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Personalising Outcomes after Child Cardiac Arrest (POCCA): design and recruitment challenges of a multicentre, observational study

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ABSTRACT

Introduction Blood and imaging biomarkers show promise in prognosticating outcomes after paediatric cardiac arrest in pilot studies. We describe the methods and early recruitment challenges and solutions for an ongoing multicentre (n=14) observational trial, Personalising Outcomes following Child Cardiac Arrest to validate clinical, blood and imaging biomarkers individually and together in a clinically relevant panel.

Methods and analysis Children (n=164) between 48 hours and 17 years of age who receive chest compressions irrespective of provider, duration, or event location and are admitted to an intensive care unit are eligible. Blood samples will be taken on days 1–3 for the measurement of brain-focused biomarkers analysed to predict the outcome. Clinically indicated and timed brain MRI and spectroscopy biomarkers will be analysed to predict the outcome. The primary outcome for the trial is survival with favourable (Vineland Adaptive Behavioural Scale score >70) outcome at 1 year. Secondary outcomes include mortality and pre-event and postdischarge measures of emotional, cognitive, physical and family functioning and health-related quality of life. Early enrollment targets were not met due to prolonged regulatory and subcontract processes. Multiple, simultaneous interventions including modification to inclusion criteria, additional sites and site visits were implemented with successful improvement in recruitment. Study procedures including outcomes and biomarker analysis are ongoing.

Ethics and dissemination Twelve of 14 sites will use the centralised Institutional Review Board (IRB) at the University of Pittsburgh (PRO14030712). Two sites will use individual IRBs: Children's Healthcare of Atlanta Institutional Review Board and Children's Hospital of Wisconsin IRB. Parents and/or guardians are consented and children assented (when possible) by the site Primary investigator (PI) or research coordinator for enrollment. Study findings will be disseminated through scientific conferences, peer-reviewed journal publications, public study website materials and invited lectures.

Trial registration number NCT02769026.

Strengths and limitations of this study

- This study will be the first to validate blood and imaging biomarkers to prognosticate outcome following pediatric cardiac arrest.
- Outcomes important to all stakeholders—physical, cognitive and emotional health and health-related quality of life—will be assessed.
- Findings may assist to identify children at risk for neurological morbidity, monitor response to targeted therapies, guide critical care and rehabilitation strategies and discover innovative biomarkers leading to breakthrough therapeutics to improve outcome.
- Results from Personalising Outcomes following Child Cardiac Arrest may be useful to incorporate into the study design of trials to improve the conduct of successful interventional trials in children with cardiac arrest.
- Limitations of the study include the potential impact on results given the heterogeneity of the pediatric cardiac arrest population.

INTRODUCTION

Background

Children with cardiac arrest have mortality and morbidity rates of 70%–90%, largely due to global hypoxic–ischaemic neurological injury.[1 2] Accurate information on prognostication is necessary for clinical decision-making by families and providers. Current tools to assess prognosis including laboratory and imaging tests are inadequately validated; neurological examination is frequently hampered by medication effects or developmental stage.[3–5] The American Heart Association paediatric prognostication guidelines suggests that 'Providers must consider multiple variables when attempting to prognosticate outcomes during and after cardiac arrest. Although there are factors associated with better or worse outcomes, no single

factor studied predicts outcome with sufficient accuracy to recommend termination or continuation of CPR or to enable prognostication after postreturn of spontaneous circulation (ROSC)'.[6] Thus, validation of multimodal assessment is needed in paediatric cardiac arrest.

Further, accurate characterisation of brain injury may facilitate utilisation of neuroprotective interventions and study criteria for entry into personalised trials with targeted interventions. As a case in point, every successful randomised clinical trial (RCT) of neuroprotective therapies has used targeted entry criteria to search for groundbreaking interventions that improve outcomes.[6 7]

Blood and brain MRI-based biomarkers are promising tools to evaluate in validation studies.[8 9] Studies evaluating blood and MRI biomarkers often have small sample sizes or were tested other populations—adults with cardiac arrest, newborns with hypoxic–ischaemic encephalopathy or patients with traumatic brain injury.[10 11] Evidence suggest that biomarker concentration vary by sampling site, cell origin, patient age, developmental status, time from event and condition and thus should be prospectively evaluated.[12] Our and other investigators' work in paediatric cardiac arrest patients found that specific blood-based brain injury biomarkers and brain MRI and spectroscopy (MRI/S) biomarkers performed well in univariate analyses to prognosticate outcome.[13–18] We propose to validate and model the best performing blood and imaging biomarkers of brain injury and assess their accuracy in combination with clinical variables in classifying outcome after paediatric cardiac arrest in a multicentre, observational trial. Further, we will include an exploratory analysis of a brain-specific mitochondrial cardiolipin (CL) that when measured in the blood predicted outcome in adults with cardiac arrest and may have utility as a therapeutic target.[19] This manuscript describes the study design, trial management and oversight for the Personalising Outcomes after Child Cardiac Arrest (POCCA) trial.

