Supplemental Online Content

Bernard SA, Bray JE, Smith K, et al; for the EXACT Investigators. Effect of Lower vs Higher Oxygen Saturation Targets on Survival to Hospital Discharge Among Patients Resuscitated After Out-of-Hospital Cardiac Arrest. *JAMA.* Published online October 26, 2022. doi:10.1001/jama.2022.17701

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1: Discrepancies between the Manuscript and the Protocol and Statistical Analysis Plan

There are a few minor discrepancies between the manuscript, the protocol and statistical analysis plan (SAP). These discrepancies are:

1. Secondary outcomes: Slight variation to secondary outcomes listed and their order across protocol, SAP and manuscript. Final secondary outcomes and order are as listed in the SAP (Tables 3 and 5) and have been divided into hospital and 12-month outcomes with the following changes:
    a. Discharge destination was accidently not included in the protocol but is included in SAP (eAppendix 3 Supplement 1 Table 3). The SAP was not explicit that analysis of this variable would be restricted to survivors, however this was prespecified in instructions to the statistician. In the manuscript this variable has been moved to the end of the table to reflect patient flow.
    b. Myocardial injury -peak Troponin was accidently excluded in SAP (included in protocol). Myocardial injury -echocardiogram and ST-resolution were included in the protocol publication but removed from the protocol (Version 1.5 25/5/2020) as a secondary outcome due to difficulties in collecting this data from the medical records.
    c. Further categories for cause of in-hospital mortality were added to the manuscript on review of the “other” category: treatment withdrawn -palliation, treatment withdrawn -catastrophic event, treatment withdrawn -medical (multi-organ failure).
    d. ICU and hospital length of stay are reported separately for survivors and non-survivors at a Reviewer’s request.
    e. Twelve-month outcomes (survival and quality of life measures) are listed separately as per SAP and the statistical planned analysis was not performed due to the smaller than expected sample size as a result of the trial stopping early. GOS-E is incorrectly categorised in the SAP compared to the final manuscript and is presented as Good recovery, Moderate disability and Severe Disability. Health-

related quality of life data are restricted to survivors who were followed-up. Modified Rankin Scores are calculated with and without in-hospital deaths.

2. The subgroup analysis (section 5.4.4) in the protocol states, "*Primary and secondary outcomes analysis by treatment group will also be examined in the following a priori subgroups: age ≥65years; sex; witnessed arrest; bystander CPR; witnessed and bystander CPR; initial shockable and non-shockable rhythms; collapse to ROSC >20 minutes; use of drugs for airway insertion; and ambulance service*." The following subgroups were not analysed in the final paper because of the smaller sample size and data collection: drugs for airway insertion, ambulance service, and witnessed and bystander CPR. The SAP states NSTEMI but this was not collected so is presented as STEMI -yes/no.
3. Due to the reduced sample size, only the primary outcome was compared for the sensitivity analysis conducted on eligible patients.
4. During the analysis, the variables for oxygen level data (FiO2 and liters/min) on arrival at the emergency department would not converge so were examined closely. The histogram showed that the bulk of the FiO2 observations were 0.6 and 1.0 hence this variable was categorised and logistic regression was undertaken. The majority of the last recorded oxygen delivered in ED were 15 liters/min (19 of 27) so this data was not analyzed.
5. The prehospital variables mechanical ventilation and STEMI were included in the manuscript as per the protocol, and should have been included in the statistical analysis plan.
6. Additional post-hoc analyses included:
    a. Reviewer request: Primary outcome analysis adjusting for clustering of site using mixed effects logistic regression. This analysis adjusted for the clustering of site, age, sex, witnessed±CPR, presumed cause, shockable initial rhythm and downtime (time of emergency call to ROSC).

b. Reviewer request: subgroup analysis of time from collapse to randomisation. This was performed using the difference between the time of emergency call to randomisation stratified into quartiles.
c. Reviewer request: proportion of time to death <72 hours in patients who had treatment withdrawn by treatment allocation.

eAppendix 2. Prehospital arrest and post-arrest management during the EXACT trial.

In Australia, paramedics are currently trained over three years at university, and undergo an additional year of training to become intensive care paramedics. At the time of trial at least two paramedics and one intensive care paramedic respond to most patients with suspected cardiac arrest. Cardiac arrest treatment included airway management, administration of intravenous adrenaline (1mg) every 4 minutes and administration of intravenous amiodarone (300mg) for ventricular fibrillation and pulseless ventricular tachycardia refractory to 3 shocks. In Victoria and South Australia patients were managed with a supra-glottic airway during CPR, with the option of endotracheal intubation available to intensive care paramedics during cardiac arrest or post-ROSC. In Victoria post-ROSC intubation was performed by rapid sequence induction, whereas in South Australia all intubation was performed without drug assistance. Mechanic ventilators were only available to Victorian intensive care paramedics. Post arrest care includes monitoring with ECG, pulse oximetry, capnography and regular non-invasive blood pressure.

eTable 1. Reasons for exclusion from the sensitivity analysis.

