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Clinical paper

Protocol for outcome reporting and follow-up in the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest trial (TTM2)



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Abstract

Aims: The TTM2-trial is a multi-centre randomised clinical trial where targeted temperature management (TTM) at 33 °C will be compared with normothermia and early treatment of fever (≥ 37.8 °C) after Out-of-Hospital Cardiac Arrest (OHCA). This paper presents the design and rationale of the TTM2-trial follow-up, where information on secondary and exploratory outcomes will be collected. We also present the explorative outcome analyses which will focus on neurocognitive function and societal participation in OHCA-survivors.

Methods: Blinded outcome-assessors will perform follow-up at 30-days after the OHCA with a telephone interview, including the modified Rankin Scale (mRS) and the Glasgow Outcome Scale Extended (GOSE). Face-to-face meetings will be performed at 6 and 24-months, and include reports on outcome from several sources of information: clinician-reported: mRS, GOSE; patient-reported: EuroQol-5 Dimensions-5 Level responses version (EQ-5D-5L), Life satisfaction, Two Simple Questions; observer-reported: Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest version (IQCODE-CA) and neurocognitive performance measures: Montreal Cognitive Assessment, (MoCA), Symbol Digit Modalities Test (SDMT). Exploratory analyses will be performed with an emphasis on brain injury in the survivors, where the two intervention groups will be compared for potential differences in neuro-cognitive function (MoCA, SDMT) and societal participation (GOSE). Strategies to increase inter-rater reliability and decrease missing data are described.

Discussion: The TTM2-trial follow-up is a pragmatic yet detailed pre-planned and standardised assessment of patient's outcome designed to ensure data-quality, decrease missing data and provide optimal conditions to investigate clinically relevant effects of TTM, including OHCA-survivors' neurocognitive function and societal participation.

Keywords: Cardiac arrest, Treatment outcome, Cognitive function, Patient Reported Outcome Measures, Quality of life

Introduction

In countries where withdrawal of life-sustaining therapies (WLST) is routinely employed, only 5–10% of patients discharged alive from hospital after out-of-hospital cardiac arrest (OHCA) experience a poor neurological outcome when crude outcome scales are used.¹ With more detailed outcome evaluation, approximately half of OHCA-survivors show long-term neurocognitive impairment, especially in the domains of memory, attention/processing speed and executive functions.^{2,3} Neurocognitive impairment in OHCA-survivors is associated with lower levels of societal participation and less return-to-work.⁴

The Targeted Hypothermia versus Targeted Normothermia after OHCA (TTM2) trial was designed to assess whether targeted temperature management (TTM) at 33 °C is superior to early treatment of fever (≥ 37.8 °C).⁵ The primary outcome of the TTM2-trial is all-cause mortality at six months after randomisation. Secondary outcomes include poor functional outcome and patient-reported health related quality-of-life (HRQoL). The explorative analyses of the TTM2-trial are specified to provide increased granularity in the estimation of brain dysfunction for the comparison of the two intervention regimens.

The aims of this manuscript are:

- 1 To provide detailed information on the design of the TTM2-trial follow-up, in line with the SPIRIT-PRO Extension guidelines.⁶
- 2 To describe the exploratory analyses of the TTM2-trial that focus on the survivors outcomes of neurocognitive function and societal participation.

Methods

Time-points

The main time-point for primary, secondary and exploratory outcomes is six months after randomisation. At this time-point most neurological recovery has occurred.^{7–9} Furthermore, return-to-work typically occurs around 4-months post-OHCA.¹⁰ Consequently most participants will, at least to some extent, be reintegrated into their normal lives at 6-months. In the previous TTM-trial,¹ the six month time-point for follow-up was feasible in terms of patient inclusion, with 92% of survivors participating.¹¹ In the TTM2-trial additional time-points at 30-days and 24-months post-randomisation will be used to explore the time-course of recovery in survivors.