Finally, recruitment and retention in studies of critically ill children are fraught with under-enrollment, early termination and low power.[20 21] Thus, we discuss our experience with early recruitment challenges and solutions implemented that resulted in meeting our enrollment goals as well as steps taken to achieve maximal retention as we secure 12-month outcomes.

METHODS

Objectives and hypotheses

We hypothesise that blood and imaging biomarkers of brain injury together with clinical variables will optimise outcome classification after paediatric cardiac arrest. We are testing our hypothesis in a prospective multicentre study in paediatric cardiac arrest (~14 sites, 164 subjects). Validated functional health and health-related quality of life outcomes important to patients and families will be assessed. POCCA has three specific aims:

Aim 1: Determine the accuracy of serum biomarkers of neuronal (neuron-specific enolase (NSE), ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCH-L1)) and glial (S100b, glial fibrillar acidic protein (GFAP)) injury to classify favourable outcome at 1 year postcardiac arrest. We hypothesise that these biomarkers will have high sensitivity and specificity for the early classification of favourable outcome at 1 year (postcardiac arrest Vineland Adaptive Behavioural Scale (VABS) score >70). Further, we will perform an exploratory study of the accuracy of innovative blood biomarkers of brain mitochondrial injury (CL and oxidised cardiolipin (CLox)) to classify outcome in a subset of patients.

Aim 2: Define the accuracy of regional (occipital–parietal cortex, basal ganglia and thalamus) brain MRI (T1/T2 and diffusion-weighted imaging (DWI)) and MRS (N-acetylaspartate (NAA), lactate) biomarkers to classify favourable outcome at 1 year postcardiac arrest. We hypothesise that regional MRI/S biomarkers of brain injury will strongly classify outcome at 1 year.

Aim 3: Evaluate the combination models of blood and imaging biomarkers of brain injury and clinical variables to classify favourable outcome at 1 year postcardiac arrest. We will consider inclusion of clinical variables associated with outcome after cardiac arrest in children such as witnessed status and first rhythm.[1 22] We hypothesise that the combination of a novel panel of blood and imaging biomarkers and clinical variables will optimise early outcome classification accuracy at 1 year.

Design, participants and timeline for biomarkers and outcomes sampling

Study design and funding

POCCA is a 5-year multicentre, observational study funded by the National Institute of Neurological Disorders and Stroke (R01 NS096714; Principal Investigator: Fink; Study Protocol 1.9 10/08/19) and supported by the Coordinating Center at the Epidemiology Data Center, University of Pittsburgh (Co-I Fabio) (figure 1). Participating sites each confirm adequate numbers of potentially eligible patients, have a physician champion to serve as site primary investigator and a research coordinator and have the ability to perform the blood, imaging and outcomes protocols.

Participants

Inclusion criteria

Includes children with cardiac arrest between 48 hours and 17 years of age. Cardiac arrest is defined as 'receipt of chest compressions irrespective of provider (healthcare worker, lay bystander) duration of compressions, or event location' to capture the full breadth of the range of neurological outcomes. Children will be admitted to a paediatric or cardiac intensive care unit (ICU) within 24 hours post-ROSC and have a precardiac arrest Paediatric Cerebral Performance Category score of 1–3 (no, mild or moderate disability). Caregivers are required to be fluent in either English or Spanish, the two languages available

