

LOGICAL Anaemia Statistical Analysis Plan

Haemoglobin as an effect modifier of conservative oxygen therapy after cardiac arrest

LOGICAL trial secondary analysis

SAP Version 1.2 | 5 October 2026

Primary analysis: treatment by lowest first 24 hour haemoglobin interaction for favourable functional outcome at 180 days.

This revision incorporates statistical and management committee review of Version 1.1. It retains the linear primary interaction and the primary trial adjustment set, adds fractional polynomial modelling and expanded adjusted sensitivity analyses, and specifies treatment group specific imputation of missing haemoglobin and outcomes.

1. Background and rationale

The LOGICAL trial evaluated conservative versus liberal oxygen therapy in adults who remained unresponsive after cardiac arrest and were mechanically ventilated in the ICU. The primary trial question addressed the average treatment effect of oxygen strategy on survival with favourable functional outcome at 180 days [1].

Haemoglobin concentration is a key determinant of arterial oxygen content. It is biologically plausible that the effect of an oxygenation strategy could vary according to oxygen carrying capacity. Patients with lower haemoglobin may have reduced tolerance of lower arterial oxygenation.

This secondary analysis will examine the interaction between randomised oxygen allocation and early nadir haemoglobin. Because the nadir may be measured after randomisation, this is an exploratory assessment of heterogeneity according to an early clinical measurement. A causal interpretation requires additional assumptions, as set out in Section 8.4.

2. Objectives and hypotheses

2.1 Primary objective

To determine whether the lowest haemoglobin concentration recorded during the first 24 hours after ICU admission modifies the effect of assignment to conservative versus liberal oxygen therapy on favourable functional outcome at 180 days.

2.2 Primary hypothesis

The effect of conservative versus liberal oxygen therapy differs according to early nadir haemoglobin concentration.

The primary null hypothesis is that the relative treatment effect on favourable functional outcome does not vary linearly with haemoglobin on the model link scale. This differs from the broader absence of any treatment effect modification, which is assessed in supporting nonlinear analyses.

The interaction test will be two-sided.

2.3 Secondary objectives

Secondary objectives are:

- To estimate treatment effects across clinically relevant haemoglobin concentrations.
- To assess whether treatment-effect modification is nonlinear.
- To evaluate haemoglobin modification of treatment effects for mortality, survival time and ordinal neurological outcome.
- To assess robustness using alternative haemoglobin definitions and modelling approaches.

3. Study design and data sources

This is a secondary analysis of the LOGICAL multicentre randomised controlled trial, whose design and original analysis plan were published before trial completion [2].

Data sources:

- The locked LOGICAL trial dataset, including allocation, cardiac arrest characteristics and follow-up outcomes.
- ANZICS CORE Adult Patient Database linkage for haemoglobin, illness severity and relevant ICU variables.

Treatment will be analysed as randomised. The source population and consent exclusions will follow the primary LOGICAL intention-to-treat analysis. The haemoglobin analysis is restricted to the population in which the APD exposure can be defined; it is not the full trial intention-to-treat population.

4. Analysis populations

4.1 Source population

The source population will include all LOGICAL participants eligible for use of trial data according to the primary trial analysis population.

4.2 Primary haemoglobin analysis population

The primary haemoglobin analysis population will comprise source-population participants with successful APD linkage and an applicable first 24 hour haemoglobin field at a centre where haemoglobin collection is supported by observed data. Participant-level missing or invalid haemoglobin and missing outcomes will be handled

by multiple imputation under Section 11; an observed outcome or haemoglobin is not required for inclusion.

Absence of an APD record, or an entire centre without haemoglobin collection, will be classified as structural missingness and will not be resolved by routine imputation. These participants will be shown separately in the flow diagram. The linked analysis population will be compared descriptively with the remaining source population.

Participants will not be excluded because of treatment adherence, transfusion status or clinical characteristics. A complete-case population will be used for a prespecified sensitivity analysis.

5. Haemoglobin exposure definition

The primary haemoglobin variable is HMGNLO, the lowest haemoglobin concentration recorded during the first 24 hours after ICU admission. It will be analysed continuously in g/L. APD values recorded in g/dL will be multiplied by 10 before analysis or imputation.