Population

Established from the *a priori* power calculation for the primary outcome,⁵ the TTM2-trial will include 1900 unconscious OHCA-patients, ≥ 18 years of age, with a presumed cardiac or unknown cause of arrest. Detailed inclusion and exclusion criteria, routines for neurological prognostication and criteria for WLST have been published.⁵ Efforts to minimise avoidable missing data is an important part of the study-design, and includes user-friendly tests, training sessions, regular monitoring, and remote support of each participating site by a central coordinator.

Setting

Participants in the TTM2-trial are recruited at multiple sites in several countries (Table 1). The 30-day follow-up is a telephone interview. The

Outcome	Outcome assessment	Scoring	Time-point			Source of information				Translations*
			30-days	6-months	24-months	PRO	ObsRO	ClinRO	Performance test	
Functional outcome related to neurological function	mRS	Range 0–6 0 = no symptoms 6 = dead Poor outcome mRS 4–6	•	•	•	•	•	•		Yes ^a Available at www.modify-drinkin.com
Functional outcome related to neurological function, with a focus on societal participation	GOSE	Range 1–8 1 = dead 0 = upper level of good recovery Poor outcome GOSE 1–4	•	•	•	•	•	•		Yes ^b
Generic health	EQ-5D-5L	Dimension scores; range 1–5 1 = No problems 5 = Extreme problems Scores ≥ 2 indicates problems Index scores; range –0.285 to 1.00 <0.00 = health status worse than being dead VAS scores: range 0–100 Scores <70 represent poor health		•	•	•				Yes By the Euroqol group
Global cognitive function	MoCA	Scores 0–30 Scores <26 indicates cognitive impairment 25–18 mild impairment 7–10 moderate impairment <10 severe impairment		•	•				•	Yes Available at mocatest.org
Mental processing speed	SDMT	Number of correct symbols 0–110 Scores 1–1.5 standard deviations below the mean of a specific age and education level are considered suggestive of cerebral dysfunction. Scores 2 standard deviations below the mean of a specific age and education level are considered very low.		•	•				•	Not language specific
Cognitive problems in daily life	IQCODE-CA	Total score ranges from 1.0 to 5.0.		•	•			•		Yes ^c

Table 1 (continued)

Outcome	Outcome assessment	Scoring	Time-point			Source of information				Translations*
			30-days	6-months	24-months	PRO	ObsRO	ClinRO	Performance test	
Mental recovery/ dependency	TSQ	Scores at or above 3.04 was found to be an optimal cut-off to indicate cognitive problems after cardiac arrest								Original version available at www.rsph.anu.edu.au/research/tools-resources/informant-questionnaire-cognitive-decline-elderly . Yes
		Yes to question 1a and Yes to question 1b indicate new problems with dependency after cardiac arrest No to question 2 indicate problems with mental recovery after cardiac arrest		•	•	•				Translated by the TTM-trial investigators.
Life satisfaction	One question on life satisfaction from the World Value Survey	Score range from 0 (=completely dissatisfied) to 10 (=completely satisfied) National normative data available		•	•	•				Yes Provided from the www.worldvaluessurvey.org/wvs.jsp and by the secretariat of the World Values Survey Association (2017-11-23)

Abbreviations: PRO = Patient Reported Outcome; ObsRO= Observer Reported Outcome; ClinRO = Clinician Reported Outcome; mRS=modified Rankin Scale; GOSE = Glasgow Outcome Scale Extended; EQ-5D-5L = EuroQol health survey 5 Dimensions 5 Levels responses version; MoCA = Montreal Cognitive Assessment; SDMT = Symbol Digit Modalities Test; IQCODE-CA = Informant Questionnaire on Cognitive Decline in the Elderly, Cardiac Arrest version; TSQ = Two Simple Questions.

[†] Participating countries in the TTM2-trial: Australia, Austria, Belgium (French and Flemish), Czech Republic, Denmark, France, Germany, Italy, New Zealand, Norway, Sweden, Switzerland (French, Italian, German), United Kingdom and USA.

^a mRS 9 Questions (mRS-9Q) was available in English and Danish. Remaining versions were translated for the TTM2-trial by the national investigators (accepted by dr Flint personal communication 2017-11-25).