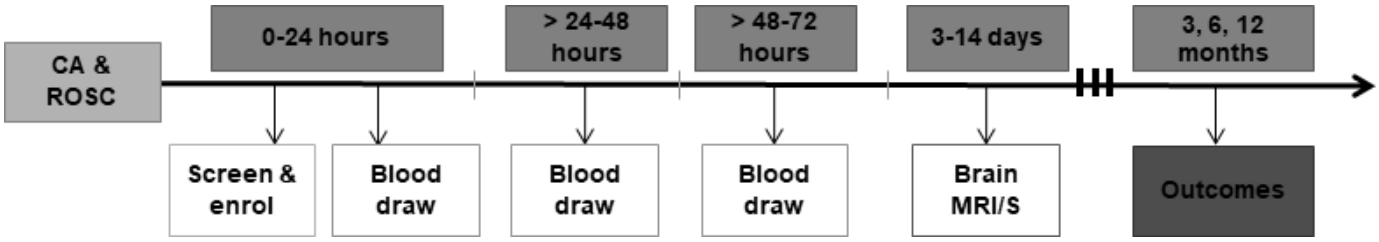

Figure 1 Personalising Outcomes after Child Cardiac Arrest study design. CA, cardiac arrest; ROSC, return of spontaneous circulation; MRI/S, MRI and spectroscopy.

for the VABS 3. Final adjudication on whether the child had a cardiac arrest will be determined by the site primary investigator.

Exclusion criteria

Includes children with active care limitations such as do not resuscitate, in foster care or the judicial system, pregnancy, actively undergoing brain death evaluation procedures, unable to obtain blood sample within 24 hours post-ROSC or other exclusionary factors as determined by the site investigator.

Recruitment

All sites will screen ICUs daily for eligible participants. Screening is completed using various methods including chart reviews internal paging systems, code sheets, charge nurse reports or daily census queries. Attending physicians will be asked for permission to approach patient parents/guardians if the child is not in the care of the site investigator. We anticipate consent rates of 60%–70% based on our prior single-site study and other trials in cardiac arrest.[10 23 24] Because families with children admitted to the ICU following cardiac arrest are under such great stress, we have a broad consenting window if a blood sample from day 1 could be secured. In addition, training will include a consenting approach that is empathetic, patient and informative.

Data collection

Clinical data, demographics, medical history, cardiac arrest details, clinical imaging, clinical course and outcomes will be collected and entered by the clinical site coordinator via a secure web-based Data Management System into the research database. The data system can be accessed using a login and password-protected portal located on the study website (https://pocca.ccm.pitt.edu/). Tracking materials with participant identifiers needed for later contact to obtain outcome assessments will be kept at the clinical site only and will not be entered as part of the research database. Data quality will be monitored and validated at entry and postprocessing by the Data Coordinating Centre. Postprocessing data validations will be performed on a biweekly basis and sent to study coordinators through the data system for resolution. Monitoring of visit completeness and enrollment status are provided via weekly reports that will be emailed to the site PIs and study coordinators.

Patient and public involvement

No patients or families are involved in the design of this study. Families will be mailed a copy of the primary manuscript once accepted for publication.

Primary outcome

The primary outcome variable is survival with favourable (VABS score >70) outcome scores at 1 year.[25] The VABS has been used previously in RCTs in paediatric cardiac arrest to assess the child's independent functioning in their environment.[23 24]

Secondary outcomes

Hospital mortality, and emotional, cognitive and physical functioning and health-related quality of life (table 1). Parent and child reported outcomes are administered by site investigators and/or coordinators using in-person interview at ICU admission and mixed methods (eg, in-person, phone, mail) to assess outcomes at 3, 6 and 12 months.

The POCCA Outcomes Manual includes best practices and all persons administering outcomes will be trained prior to use.[26] Outcomes and instruments in POCCA were chosen because they are feasible to deploy and are responsive to family preferences (eg, emotional and adaptive functional health and health-related quality of life) and common morbidities following cardiac arrest (table 1).[23 24 27 28] Multiple time points are helpful to retain subjects and analyse recovery trajectories. Precardiac arrest measures are administered following consent with the primary caregiver. Posthospital discharge (3, 6 and 12 months) outcomes are administered over the phone or at the time of a scheduled outpatient visit, preferably with the same respondent. Families that are non-responsive to these attempts are given the option to mail in completed outcomes forms with prepaid postage. Reliability codes are completed for each subject and time point. Outcomes will be collected and scored by site investigators and coordinators and then sent to the study's primary coordinator for review for quality.