	Target SpO_2 90-94% n=18	**Target SpO_2 98-100% n-=14**
Dependant on others for activities of daily living	4	2
Cardiac arrest due drowning, trauma or hanging	8	4
Glasgow Coma Scale >8	2	1
Pulse oximetry <95% at randomization	4	7

eTable 2. Time from randomization to first arterial blood gas in the ED and ICU.

	Target SpO_2 90-94%	**Target SpO_2 98-100%**
ED, median (IQR) [n], min	53.5 (40.0, 87.0) [174]	51.0 (38.0, 74.0) [170]
ICU, median (IQR) [n], min	238.0 (195.0, 319.0) [190]	247.0 (183.0, 322.0) [193]

eTable 3: Sensitivity analysis of outcomes in eligible cases.

	Target SpO_2 90-94% (n=196)	Target SpO_2 98-100% (n=197)	OR[a] (95% CI)	*P* value
Primary outcome				
Survival to hospital discharge, No. (%)	77 (39.3)	94 (47.7)	0.71 (0.48, 1.06)	.09
Secondary outcomes				
Re-arrest pre-ICU, No. (%)	24/196 (12.2)	19/196 (9.7)		
Re-arrest pre-hospital	7 (3.6)	2 (1.0)		
Re-arrested in ED	23/196 (11.7)	18/196 (9.2)		
Hypoxia (any SpO2<90%) prior to ICU admission, No. (%)	60 (30.6)	32 (16.2)		
Peak Troponin, n	178	186		
Troponin T, median (IQR)	554 (134, 1924)	493 (161, 2224)		
Troponin I, median (IQR)	2118 (327, 8578)	1573 (270, 6876)		
Survival to ICU discharge, No. (%)	92/181 (50.1)	100/188 (53.2)		
Length of ICU stay (days), median (IQR)	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)		
Length of hospital stay (days), median (IQR)	6.0 (2.0, 11.0)	7.0 (3.0, 12.0)		
Cause of in-hospital mortality, No. (%)				
Re-arrest with no ROSC				
Treatment withdrawn - Hypoxic brain injury	67 (56.3)	67 (65.0)		
Treatment withdrawn - cardiogenic shock	12 (10.1)	10 (9.7)		
Treatment withdrawn - palliation				
Treatment withdrawn - catastrophic event	13 (10.9)	4 (3.9)		
CPC[b], No. (%)				
CPC 1-2	77 (37.8)	82 (41.8)		
CPC 3-5	122 (62.2)	114 (58.2)		
Discharge destination, No. (%)				
Home	50 (65)	68 (72)		
Rehabilitation	27 (35)	23 (24)		
Other Hospital	0 (0)	3 (3)		

Abbreviations: ICU, Intensive care unit; ED, emergency department; IQR, Interquartile range; ROSC, return of spontaneous circulation; CPC, Cerebral Performance Category.

[a] Unadjusted logistic regression used for survival to discharge. Other analyses were not performed due to reduced sample size.

[b]Cerebral Performance Category is a 5-point scale assessing neurologic outcomes after brain damage, with higher scores indicating worse outcomes. A score of 1 or 2 is considered a favourable outcome. CPC was determined from medical record review.

eTable 4: Outcomes and quality of life measures at 12-months**.**

Factor	**Target SpO_2 90-94%**	**Target SpO_2 98-100%**
N		
12 month follow up for those discharged alive, No. (%)	82	101
Deceased	4 (4.9)	2 (2.0)
Loss to follow-up	5 (6.1)	14 (13.9)
Non-Victorian resident	1 (1.2)	4 (4.0)
Refused	5 (6.1)	7 (6.9)
Responded	67 (81.7)	74 (73.3)
N	67	74
SF-12 Mental Component, median (IQR)	55.0 (45.0, 58.0)	55.5 (45.0, 59.0)
SF-12 Physical Component, median (IQR)	52.0 (42.0, 56.0)	51.0 (38.0, 57.0)
EQ-5D-5L index, median (IQR)	0.9 (0.8, 1.0)	0.9 (0.7, 1.0)
GOS-E, No. (%)		
Good recovery	41 (61)	44 (59)
Moderate disability	14 (21)	17 (23)
Severe disability	12 (18)	13 (18)
Modified Rankin Score Survivors, No. (%)		
0-2	54/71 (76)	58/76 (76)
3-6	17/71 (24)	18/76 (24)
12-month modified Rankin Score including in-hospital deaths, No. (%)		
0-2	54/203 (27)	58/186 (31)
3-6	149/203 (73)	128/186 (69)
N		
12-month survival (including in-hospital deaths), No. (%)	72/208 (35)	81/193 (42)

Abbreviations: SF-12, Short Form Health Survey; EQ-5D-5L, EuroQol 5 Dimension 5 Level; mRS, Modified Rankin Score; GOS-E, Glasgow Outcome Scale Extended; IQR, Interquartile range.
Data were collected by telephone from patients or proxies.
The SF-12 is a measure of self-reported physical and mental health. Scores range from 0-100 with higher scores indicating better physical and mental health functioning.
The EQ-5D-5L is reported as an indexed value with values ranging from -0.59 to 1, where the maximum score of 1 indicates better health-related quality of life.
The mRS is a seven-point scale measuring the degree of disability and dependence in daily living, with a favourable outcomes considered be scores of 0-2 (no or minimal disability), and unfavourable outcomes scores of 3-5 (significant disability) or 6 (death).
The GOS-E is a measure of recovery divided into good recovery (1,2), moderate disability (3,4) or severe disability/or death (5-8).