^b For the GOSE translated versions was shared from the CENTER-TBI project and further modified for cardiac arrest use for the TTM2-trial (approved by Professor Lindsay Wilson, personal communication 2017-01-24). The modifications were translated by the TTM2-trial national investigators. The Danish version was translated specifically for the TTM2-trial.

^c For IQCODE-CA a slight modification for cardiac arrest use was performed (approved by Professor Anthony Jorm, personal communication 2010-05-13) and translated for the TTM and/or TTM2-trial by the national investigators.

Table 2 – Overview of patient characteristics collected. Full information on different variables collected in the TTM2 trial CRF is available at <https://ttm2trial.org/documents>.

	During hospital stay	At 30 days follow-up	At 6 months follow-up	At 24 months follow-up
Socio-demographical information <i>including age, sex</i>	•			
Resuscitation variables including <i>scene of cardiac arrest, witnessed arrest, bystander CPR, first monitored rhythm, use of active mechanical CPR, Time to ROSC, cause of the arrest etc.</i>	•			
Medical background data <i>collected by Charlson comorbidity index, pre-arrest frailty score, pre-arrest mRS score, and information on previous cardiac disease; PCI, CABG, known cardiomyopathy, ICD, atrial fibrillation or flutter, hypertension with pharmacologic treatment</i>	•			
Days at ICU	•			
Days at hospital	•			
Native language other than the test language (yes/no)			•	•
Difficulties that may interfere with the test results; <i>non-correctable problems with hearing, vision, speech, dyslexia, paresis, other</i> (yes/no)			•	•
Memory problems prior to cardiac arrest (yes/no)			•	•
Known neurological disease (yes/no)			•	•
Education level based on an international standard classification of education by UNESCO			•	•
Living situation (<i>married/living as married/or living alone</i>)			•	•
Current place-of-stay		•	•	•
Occupational status prior to cardiac arrest			•	•
Current occupational status, and time-point for return-to-work			•	•
Rehabilitation provided			•	•
Cardiovascular risk by the <i>Framingham coronary heart disease risk score(=age, gender, smoker, total cholesterol, HDL cholesterol, systolic blood pressure, on medication for hypertension, diabetes), BMI, HbA1C and frequency of physical activity</i>			•	•
General physical function by the Timed Stands Test			•	•

Abbreviations: CPR = Cardio Pulmonary Resuscitation, ROSC = Return of Spontaneous Circulation, mRS = modified Rankin Scale, PCI = Percutaneous Coronary Intervention, CABG = Coronary Artery Bypass Grafting, ICD = Implantable Cardioverter Defibrillator, ICU = Intensive Care Unit, UNESCO = United Nations Educational, Scientific and Cultural Organization, HDL = High Density Lipoprotein, BMI = Body Mass Index.

follow-ups at six and 24 months are performed as face-to-face interviews in a clinical setting. Alternative follow-up strategies; such as visiting the participant's place of residence or interview by telephone are used to avoid missing data. Since some tests are impossible to perform by telephone, this approach is only used when no other options are available. As a last resort, information may be provided by a proxy.

Procedures

Blinded outcome assessors e.g. occupational therapists, psychologists, physiotherapists, physicians or research nurses distribute the assessment tools in a pre-specified order according to the follow-up manual. The duration of the 6 and 24-months follow-up visit is approximately 40–60 min. For participants who are unable to speak the local language, an authorised interpreter is used.

Efforts to increase inter-rater reliability include the use of psychometrically sound measures, a written follow-up manual (<https://ttm2trial.org/documents>) and a four hour training session for outcome assessors. A central coordinator provide support during the study and review the outcome data at regular intervals to check for completeness and data-quality.