The Glasgow Outcome Score—e-Peds, initially validated in paediatric traumatic brain injury, is being evaluated as an outcome measure for the first time in paediatric cardiac arrest.[29] The Functional Status Scale is a validated tool developed to consider six health domains in hospitalised children that will be assessed longitudinally for

Table 1 Primary and secondary outcomes

Instrument	Domain (estimated time to complete in minutes)	Data source	Time points
Vineland Adaptive Behavioural Scale, Parent/Caregiver Rating Form	Independent functioning[30–40]	Subject/caregiver	Enrollment (pre-CA) 1 year post-CA
Paediatric Cerebral Performance Category	Neurological outcome[5]	Subject/caregiver/medical records	Enrollment (pre-CA), HD, 6–12 months post-CA
Glasgow Outcome Score—e-Peds	Global outcome[15–20]	Subject/caregiver/medical records	3, 6, 12 months post-CA
Paediatric Quality of Life Inventory TM	Health-related quality of life[5]	Subject/caregiver	1 year post-CA
Child Behaviour Checklist and Parent Self-Report	Cognitive and emotional health[10–20]	Subject/caregiver	1 year post-CA
Functional Status Scale	Functional status[5]	Subject/caregiver/medical records	3, 6, 12 months post-CA

CA, cardiac arrest; HD, hospital discharge.

the first time in a multicentre paediatric cardiac arrest study.[30]

Blood-based biomarkers

Sites will collect and process 3–5 mL blood (3 mL for <10 kg participant, 5 mL for ≥10 kg participant) at three time points after ROSC: 0–24 hours, >24–48 hours and >48–72 hours (minimum of 12 hours between samples). Most sites are able to obtain one blood collection sample prior to the consent, to be disposed of if informed consent for the study cannot be obtained prior to the end of the second timed collection. If a preconsent sample cannot be drawn, sites may collect surplus blood from their hospital's laboratory if the sample collection is within 24 hours post-ROSC. Each site is provided with materials for processing and shipping specimens. Sites are responsible for deidentifying, labelling and shipping the samples to the centralised processing lab.

Our preliminary data showed that serum biomarkers of neuronal injury (NSE, UCH-L1) and glia (S100b, GFAP), were strongly linked with the outcome and will be examined in POCCA.[13 17] GFAP and UCH-L1 were Food and Drug Administration-approved as a brain trauma assessment tests that may translate into future point-of-care testing availability[31] (https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-first-blood-test-aid-evaluation-concussion-adults). Other biomarkers demonstrating the potential for prognostication following the cardiac arrest that may be evaluated in POCCA include neurofilament light chain, tau, myelin basic protein and inflammatory cytokines and chemokines.[32 33] We plan an exploratory investigation into the prognostication accuracy of brain mitochondria-specific CL and CLox, biomarkers developed by our collaborators.[34 35] Finally, families could opt-in for genetic biomarker analysis in which a blood clot remaining from blood biomarker processing procedures is banked for future analysis.

Brain MRI/S

Published preliminary data by our group and others as well as our group's expertise in multicentre imaging harmonisation guide our imaging approach to validate imaging biomarkers. Further, we focused on brain regions that are classically vulnerable to hypoxic–ischaemic injury. In our preliminary study of 23 children admitted to our pediatric intensive care unit (PICU) postcardiac arrest who had a brain MRI/S within 14 days post-ROSC, we found that the most frequent T2-weighted lesions were in the lentiform 15 (68%) and caudate (55%) nuclei of the basal ganglia and thalamus (50%). The most frequent lesions DWI were in the lentiform nucleus (41%), thalamus (32%) and frontal and parietal lobes (30%) each.[18] MRS Lactate and NAA are MRS biomarkers of energy failure and neuronal injury, respectively, that will be assessed in POCCA for prognostication accuracy.[16] In our pilot study, children with unfavourable outcome had increased lactate and decreased NAA concentrations in the parietooccipital grey matter and decreased NAA in the parietal white matter compared with those having favourable outcome at hospital discharge.[18]

POCCA's imaging protocol is featured in box 1. If clinically indicated, MRI/S will be preferably performed within 14 days post-ROSC, optimal for lesion identification and prognostication. In POCCA, T1, T2 and DWI will be analysed for signal intensity abnormalities and scored using a system adapted from Christophe.[36] Brain regions from both hemispheres will be examined for the severity of the injury. Interobserver variability will be described, disagreement resolved by consensus and kappa statistic reported.