This is early nadir haemoglobin rather than untreated baseline haemoglobin: the collection window can extend beyond randomisation and the timing of transfusion relative to the nadir may not be ascertainable. HMGNHI, the highest first 24 hour haemoglobin, and the midpoint of HMGNHI and HMGNLO are alternative definitions, not necessarily pretreatment measurements.

Data validation:

- Check units, APD validity ranges and the requirement that HMGNLO does not exceed HMGNHI.
- Investigate extreme values using HMGNHI and haematocrit where available.
- Retain extreme values if internally plausible. Unresolved values judged invalid by a documented rule will be set to missing and handled under Section 11.
- Record all queries, corrections and exclusions before interaction results are inspected.

6. Outcomes

6.1 Primary outcome

Favourable functional outcome at 180 days after randomisation is defined as a GOS-E score of 5 to 8, consistent with the primary LOGICAL publication [1]. Death by day 180 or a GOS-E score of 2 to 4 constitutes an unfavourable outcome. Known deaths by day 180 will be coded as GOS-E 1 and will not be treated as missing functional outcomes.

Outcome assessments, follow-up windows and any adjudication will use the locked trial definitions. Any unresolved outcome inconsistency will be documented before analysis.

6.2 Secondary outcomes

Secondary outcomes:

- All-cause mortality at 180 days.
- All-cause mortality at 90 days.
- Time to death through 180 days.
- Ordinal GOS-E outcome.

- Duration of mechanical ventilation.
- ICU and hospital length of stay where available.

7. Descriptive analyses

Descriptive analyses will include:

- APD linkage and structural missingness overall, by centre and by randomised treatment group.
- Participant-level missingness in haemoglobin, outcomes and covariates.
- Haemoglobin mean, standard deviation, median, interquartile range and selected percentiles by treatment group.
- Baseline characteristics by treatment group in the haemoglobin analysis population and comparison with the remaining source population.
- Availability and timing of illness severity measures and any genuinely pretreatment haemoglobin.

Baseline tables will follow the primary LOGICAL manuscript and appendix [1], adding haemoglobin and illness severity as linked variables. Counts and descriptive percentages will use observed data and show their denominators. Treatment group differences in haemoglobin will be described; a nonsignificant comparison will not establish that treatment could not have affected haemoglobin.

8. Primary analysis

8.1 Primary estimand

The primary estimand is the change in the model-estimated relative risk of favourable functional outcome for conservative versus liberal oxygen per 10 g/L higher early nadir haemoglobin, in the linked analysis population.

This conditional interaction only has a causal interpretation under further assumptions (e.g. an absence of unmeasured confounding between the outcome and the early nadir haemoglobin). It is not, without those further assumptions, the causal treatment effect within subgroups defined by an untreated baseline biomarker. Predicted risks and risk differences are model-based conditional comparisons are subject to the same limitation.

8.2 Primary regression model

A log-binomial model with a random intercept for site will be used, matching the binary outcome model in the primary LOGICAL publication [1]. The model will include:

- Randomised treatment allocation, with liberal oxygen as the reference.
- Continuous haemoglobin, centred at 120 g/L and scaled per 10 g/L.
- Treatment by haemoglobin interaction.
- Baseline sepsis.
- Non-ischaemic encephalopathy related acute brain injuries or conditions, using the primary trial definition.

Site and the two baseline clinical variables constitute the core adjustment set. All inferential regression analyses will retain this set, with the site formulation appropriate to the outcome model. These baseline conditions were included in the primary trial

because adaptive randomisation could create imbalance across its overlapping nested populations [1].

The primary test is of the treatment by haemoglobin interaction term at a two-sided significance level of 0.05. Its exponentiated coefficient is the ratio of treatment risk ratios per 10 g/L higher haemoglobin, reported with a 95% confidence interval. Multiply imputed estimates will be pooled using Rubin's rules and an appropriate pooled Wald test.