Outcome assessments

Instruments to assess secondary and exploratory outcomes (Table 1) were chosen based on their ability to capture the outcomes of interest, acceptable psychometric properties, and previous use in Cardiac Arrest (CA) and brain injury. In addition, instruments should be extensively translated and not too time consuming. The choice was

further informed by the recommendations for a Core Outcome Set after Cardiac Arrest (COSCA) to allow for comparisons with other CA-trials.¹²

Secondary outcome assessments

Modified Rankin Scale (mRS) is a clinician-reported ordinal rating scale representing an overall view of functional outcome after a neurological event or condition, previously used in a number of CA-trials.¹² It has seven categories, ranging from 6 = dead to 0 = no symptoms; including both information on survival, limitations in basic or instrumental daily activities, restrictions participating in normal social roles and effects of physical, cognitive and emotional symptoms. Substantial inter-rater variability was reported for the mRS, when used by multiple raters and sites,¹³ but reliability improves with a structured approach.^{13,14} In the TTM2-trial the mRS will be based on a structured interview with nine questions (mRS-9Q), and a web-based scoring tool (www.modifiedrankin.com).¹⁴ Information for the mRS is collected from several reporters; the participant, observer (e.g. relative or close friend) and the outcome-assessor.

*EuroQol 5 Dimensions 5 Levels response version (EQ-5D-5L)*¹⁵ is a patient-reported generic-HRQoL questionnaire with five questions/dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) together with a visual analogue scale (VAS) of self-reported health (0–100 = best health possible).¹⁵ Each dimension has five levels of scoring, from no problems (1) to extreme problems (5) and is used to present a descriptive health profile (scores ≥ 2 indicate problems),¹⁵ or converted to a single value of health (EQ-5D-5L index). The EQ-5D-5L index facilitates statistical analyses and can be used to calculate quality-adjusted life years

Table 3 – Questions for self-reported physical activity in the TTM2-trial.

Questions on physical activity		
Question 1 (Q1)	<i>In the last week, how many days have you engaged in moderate physical activity for at least 30 min a day? (could be performed in blocks that last for at least 10 min adding up to a total of 30 min or more)</i>	
<i>Physical activity</i>	<i>Note: Moderate activities means pursuits that requires to a moderate level of effort and noticeably increase in heart rate. Examples includes a brisk walk, rigorous cleaning, washing windows, cleaning the car, carpentry, bicycling with light effort, golf, swimming or similar. For more examples see Haskell et al. 2007. Circulation.</i>	
Question 2 (Q2)	<i>In the last week, how many days have you engaged in vigorous (intense) aerobic physical activities for at least 20 min (in one block)?</i>	
<i>Physical training</i>	<i>Note: Vigorous or intense aerobic physical pursuits are activities that lead to substantial increase in heart rate and rapid breathing. Examples of activities at this level include jogging, running, walking very briskly, shovelling/digging, cycling with a moderate effort/fast, swimming moderately/hard, tennis or similar. For more examples see Haskell et al. 20007. Circulation.</i>	
Categorization of physical activity		
Physical activity below recommended levels for primary and secondary prevention	Sedentary	<5 on Q1 <3 on Q2 =less than 150 activity minutes in a week
Physical activity to a level recommended for primary prevention	Physical activity	≥5 on Q1 OR ≥3 on Q2
Physical activity to a level recommended for primary, and secondary prevention after coronary artery disease	Physical training	≥2 on Q1 AND ≥3 on Q2

(QALYs) in health-economic evaluations.¹⁵ The EQ-VAS is reported separately. When a patient is unable to report their health (e.g. severe neurological impairment/lack of awareness) proxy-completion is allowed.

Exploratory outcome assessments

Glasgow Outcome Scale Extended (GOSE) is a clinician-reported global outcome scale to describe functional outcome after brain injury.¹⁶ GOSE is an extended version of the Glasgow Outcome Scale (GOS), developed to decrease ceiling-effects and increase discrimination in the upper levels of recovery.¹⁷ GOSE has 8 categories ranging from 1 = dead to 8 = upper level of good recovery, preferably defined using a structured interview^{16,17} and information from several sources.¹⁷ For TTM2 the structured GOSE interview was modified from its original wording of “injury” to read “cardiac arrest”. In addition to the total score, the structured interview includes descriptive information regarding pre-arrest function, and the most important factor for the outcome (brain injury or other). GOSE can be converted to a simple GOS,^{16,17} which corresponds to the much used, but criticized,¹² Cerebral Performance Category (CPC)-scale.