Brain MRS was performed in four regions of interest: (1) basal ganglia, (2) thalamus, (3) parietal white matter and (4) parietooccipital grey matter (figure 2). Regions of interest placements will be verified by an experienced board-certified paediatric neuroradiologist. Raw MRS data

Box 1 Brain MRI protocol

Required sequences
- Conventional sequences: T1-weighted and T2-weighted.
- Diffusion-weighted.
- MR spectroscopy.
- Regions of interest: basal ganglia, grey and white matter occipital–parietal cortex, thalamus.
- Quality assurance protocol.

Timing
- One time imaging optimally performed 3–14 days postcardiac arrest.

Analysis
- Regional MRI lesion score.
- Regional MR spectroscopy quantification.

files will be transferred offline for fully automated post-processing using LCModel software (LCModel, Stephen Provencher, Ontario, Canada).[37] Absolute concentrations of Lactate and NAA will be determined using the unsuppressed water signal as an internal reference. LCModel processing provides objective measures for the signal-to-noise ratio and the spectral linewidth (full width at have maximum) for objective quality assessment. MRS measurements will be performed on one hemisphere due to the global nature of hypoxic–ischaemic injury and due to the additional imaging time required for MRS.

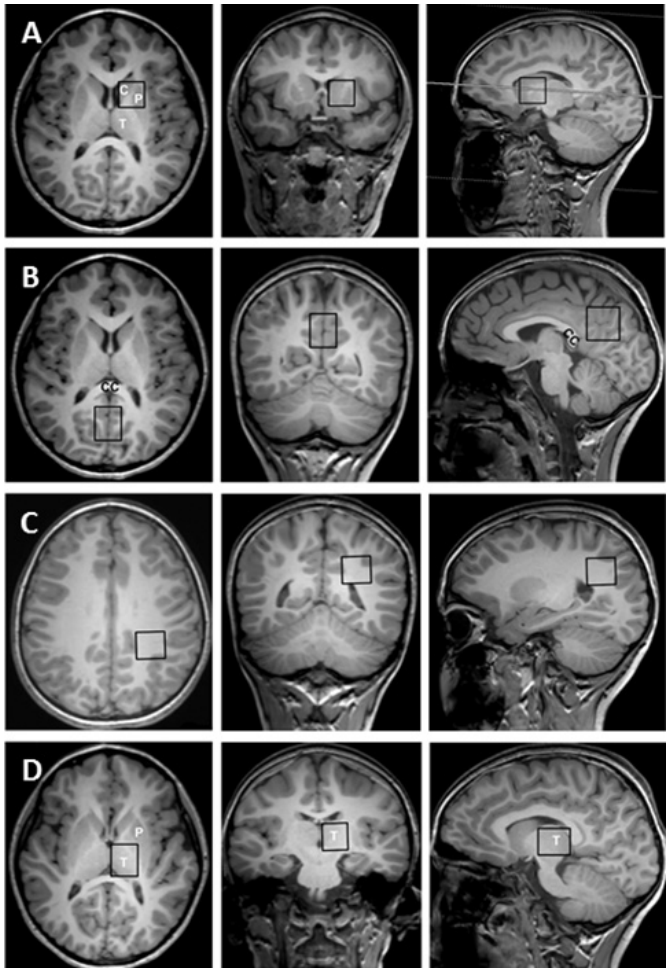

Figure 2 Magnetic resonance spectroscopy regions of interest. (A) Basal ganglia: caudate (C) and putamen (P); (B) parietooccipital grey matter; (C) parietal white matter and (D) thalamus (T). CC, corpus callosum.

All sites will perform brain MRI and some will perform MRS as an clinical standard of care to assist in prognostication. If a site participating in POCCA has not included MRS as a clinical standard of care, it can be completed as a research measure immediately following the clinically indicated MRI scan. All sites participate in a standard MRI quality assurance programme. Enrolled participants for whom the clinical team requests a brain MRI should first complete local MRI safety screening protocols as per site requirements. Imaging data will be uploaded to the study research cloud and stored for batch analysis.

Training procedures

Each site's study team includes a PICU physician and research coordinator responsible for POCCA study procedures. Site primary investigators and research coordinators will participate in startup meetings and complete a competency-based training programme and certification process prior to enrolling patients. This process includes a review of the study materials including the study protocol, Manual of Operations for data collection, outcomes and imaging and Data Management System and study training slides. After the review of materials, the site's study team (investigators, research coordinators, imaging personnel) will participate in start-up calls to review and provide training on the protocol and procedures associated with the study. The study team members are also required to participate in a hands-on data system training call. Prior to being able to screen participants, the study team members are required to demonstrate their understanding by completing a scenario-based certification case requiring a score of ≥95%. If a score was <95%, retraining is required and the certification process repeated until the score is ≥95%.