If log-binomial fitting fails despite standard convergence measures, the prespecified fallback will be modified Poisson regression with the same clinical covariates, site fixed effects and site-clustered robust standard errors. This retains the risk-ratio scale. Any fallback, convergence problem or change in site formulation will be reported. Predictions outside the probability range will not be truncated and presented as valid risks; a bounded binomial model will be used for a separately labelled supportive probability analysis.

8.3 Functional form of haemoglobin

The primary model will use a linear haemoglobin interaction because it is parsimonious and clinically interpretable. Nonlinear supporting analyses will be conducted regardless of the primary interaction p-value.

A restricted cubic spline model will use three knots at the 10th, 50th and 90th percentiles of valid observed haemoglobin in the pooled linked population, fixed across imputations. The model will retain all spline main effects and their treatment interactions. A joint test of all interaction terms assesses any heterogeneity; a separate test of the nonlinear interaction term assesses departure from a linear treatment interaction. The main-effect spline will remain in both comparison models.

An additional multivariable fractional polynomial interaction analysis will allow treatment groups to have different haemoglobin powers as well as different coefficients. Using the FLEX4 approach described by Royston and Sauerbrei [3], a first degree fractional polynomial function will be fitted in each group. Haemoglobin divided by 100 will be used as a positive scaled variable, with powers selected from -2, -1, -0.5, 0, 0.5, 1, 2 and 3; power 0 denotes the logarithm. The null model has one common haemoglobin function plus treatment, whereas the alternative has separately selected treatment-specific functions. Adjustment variables will be retained without stepwise selection.

For fractional polynomial selection, a common pair of powers across completed datasets will minimise the mean completed-data deviance. This is a selection criterion, not a pooled likelihood-ratio test. Treatment-effect curves will be combined on a fixed haemoglobin grid. Site-level cluster bootstrap resampling, retaining participants within each sampled site, will repeat imputation and power selection to account for selection uncertainty; at least 1000 successful resamples will be used. Interaction testing will use a parametric bootstrap under the fitted common-function null, repeating imputation and the full power search. The test statistic will be the improvement in mean completed-data deviance, calibrated against its simulated null distribution. Selection and calibration will use a binomial likelihood. If log-link binomial fitting fails, the fractional polynomial analysis will use a logistic model and explicitly identify the changed interaction scale.

Naive likelihood-ratio p-values conditional on selected powers will not be treated as confirmatory evidence. Selected powers, stability and resampling details will be reported. This analysis remains exploratory.

8.4 Timing of haemoglobin and causal interpretation

Randomisation protects comparisons by allocation, but it does not guarantee exchangeability within subgroups defined by a measurement that treatment may have affected. If oxygen allocation influences early haemoglobin, conditioning on haemoglobin could block part of a treatment pathway or introduce selection bias through shared causes of haemoglobin and outcome [4]. Whether this occurs in LOGICAL is a clinical and causal assumption, not something established by a nonsignificant treatment group comparison of haemoglobin.

Age, sex and pretreatment cardiac arrest features may improve prognostic adjustment and address measured common causes of haemoglobin and outcome. Adding them does not, by itself, remove bias from a postrandomisation mediator or identify a direct treatment effect. Therefore the original primary trial adjustment set is retained, with prespecified expanded sensitivity models. Illness severity assembled from the first ICU day may also be affected by treatment and is handled separately.

Genuinely pretreatment haemoglobin will be examined if available. Otherwise causal conclusions about baseline haemoglobin effect modification will remain limited. No mediation or principal stratification estimand is specified in this SAP.

8.5 Expanded covariate adjustment

The first adjusted sensitivity model adds the complete cardiac arrest prognostic set used in the primary LOGICAL publication and appendix [1]:

- Age, as a continuous variable.
- Out-of-hospital versus in-hospital cardiac arrest.
- Shockable versus nonshockable first monitored rhythm.
- Time to sustained return of spontaneous circulation, as a continuous variable.
- Medical versus other cause of cardiac arrest.
- ST elevation myocardial infarction at presentation.

Sex will also be included as a prespecified additional covariate. The second adjusted sensitivity model adds APACHE II score as a continuous illness severity measure. Core adjustment variables and site will remain in both models. These two models distinguish adjustment for pretreatment characteristics from additional adjustment for an ICU day one severity score.