*Montreal Cognitive Assessment (MoCA)*¹⁸ is a cognitive performance-measure, reported to perform well for cognitive screening after cardiac arrest (CA),¹⁹ and recommended in current guidelines.²⁰ The MoCA consists of 11 sub-tests of six cognitive domains; short-term memory, attention, working memory, visuo-spatial ability, executive function and language, all summed into a composite score of global cognitive function (0–30 points, higher is better). Scores <26 indicate cognitive impairment. Test-retest reliability for the MoCA is excellent (0.92).¹⁸

*Symbol Digit Modalities Test (SDMT)*²¹ is a cognitive performance-measure of mental processing speed and attention, considered as one of the most sensitive tests to identify effects of brain injury,²¹ which possibly also includes OHCA-specific cognitive impairment.² The combination of MoCA and SDMT increased the sensitivity of cognitive screening.²² In TTM2 the oral version of the SDMT is used,²¹ and the written version only employed in cases of speech or language

problems. Test-retest reliability of the SDMT is 0.76 for the oral version.²¹

Life Satisfaction is reported by a single item from the World Values Survey (www.worldvaluessurvey.org) used together with a VAS scale (0–10 = completely satisfied). This question reflects the patients' subjective overall satisfaction with life.

Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest version (IQCODE-CA)^{23,24} is an observer-reported questionnaire to investigate change/decline of performance in 26 everyday activities related to cognitive function,²³ modified to better suit a CA context (IQCODE-CA).^{24,25} IQCODE-CA does not involve participation from the patient, and information on outcome can also be obtained for participants who do not speak the local language or have severe cognitive impairment.

Two Simple Questions (TSQ) was developed to assess the patient's own perception of mental recovery and dependency in daily activities after CA.^{25,26}

Return-to-work is studied by collecting information on the patient's occupational status before the index hospitalization and at time of the follow-up.

Clinical characteristics

Patient characteristics are obtained at several time-points (Table 2). At both the 6 and 24-months follow-up objective information of the participants' general physical function and current cardiovascular risk is collected. General physical function is measured by the *Timed-Stands Test (TST)*,²⁷ assessing lower-limb function by recording the time required for the participant to rise 10 times from a chair to a standing position (shorter time = better).²⁷ Cardiovascular risk is assessed by the Framingham coronary heart disease risk score,²⁸ Body Mass Index (BMI), HbA1C, and physical activity. Physical activity is measured by two self-reported questions created for the TTM2-trial (Table 3) based on recommendations for primary and secondary cardiovascular prevention.²⁹ These questions will be validated in a TTM2 sub-study on physical activity (Clinicaltrials.gov NCT03543332).

Statistical methods

The primary and secondary outcomes of the TTM2-trial will be reported in the main paper.⁵ The exploratory outcomes presented here will be reported separately focusing on the OHCA-survivors at six months.

The comparisons of detailed outcomes for OHCA-survivors in the two intervention groups will be restricted to global cognition (total MoCA score, 0–30), mental processing speed/attention (SDMT raw score, 0–110) and societal participation (GOSE score, 1–8) to limit problems with multiplicity. In the first analyses all participants will be included to avoid survival bias. For MoCA and SDMT, deceased participants will be assigned a score lower than the lowest possible for survivors, and for all analyses (MoCA, SDMT, GOSE) the non-parametric van Elteren test will be used, stratified by site.

The second analyses will include survivors only, and mixed effects ordinal regression will be used for the GOSE, and mixed effects linear regression models for the MoCA and SDMT. Analyses will be performed adjusted for site (random intercept) and co-enrolment in TAME cardiac arrest trial.⁵ As the balanced allocation by the randomisation process may no longer be valid due to differences in mortality, additional analyses will be performed including also adjustment for age, sex, education, and pre-arrest clinical frailty score (1–4 vs. 5–9). An alpha value of <0.05 will be used to indicate statistically significant results without any further adjustment for multiplicity due to the exploratory design. In addition to statistical significance, effect measures will be reported.