To assure protocol compliance, reinforce education and assess safety during the intervention period, monthly site investigator and coordinator calls will be scheduled. In addition, site visits will be conducted by the POCCA study investigator and project coordinator, the Data Coordinating Centre and the funding agency's scientific officer. Site visits will include a review of current screening practices, data collection, protocol compliance and a walkthrough of the clinical and research areas as well as a discussion of site-specific challenges and solutions focused on recruitment and retention. Issues identified prior to and during the site visit will be addressed and retraining provided as needed to assure compliance with the protocol.

Planned statistical analysis

Statistical approach

We will use propensity score adjustment to control for the large number of confounders, where comparisons of participants with similar scores detect variability based on the biomarker level in question while concurrently

controlling for the covariates that contribute to the propensity score.

To test whether there are distinctive patterns, descriptive summaries, including mean, median and SD of each blood and MRI/S biomarker (NSE, S100b, UCH-L1, GFAP, T1/T2, DWI, NAA and lactate) will be displayed overall and by the outcome at the 12-month endpoint. Receiver operating curves will be used to evaluate the effectiveness of classifying outcome for each marker separately. We will present the area under the curve data along with sensitivity and specificity for key values, including 80% and 90%. We put special focus on sensitivity vs specificity when different biomarker cut points are used to classify a participant as having a favourable vs unfavourable outcome. Propensity analysis will be used to control for confounding effects. In the case of continuous variables of interest, a stratified propensity score analysis will be employed, generating a propensity score for each participant from linear regression modelling (with the continuous exposure variable as dependent and the patient characteristics as independent variables). Five strata are sufficient to eliminate bias from measured confounders in most datasets. In general, the statistical models used to generate each propensity score will include demographic characteristics (eg, age, sex), clinical characteristics (eg, witnessed status, initial rhythm) and study site. Other approaches, such as direct adjustment, instrumental variables, marginal structural models and inverse probability weighting will be investigated, if necessary.

To test whether there are distinctive patterns of biomarker level over each time point, group-based trajectory analysis (TRAJ) will be performed using the PROC TRAJ Macro available in SAS software (V.9.2 of the SAS system for windows. Copyright (c) (2002–2008) SAS Institute).[38] To identify the number of distinct trajectories, we will use a combination of the Bayesian Information Criterion and clinical judgement. The comparison of alternative specifications of both the number and shapes of trajectories will be based on theoretical predictions and the comparison of the goodness-of-fit of alternative models such as the Bayesian. Two through five groups will be tested and we will choose the best model in conjunction with the statistical results as well as clinical judgement when models are statistically similar. The association of the trajectory variables will be assessed with outcome using multivariate logistic regression analysis. The dependent variable will be the VABS Composite score. Several different models will be tested. First, we will assess the predictive value of conventional neuronal and glial markers (NSE and S100b) for 12-month outcome. A second model will assess the ability of the commercial biomarkers (UCH-L1 and GFAP) to predict 12-month outcome. A third model will estimate the predictive value of the imaging variables (NAA, lactate, T1/T2 and DWI) to predict 12-month outcome. Finally, based on the results of these analyses, we will estimate the combined impact of the best fitting blood and imaging biomarker scores along with specific clinical variables when predicting 12-month outcome. Adjustment for confounders will be carried out by including the propensity score.

Clinical variables that will be tested for inclusion in the panel include those that have an association with patient outcome including pupil reactivity and motor response, age, witnessed status, initial rhythm, location of arrest, duration of pulselessness and site. Missing data will not be imputed.

Power analysis

To estimate the sample size required for this design, we made use of the probabilities obtained from our previous pilot studies involving serum biomarkers and imaging data. The lowest area under the curve probability from our pilot study involving these biomarkers was 0.74 and we would expect that probability to be 0.5 under the null hypothesis. This analysis assumed an even distribution of favourable and unfavourable outcome (which was observed on our pilot data) and a probability of type 1 error of 0.05. We base our sample size on combined logistic regression. A sample size of 164 achieves 80% power to detect an R^2 of 0.10 attributed to 15 independent variables (various combinations of trajectory groups with varying numbers of trajectories) using an F-test with a significance level (alpha) of 0.05. The variables tested are adjusted for an additional two independent variable (PS) with an R^2 of 0.10.