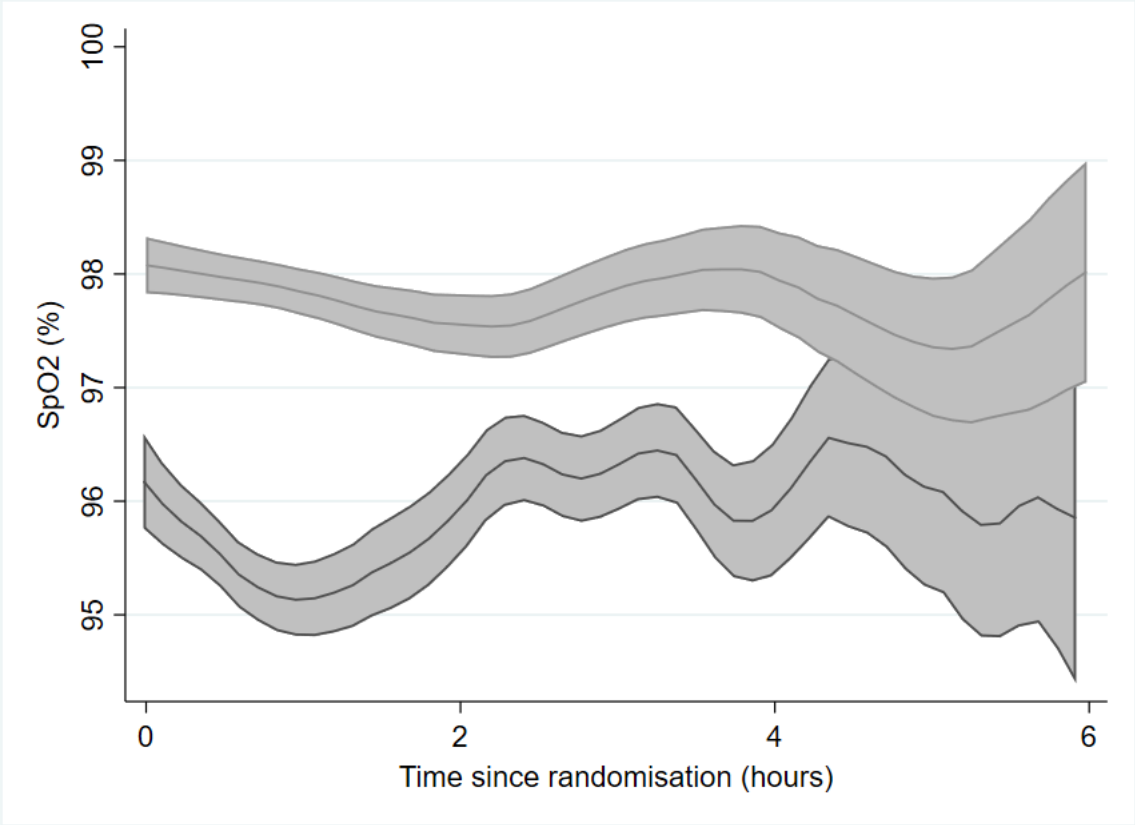
eTable 5: An exploratory subgroup analysis of survival to discharge stratified for time from emergency call to randomization.

Time from emergency call to randomization – quartiles (mins)	**Target SpO_2 90-94% (n=214)**	**Target SpO_2 98-100% (n=211)**	**Interaction *P* value**
14-51	25/45 (56%)	36/63 (57%)	.50
52-63	13/48 (27%)	27/57 (47%)	
64-79	18/61 (30%)	17/47 (36%)	
80-191	26/60 (43%)	21/44 (48%)	

eTable 6: An exploratory analysis of the timing of withdrawal of life-sustaining treatment[a].

	Target SpO_2 90-94%	**Target SpO_2** 98-100%	***P* value**
Treatment withdrawn <72 hours	38/107 (36%)	28/92 (30%)	.45
Treatment withdrawn ≥72 hours	69/107 (64%)	64/92 (70%)	
Includes cases classified as: Hypoxic brain injury -Treatment withdrawn, Cardiogenic shock -Treatment withdrawn and Treatment withdrawn – medical (multiorgan failure).			

efigure1. Recorded Mean and Standard Deviation Oxygen Saturation Measurements over the First Six Hours by Treatment Allocation.



eFigure 2: Modified Rankin Scores by treatment group at 12 months including in-hospital deaths (excluding patients loss-to follow-up).