Coding and availability will be verified against the locked trial data and APD dictionary before interaction estimates are examined. APACHE II includes age and haematocrit components and may incorporate postrandomisation physiology; overlap with age and haemoglobin and model stability will be assessed. If component data are available, a further sensitivity may use severity components excluding age and haematocrit. A severity score will not be relabelled as pretreatment when its timing is uncertain.

Continuous age, return-of-circulation time and APACHE II will initially enter linearly; a sensitivity will allow nonlinear prognostic effects using fixed three-knot splines.

Covariates will not be selected by significance, treatment group imbalance or their effect on the interaction p-value. Any unavailable prespecified variable or reduced model required by sparse data or convergence will be documented, rather than silently omitted.

9. Presentation of treatment effects

Treatment effects will be presented at haemoglobin concentrations supported by the observed distributions in both treatment groups. Planned representative values are 80, 100, 120 and 140 g/L where sufficient data exist. Curves will ordinarily cover the shared 5th to 95th percentile range, with sparse tails identified and no extrapolation beyond supported haemoglobin values.

At each concentration, report model-estimated favourable outcome probabilities under each allocation, the absolute risk difference (conservative minus liberal), and the relative risk with 95% confidence intervals. Covariate standardisation will use the same linked-population distribution for both allocations and the same handling of site effects. With imputation, prediction and variance estimation will occur within each completed dataset before appropriate pooling.

Linear, spline and fractional polynomial curves will be identified separately. Confidence intervals for the fractional polynomial analysis will reflect power selection as specified in Section 8.3. All curves are conditional model comparisons; they will not be presented as a validated rule for choosing oxygen therapy using haemoglobin measured before treatment.

10. Secondary and sensitivity analyses

Prespecified supporting and sensitivity analyses are:

1. Repeat the primary interaction using the expanded cardiac arrest adjustment set and then the additional illness severity set in Section 8.5. Apply these adjustment sensitivities to mortality, ordinal GOS-E and the supporting nonlinear models where estimable.
2. Restricted cubic spline and treatment-specific fractional polynomial models, as specified in Section 8.3.
3. Haemoglobin below 100 versus at least 100 g/L, using one treatment by category interaction. Within-category significance tests will not substitute for an interaction test.
4. Highest first 24 hour haemoglobin and the midpoint of highest and lowest haemoglobin, each with a treatment interaction. The midpoint will be derived after imputation of its components, not imputed independently.
5. Retain all validated extremes in the primary analysis; repeat after restricting to the pooled observed 1st to 99th percentiles. The thresholds will be fixed before inspecting interaction estimates and applied consistently to completed datasets.
6. Complete-case analysis, and the missing-not-at-random and alternative imputation sensitivities in Section 11.
7. Repeat using haemoglobin measured before randomisation if a genuine pretreatment value and its timestamp are available. First-day minima or maxima will not be relabelled as pretreatment values. If these measurements are unavailable, report that this sensitivity could not be conducted.
8. Mortality at days 180 and 90: binary outcome models with the treatment by haemoglobin interaction and core adjustment. Time to death through day 180: a Cox

model with the interaction and site accounted for by a frailty term or site stratification, with the choice documented. Assess proportional hazards using residual-based tests and plots; if materially violated, use a prespecified time-varying treatment and interaction model and report time-specific estimates.

9. Ordinal GOS-E: a proportional odds model including treatment, haemoglobin, their interaction and core adjustment. Assess proportional odds for both treatment and the interaction. If materially violated, use a partial proportional odds model or a multinomial model and report category-specific effects and a joint interaction test.

10. Ventilation duration and ICU and hospital stay: analyse time to successful liberation or live discharge with death as a competing event, retaining treatment by haemoglobin and the core clinical adjustment set and accounting for site. Report cumulative incidence estimates and distinguish these endpoints from duration among survivors. Death will not be treated as ordinary noninformative censoring.

11. Missing data

Missingness will be described separately for linkage, haemoglobin, outcomes and covariates, overall and by treatment group and centre. Reasons for missing follow-up will distinguish loss to follow-up, refusal of further follow-up with permission to retain data, and withdrawal of permission to use all data. Participants whose data cannot be used will not be included or imputed.