PRELIMINARY RESULTS

Trial status

The period necessary to complete central IRB regulatory approvals and ensuring site contractual agreements was prolonged, resulting in delayed opening to enrollment and early under-enrollment. Sites began screening and enrolling on May 2017 with all initial sites (except one site that withdrew due to the site PI departure from the institution) participating by January 2018 (figure 3).

To improve enrollment, we implemented numerous, simultaneous solutions in partnership with our NIH programme official. The intervention with the most objectively positive impact was opening enrollment to include in-hospital in addition to out-of-hospital cardiac arrest patients. To support this change in criteria, we requested sites provide us with updated data estimates for the annual number of paediatric in-hospital and out-of-hospital cardiac arrest patients to support new enrollment projections and milestones to meet the originally stated sample size goal. Nearly all sites reported that the frequency of in-hospital arrests outnumbered those occurring out-of-hospital, suggesting that inclusion of in-hospital cardiac arrest patients could significantly increase enrollment. Next, we submitted rationale to the NIH for study criteria modification including these data, noting that postarrest clinical care recommendations are similar for both cohorts and that study results would be more generalisable.[6] We subsequently obtained NIH approval to open enrollment to include in-hospital cardiac arrest patients, who ultimately

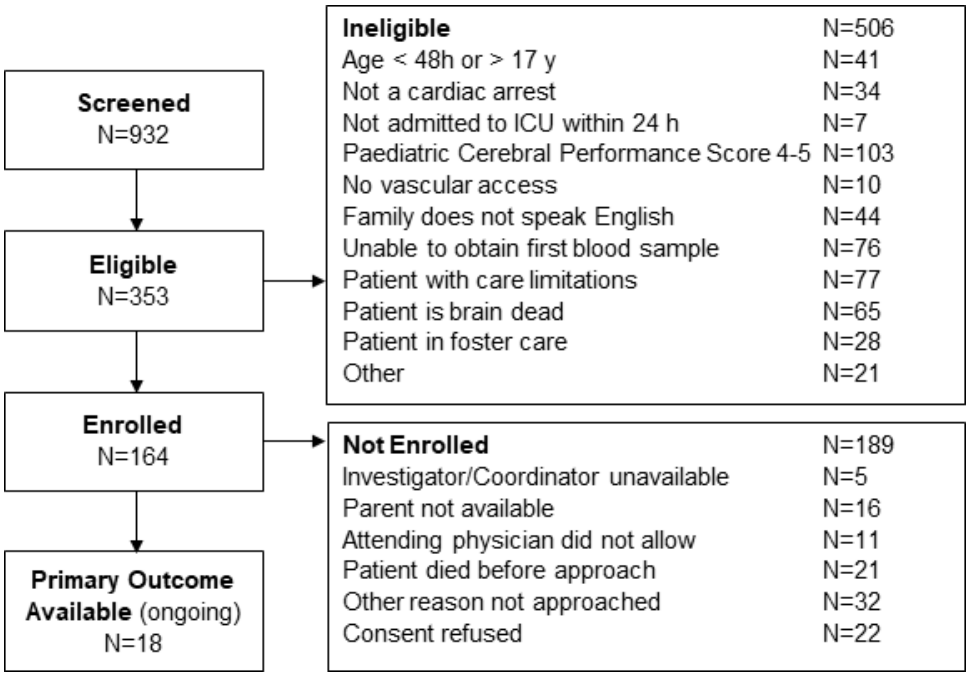

Figure 3 Diagram of patient participation through 7 February 2020. ICU, intensive care unit.

accounted for 74 of 164 (45.1%) of enrolled patients after IRB modification approvals were obtained.

Other key initiatives implemented to improve enrollment included: (1) primary investigator, coordinator and NIH Programme Officer in-person site visits that included talks on the science of POCCA, a remote session with the study's coordinating site team focused on steps needed for successful study participation (eg, enrollment, outcomes, specimens, imaging, data collection), and discussion of site-specific challenges and solutions (completed site visits: Phoenix Children's Hospital, Children's Hospital of Colorado, Johns Hopkins Children's Hospital, Children's National Hospital, Children's Hospital of Los Angeles, Children's Hospital of Philadelphia, St. Louis Children's Hospital, Nationwide Children's Hospital and Children's Hospital of Atlanta); (2) Addition of four new sites with evidence of sufficient cases and research resources along with required study team training, regulatory approvals and subcontracts; (3) Improved engagement and recruitment and retention retraining on monthly primary investigator and study coordinator conference calls with the support of our NIH Programme Officer; (4) Additional family payment for completed outcomes and (5) Addition of quarterly site progress reports and NIH enrolment/data reports.