Sensitivity analyses taking the distribution of missing data into account will be considered.³⁰

By using the survival rate assumed in the primary outcome⁵ we estimate the sample size for the exploratory outcome analyses of the survivors to be approximately 900. The estimated power will then be 99% for the MoCA assuming a minimal important difference (MID) of 2,^{31,32} and a standard deviation (SD) of 3 (based on data from patients with mild cognitive impairment).³² For the SDMT the power will be 85% using data from the TTM1-trial,² and a Cohens *d* of 0.2 to represent a MID. Power calculations for the MoCA and SDMT are based on unadjusted linear regression.

Descriptions of MID for the GOSE are rare. For the similar categorical scale mRS, small absolute differences as low as 1.1–1.5% have been suggested clinically relevant for the transition from poor to good functional outcome,³³ although differences of 5–10% were also suggested.³³ Using both thresholds, data from the TTM1-trial and ordinal regression provided an OR = 1.2 for the lower MID (1.5%) with a power of 32%, and a OR = 1.6 for the higher MID (5%) with a power of 97%.

To facilitate interpretation of the results, categorical information of each assessment (GOSE, MoCA, SDMT) will be presented descriptively based on pre-specified cut-off values for the MoCA and age and education adjusted z-scores for the SDMT. Descriptive information will be presented stratified by the intervention groups, but without further testing of statistical significance. The other outcomes (IQCOC-CA, TSQ, Return-to-work and Life Satisfaction) will be presented to provide supplementary information from a more general perspective on outcome of OHCA-survivors only. Clinical data and patient characteristics of importance to interpret the results will be reported.

For all analyses categorical values will be presented as both numbers and percentages, and for the continuous values median (IQR) and/or mean (SD).

The analyses of the 24-month outcome data will be reported separately.

Discussion

This paper presents the design and rationale of the TTM2-trial follow-up, where information on secondary and exploratory outcomes will be collected. We also present the explorative outcome analyses which will focus on neurocognitive function and societal participation in OHCA-survivors. The TTM2 follow-up design complies with current recommendations that resuscitation trials focusing on the quality-of-survival should report neurological function and long-term outcomes at 3-months post-arrest or later, and preferably include more detailed neurocognitive testing and patient-reported HRQoL.^{12,34,35}

A major strength of the TTM2-trial is the size of the trial and the global distribution of participating sites. This will provide unique information on outcome related to temperature control, but also regarding outcome of OHCA-survivors in general. However, a concern for large clinical trials is that multiple outcome-assessors and sites may increase variability, decrease inter-rater reliability, and potentially bias the results.³⁶ A major focus of the TTM2 follow-up design is therefore to use a well-defined structure for outcome-reports, further supported by training and central feed-back. This approach is expected to increase inter-rater reliability and provide more granularity in the scoring within the good outcome categories by the mRS and the GOSE, but may impair the comparisons with other studies using a less detailed approach. Analyses where participants are dichotomized into good or poor outcome, are still assumed to be comparable.

The mRS is currently the recommended measure for overall functional outcome after CA.¹² The mRS was designed to measure outcome after stroke, with a large focus on mobility problems. The GOSE was developed with a focus on the non-physical aspects of brain injury and societal participation, but also includes a score that corresponds to vegetative state.¹⁶ GOSE was suggested as a potential outcome measure after CA,³⁴ but it is currently used less than the mRS and not recommended to be used alone.¹² Our inclusion of both scales will provide information that may inform future recommendations.

