]	3(2,9)	5(2,10)	7(2,10)	5(2,10)
OHCA VF, pulse at ED arrival, survived at least 4 h	Survive 3 days post-arrest [80%]	10(5,15)	10(5,15)	10(5,15)	10(5,15)
	Survive to discharge [58%]	5(3,10)	6(5,10)	10(3,12)	6(3,10)
	Good neuro at discharge [47%]	5(3,10)	5(4,10)	7(3,10)	5(3,10)
	ICU-free days [11.4 ± 11.4]	4(2,7)	5(3,10)	6(2,12)	5(2,10)
	Hospital-free days [8.1 ± 9.4]	3(2,9)	5(2,10)	7(2,10)	5(2,10)

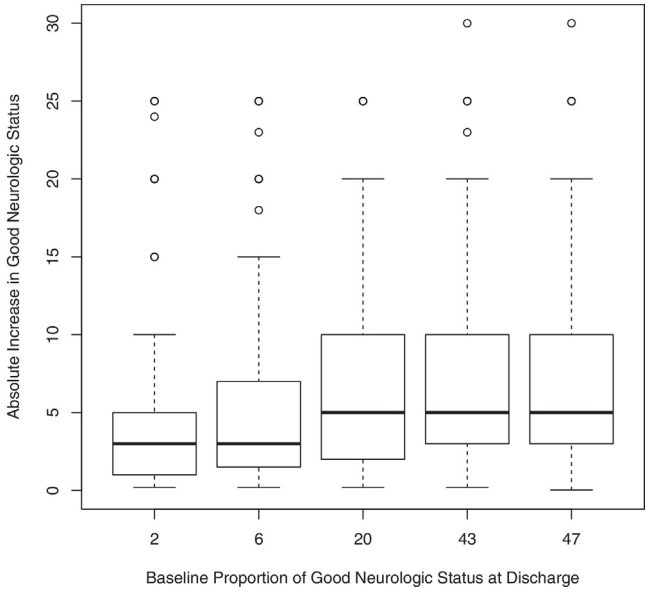

Fig. 2. Minimum clinically important difference for good neurologic status.

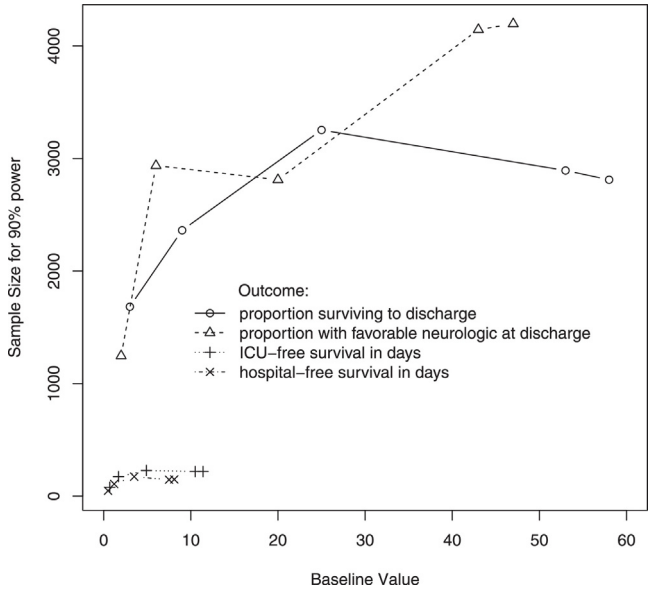

Fig. 3. Sample size required to detect minimum clinically important differences.

Table 3
Sample size for 90% power to detect median MCID.

Subgroup	Survival to discharge	Good neuro at discharge	ICU-free days	Hospital-free days
EMS-treated OHCA	1683	1247	79	48
Non-shockable OHCA	2362	2937	174	108
Shockable OHCA	3253	2811	228	188
OHCA VF, pulse at ED arrival	2893	4145	219	146
OHCA VF, pulse at ED arrival, survived at least 4 h	2811	4196	219	149

The table shows sample size required to have 90% power to detect median MCID for baseline values listed in Table 2.

if a significant difference is not achieved, then limited resources can be reinvested in use of other effective therapies.

The reported MCIDs provide a starting point for reaching consensus on how much of a difference should be demonstrated to warrant a change in clinical practice guidelines or change in clinical practice. Some of the reported MCID are large and have a large variance.

Among hypothetical populations with low (i.e. 5%) survival to hospital discharge or favorable neurologic status at discharge, reported MCIDs were within 2% of expected differences in previously completed trials (Table 3).[14,15,26] For a hypothetical population with ROSC at emergency department arrival of 10%, reported MCIDs were within 5% of expected differences in survival to hospital admission in previously completed trials.[27–29] Among hypothetical populations with high (i.e. 40–55%) survival to discharge or favorable neurologic status at discharge, reported MCIDs were within 10% of expected differences in previously completed trials.[16,30] For traditional outcomes such as admission to hospital, survival to discharge or favorable neurologic status at discharge, consideration of MCIDs may require larger sample sizes than those used in previous trials.