Successfully implementation of these measures to improve recruitment in POCCA led to the full enrolment with 164 children recruited from 14 study sites in August 2019. Twelve-month outcomes are ongoing and blood is proceeding to support final data analysis.

DISCUSSION

Paediatric cardiac arrest is uncommon but not rare and high rates of death and disability are primarily due to global hypoxic–ischaemic neurological injury.[1 2] Early recognition of hypoxic–ischaemic brain injury is often obscured by medication effects or developmental stage in children and there is no test that accurately predicts outcome.[4 5] Further, under-recognised brain injury may delay the use and efficacy of neuroprotective interventions. Promising blood and brain imaging biomarkers may accurately prognosticate outcome in combination with clinical characteristics and neurologic examination findings, but require validation in adequately powered studies in children with cardiac arrest.[13 17 18 39] The multicentre POCCA observational trial aims to test and validate a highly accurate panel of clinical, blood and imaging-based biomarkers for early prognostication of neurological outcome in children with cardiac arrest.

Successful completion of these aims will generate accurate and reliably predictive multimodal outcome classification models critical to improving outcomes after a cardiac arrest that are of the highest importance to children and families. Children surviving cardiac arrest through ICU admission with an inclusive spectrum of expected outcomes enrolled in this study will have at least 1 and up to 3 days of blood biomarkers analysed on enrollment and many will have a clinical brain MRI/S performed according to a harmonised protocol. Our study team has a focus on retention to maximise the ability to attain a trajectory of outcomes through 1 year (especially our primary outcome at 12 months), encompassing domains important to families and societies—neurological, adaptive behaviour, health-related quality of life and emotional health—to relate to clinical, blood and imaging biomarkers.

Identifying an accurate panel of biomarkers may change the status quo for clinical prognostication, strengthening the confidence of families and clinician decision-making

in dealing with this challenging condition. Positive results may also encourage the translation of best performing innovative biomarkers to clinical use. Our findings may also assist to identify children at risk for neurological morbidity, monitor response to targeted therapies, guide critical care and rehabilitation strategies and discover innovative biomarkers leading to breakthrough therapeutics to improve outcome. Finally, results from POCCA may be useful to incorporate into trial study design to improve the conduct of successful interventional studies in children with cardiac arrest.

Study limitations include the limited number of covariates that can be included in a multivariable analysis given the heterogeneity of the paediatric cardiac arrest population. In addition, not all children surviving cardiac arrest will be considered clinically eligible for evaluation with brain MRI/S by the treating team although all enrolled children will have at least one blood biomarker set from the day of enrollment. Our study is limited to 1 year outcomes, which may not allow enough time to fully explore the future developmental impact of the cardiac arrest event.

ETHICS AND DISSEMINATION

Regulatory approval

Participating sites used a central Institutional Review Board (cIRB) at the University of Pittsburgh (n=12) or obtained local IRB approval for human subject research (n=2). This study was regarded as 'minimal risk' or 'greater than minimal risk' as determined by the imaging standard care at each centre. Sites using brain MRS post-cardiac arrest as the standard of care were deemed as 'minimal risk' and were required to obtain single parent/guardian signature for research consent. Those that did not use brain MRS as postcardiac arrest standard of care were deemed 'greater than minimal risk' due to the added risk of additional sedation and extended imaging time and were required to obtain dual parent/guardian signatures unless the parent/guardian was not 'reasonably available'. Parents and/or guardians were consented by the site PI or research coordinator for enrollment. Participating children's assent was sought if the child was able to be approached for assent. Participants turning 18 during the study and cognitively able to provide consent were approached for the consent of continued participation.

Study findings will be disseminated through scientific conferences, peer-reviewed journal publications, public study website materials and invited lectures. Results from this study will be reported according to STROBE guidelines and submitted for peer-reviewed publication (online supplemental appendix 1).[40]

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Appendix 1. STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Item found on page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, Table 1
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, Figures 1 and 2, Table 2
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for	14, Figure 3

		eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Figure 3
		(c) Consider use of a flow diagram	Figure 3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	-
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	-
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19