It is recommended to include the patient's perspective on outcome in resuscitation trials.^{12,34,35} There is currently no patient-reported outcome measure (PROM) specifically designed for CA, but the EQ-5D-5L has been suggested.¹² EQ-5D is the most used PROM worldwide, and also extensively used after CA.³⁷ The popularity of the EQ-5D is related to its brevity and ease of use, important features in a sample at high risk of cognitive impairment, such as OHCA-survivors. The updated version with 5 levels of responses (EQ-5D-5L) has improved psychometric properties,¹⁵ but has not yet been tested in OHCA-survivors.³⁷ A high ceiling effect for the original EQ-5D-3L (46%) was reported also for CA-survivors, but it decreased (26%) when proxy reports were included.³⁸ This indicates that exclusion of poor outcome survivors in OHCA-trials may bias the results by overestimating outcome.³⁷ The TTM2-trial will allow for proxy completion of the EQ-5D-5L when necessary.^{12,37}

Since neither functional outcome measures (mRS, GOSE) or generic PROMs (EQ-5D-5L) provide detailed information on neurocognitive function, it is recommended to add condition/function-specific assessments.¹² This may be especially important when neuro-protective effects are investigated so that clinically important information is not lost. Detailed neurocognitive testing is impractical in a large international trial. We therefore chose two simple

neurocognitive assessments (MoCA, SDMT) that are widely used and recommended for cognitive screening after CA.²⁰ Whether they are sensitive enough will be further tested in a TTM2-sub-study using more extensive neuropsychological tests (ClinicalTrials.gov NCT03543371).

Cognitive performance measures in the TTM2-trial are combined with subjective reports from the patient and the observer perspective, as recommended by the US Food and Drug Administration (FDA).³⁹ Observer and patient-reports may be a sensitive approach to identify mild cognitive decline, although these reports may also be influenced by problems unrelated to brain injury, such as symptoms of depression.^{9,24} The subjective reports of the TTM2-trial will therefore be reported as descriptive information, without the intention to analyse causality.

The optimal time-point to evaluate OHCA-survivors' final outcome is unknown. With increasing time more participants may be lost to follow-up and other factors, unrelated to the initial arrest, may influence results. The first outcome-report in the TTM2-trial at 30-days post-arrest is in line with the COSCA-recommendation,¹² but this is too early to reflect the participants' long-term outcome and return to a normal life cannot be assessed. Also the second time-point suggested by the COSCA,¹² at 90-days, is assumed too early¹² and will not be used in the TTM2-trial. The COSCA-recommendation further support HRQoL assessments at 6-months and/or 1-year.¹² In the TTM2-trial all main analyses will be performed at 6-months after the CA based on neurological recovery and societal integration.^{7,8,10} A few previous smaller studies report that, at a group level, neurocognitive outcome after CA did not change between 3- and 12-months,^{7–9} but at an individual level remained stable, improved or declined. The 24-months follow-up will offer novel information on long-term prognosis of OHCA-survivors and complement the main follow-up.

The progressive cognitive decline seen in some OHCA-survivors may be associated with their cardiovascular burden. A high Framingham cardiovascular risk score is associated to increased cognitive decline⁴⁰ in the same domains typically impaired after CA.^{2,3} In line with this reasoning we previously reported similar levels of cognitive impairment among OHCA-survivors and myocardial infarction controls.² To explore the potential association between long-term cognitive impairment and cardiovascular risk-factors in OHCA-survivors is important, both for the design of follow-up programs, but also for the interpretation of responsiveness regarding effects of a neuro-protective intervention in the acute-phase.

Conclusion

This paper describes the choice of outcome measures and follow-up design of the TTM2-trial, a large international multi-centre research collaboration. Outcome assessments with established psychometric properties and a solid evidence-base were selected to capture the outcomes of interest in a pre-planned, well-defined, structured and standardised approach. This will potentially increase data-quality, decrease missing data and provide optimal conditions to investigate clinically relevant results of TTM for the OHCA-survivors' neurocognitive function, health and societal participation.

Conflicts of interest

GL, SU, EBN, JD, KH, JCJ, HL, CC, GME, JH, HK, PN, MO, PP, CR, MS, TC reports conflicts of interest: None

NN, AC, PY and FST reports receiving speaker's fees from Bard Medical

HF: Scientific advisor QuickCool

CL: Critical Event Committee Edwards Lifesciences

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FST has received lecture fees from ZOLL

MS: has performed advisory board and educational activities for Bard and his institution has received unrestricted grants for these services.

RH reports educational activities and receiving speaker's fees and travel support from BARD medical and Zoll, and advisory board of the INTREPID trial

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