We included two novel outcomes in this survey. ICU-free survival is a composite outcome that captures a treatment effect on both survival and need for intensive care post-resuscitation. Similarly, hospital-free survival is a composite outcome that captures a treatment effect on survival and need for hospital care post-resuscitation. A treatment effect in either survival or need for care would justify use of an intervention. Note that other randomized trials that enrolled patients with cardiac arrest have described similar outcomes such as days on a ventilator, in an intensive care unit or in hospital.[16–18] However the utility of such assessments were limited because they did not account for the differential timing of mortality throughout the hospitalization period. A single trial that enrolled patients with cardiac arrest has reported ICU-free survival during the first month after cardiac arrest.[19] Importantly, hospital-free survival has been used as an outcome in randomized trials in patients with heart failure,[20,21] renal failure,[22] cancer,[23] or need for intensive care.[24] As well, hospital-free survival is recommended as an outcome in trials that enroll patients with need for intensive care.[25] According to the present survey, markedly fewer patients are required to detect the MCID in ICU-free days or hospital-free days. If either of these outcomes is used as the primary outcome in trials of interventions in patients with cardiac arrest, then the pace of evidence-based change in resuscitation care can be accelerated.

ICU days as well as days of ventilation were described in recent trials of interventions in patients with cardiac arrest.[16,18] Note that such summary measures do not account for the information associated with mortality. Our novel outcomes require a smaller number of subjects required to detect an MCID than traditional outcomes for trials in patients with OHCA (Fig. 3). Thus, ICU-free survival and hospital-free survival offer some potential efficiencies compared to traditional outcomes for trials of interventions in patients with cardiac arrest.

The present study has some limitations. We surveyed a convenience sample of professional individuals interested in cardiac resuscitation without requiring them to have a predetermined level of experience. Surveys of individuals were previously adopted as a method to develop consensus by allowing participants to make considered independent opinions so as to lead to reliable conclusions.[31] Participants can be selected in multiple ways, including their position in a hierarchy, public acknowledgment or recommendation by other participants.[32] We did not include patients or caregivers as has sometimes been recommended.[33] Importantly use of experts versus non-experts is not associated with large difference in survey outcomes.[34]

We did not account for variation in the duration of hospitalization across the health systems or countries of respondents. Nor did we account for variation in the timing of prognosis assessment and withdrawal of life sustaining treatment across the health systems or countries of respondents. Although the Utstein template recommends[13] and we evaluated survival to discharge, survival to a fixed time point such as one month after cardiac arrest may mitigate some of these variations in practice.

We did not elicit MCID for outcomes assessed after discharge. Patients resuscitated from cardiac arrest may have cognitive impairment at discharge that improves over time.[35] Some experts have recommended post-discharge assessment of neurologic outcomes among survivors of cardiac arrest as the primary outcome for resuscitation trial.[36] As well, post-discharge assessment of health-related quality of life facilitates assessment of the cost-effectiveness of the intervention. Among patients who consented for follow-up, those who survived to leave hospital achieved good health-related quality of life.[37] Post-discharge cognition and quality of life were well correlated with neurologic status at discharge. However post discharge assessments are expensive, may be difficult to perform and are susceptible to bias.[37]

In this survey, we sought the MCID for individual outcomes. In practice, clinical trials often evaluate multiple outcomes. Decisions to use or not use a therapy are sometimes based on the totality of the evidence collected in a trial as opposed to whether a significant difference was observed in the primary outcome. If a significant difference in the primary outcome is observed that is smaller than the relevant MCID, it may still be rational to use the intervention if a significant benefit is observed in key subgroups or in secondary outcomes.

The wide range of responses might be interpreted as suggesting that some individuals may have misunderstood the task. We provided the survey only in the English language. We did not restrict responses to those fluent in English, or assess the fluency of the respondents. We can not differentiate whether these extreme values reflect misunderstanding or true belief. The observation that MCID varied by geography suggests that the results may have been influenced by local practice, language fluency, religious beliefs or other factors. Importantly, consensus on science and practice guidelines for treatment of patients with cardiac arrest are developed and disseminated by international collaboration.[38,39] Since clinicians in multiple countries interpret and apply the results of trials, we sought to elicit responses from a broad range of countries. We sought at least two responses from each country so that we could not identify individual responses. But two responses does not ensure that each country's view was accurately represented.

We explicitly sought MCID for absolute rather than relative percent changes. Alternative presentations of the same risks and risk reductions may impact on the understanding and behavior of care providers, policy makers, and patients.[40] Relative risk reduction as compared with absolute risk reduction may be perceived to be larger and may be more persuasive. It is unclear whether presenting relative risk reduction is likely to help people make decisions most consistent with their own values or could lead to misinterpretation. MCIDs appear to vary in part based on the method used to elicit them.[41,42] We did not assess whether alternative presentations would yield results consistent with those observed in the present study.

Some randomized trials include economic evaluations concurrent with the trial by sampling those patients who provide informed consent for an economic sub-study then following them forward over time.[6] To the best of our knowledge, there is no widely accepted method of calculating the sample size for an economic evaluation. As well, doing so would be limited by variation in the cost-effectiveness threshold (i.e. the incremental

cost-effectiveness ratio at which an intervention would or would not be considered good value for money) by jurisdiction. Therefore, we explicitly excluded cost from consideration in our survey.[7–9]

Importantly, the source data were from a trial that only enrolled adults. Our results may not apply to children, whom have different etiologies of arrest, therapies, and outcomes compared to adults.

Conclusion

Reported MCIDs for outcomes in patients with OHCA varies according to the outcome under consideration as well as the baseline rate of achieving it. MCID of ICU-free survival or hospital-free survival may be useful to design and implement efficient trials of interventions in patients with OHCA so as to accelerate the rate of evidence-based change in resuscitation care.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2016.08.004.

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