The primary analysis will use multiple imputation under a missing-at-random assumption for participant-level missing haemoglobin, outcomes and required covariates. Imputation will be performed independently within conservative and liberal oxygen groups. Corresponding completed datasets from the two groups will then be combined for the interaction analysis. Randomised treatment allocation will never be imputed. A pooled imputation model with treatment entered only as a main effect will not be used.

Start with 20 imputations per treatment group, matching the number used in the primary LOGICAL analysis [1]. Increase the number if necessary so that Monte Carlo error for the primary interaction is less than approximately 10% of its standard error. Report the final number, iterations, random seed, convergence and imputation diagnostics.

The published trial outcome imputation models included age, baseline FiO₂, arrest location, cause of arrest and centre for GOS-E; the day 180 mortality model included age, baseline FiO₂ and arrest location [1]. These predictors will be retained, and models will be extended to include haemoglobin, outcomes, all covariates required by the analysis models and useful auxiliary measurements such as highest haemoglobin and haematocrit. This extension is needed for the haemoglobin interaction analysis and is not an exact replication of the original imputation model.

Missing haemoglobin will be imputed on the validated g/L scale using predictive mean matching or a suitable substantive-model-compatible continuous model within each treatment group. Observed values will be preserved. Models will account for centre and the within-group haemoglobin–outcome relationship. The imputation procedure will enforce plausible haemoglobin values and the ordering of observed or imputed minima and maxima; inconsistent draws will be rejected or redrawn rather than silently clipped.

Missing GOS-E will be imputed using a model for its ordered categories, with a multinomial alternative if the ordinal imputation assumptions are untenable. The primary binary outcome will be derived from the completed GOS-E score. Deaths known to have occurred by day 180 will remain GOS-E 1; patients known to be alive at day 180 will not be assigned GOS-E 1. If vital status is also missing, death and functional status will be imputed coherently. Known outcome components and dates will not be overwritten. Mortality and survival outcomes at other horizons will be handled within treatment group using models that respect known vital status and follow-up bounds; exact event times will not be invented by arbitrary assignment.

Imputation and analysis models must preserve treatment-specific haemoglobin–outcome associations and the functional forms needed for spline and fractional polynomial analyses. Use substantive-model-compatible imputation where feasible; otherwise use a sufficiently flexible within-group model and examine sensitivity to the imputation specification. Merely recomputing nonlinear terms after linear imputation of haemoglobin does not establish compatibility. Derived variables will be recalculated consistently in each completed dataset.

Structural missingness from absent APD linkage or an entire centre without haemoglobin collection will not be filled by routine participant-level imputation. Any broader imputation would require a separately documented sensitivity analysis with explicit transportability assumptions.

Sensitivity analyses will include complete cases, an alternative suitably flexible arm-specific imputation specification, and outcome missing-not-at-random scenarios. For missing functional outcomes, separately shift the imputed odds of favourable outcome in each arm by factors of 0.5, 1 and 2, including differential shifts, while retaining known deaths. For missing haemoglobin, repeat after shifts of –10 and +10 g/L within each arm, subject to clinical constraints. Present the effect of these scenarios on the primary interaction; they assess departures from the missing-at-random assumption and are not estimates of the missing-data mechanism.

12. Multiplicity and interpretation

There will be one primary inferential test: the linear treatment by continuous haemoglobin interaction for favourable functional outcome at 180 days, using the core adjustment set and multiple imputation.

Secondary, nonlinear and sensitivity analyses will be supportive or exploratory. No adjustment for multiplicity will be performed. Model and power selection will not be used to replace the prespecified primary test with the most favourable result.

Interpretation will focus on the magnitude, precision and consistency of estimated heterogeneity, with attention to sparse haemoglobin ranges, selection uncertainty, missing-data assumptions and postrandomisation measurement. Differences in absolute risk can occur even without an interaction on the relative-risk scale. Findings will be described as hypothesis generating and will require independent confirmation.

13. Planned tables and figures

Table 1. Observed baseline characteristics by treatment group, following the primary LOGICAL baseline table and appendix, with haemoglobin, APACHE II and missing-data denominators added.

Table 2. Linkage, structural and participant-level missingness, consent exclusions and analysis population derivation.

Table 3. Primary interaction and supporting analyses, identifying adjustment set, outcome model, imputation method, effect scale and sample size. Include the core, expanded cardiac arrest and illness severity analyses and distinguish global nonlinear tests from tests of nonlinear interaction.

Table 4. Model-estimated risks, risk differences and relative treatment effects at supported haemoglobin values, with 95% confidence intervals.

Figure 1. Participant flow, distinguishing the imputed primary analysis and complete-case sensitivity population.

Figure 2. Observed haemoglobin distributions by treatment group.

Figure 3. Linear, spline and treatment-specific fractional polynomial treatment-effect curves, showing data support and confidence intervals.

Supplementary outputs. Covariate coding and timing, imputation diagnostics, selected fractional polynomial powers and stability, assumption checks, and missing-not-at-random sensitivity results.

Data informed implementation notes

Inspection identified high availability of HMGNLO and confirmed that APD haemoglobin was recorded in g/dL. High availability does not remove the need to handle participant-level missingness: Version 1.2 specifies imputation within each treatment group whenever values are missing.

Validation will use APD validity rules, HMGNHI and haematocrit where available. The final analytic dataset will merge the APD-linked extract with the locked LOGICAL outcomes using verified participant identifiers. The merge log will document duplicates, unmatched records, exclusions and unresolved discrepancies.

Haemoglobin definition and timing

HMGNLO remains the lowest haemoglobin in the first 24 hours after ICU admission. This is an early nadir, not necessarily untreated baseline haemoglobin. No transfusion, treatment response, achieved oxygenation or subsequent care variable will be added automatically to the core outcome model as a baseline confounder.

Missing data implementation

The primary analysis includes participant-level missing haemoglobin and outcomes through independent imputation within each randomised treatment group. The earlier complete-case-only statements in Version 1.1 are superseded. Complete cases remain

a sensitivity analysis, and structural absence of haemoglobin collection remains distinct from participant-level missingness.

Treatment effect presentation

Use haemoglobin values supported by both observed treatment group distributions. Present linear, spline and fractional polynomial models separately and identify expanded adjustment and missing-data sensitivities. Do not interpret first-day haemoglobin curves as a pretreatment treatment-selection rule.

14 References

1. The LOGICAL Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Conservative Oxygen for Unresponsive Patients after Cardiac Arrest. *N Engl J Med*. 2026;395:571–581. doi:10.1056/NEJMoa2513814. Supplementary Appendix, pp 18–19 and Table S6.
2. Young PJ, Hodgson CL, Mackle D, et al. Protocol summary and statistical analysis plan for the low oxygen intervention for cardiac arrest injury limitation (LOGICAL) trial. *Crit Care Resusc*. 2023;25:140–146. doi:10.1016/j.ccrj.2023.06.007.
3. Royston P, Sauerbrei W. Two techniques for investigating interactions between treatment and continuous covariates in clinical trials. *Stata J*. 2009;9:230–251. doi:10.1177/1536867X0900900204.
4. Lynch KG, Cary M, Gallop R, Ten Have TR. Causal mediation analyses for randomized trials. *Health Serv Outcomes Res Methodol*. 2008;8:57–76. doi:10.1007/s10742-008-0028-9.

15 Revision record

Version 1.2 replaces Version 1.1 for this analysis. The following changes incorporate the statistical review received on 30 September 2026:

1. Deleted the redundant sentence about assuming no directional effect; retained the two-sided test.
2. Added treatment-specific fractional polynomial modelling alongside the linear primary interaction and restricted cubic spline analysis, with selection uncertainty addressed explicitly.
3. Added the six cardiac arrest covariates from the NEJM analysis, sex and APACHE II to prespecified adjusted sensitivity models. Clarified why adjustment does not automatically resolve conditioning on a postrandomisation haemoglobin measurement.
4. Made independent imputation within each treatment group explicit for missing haemoglobin, outcomes and required covariates, and reconciled the analysis population and all earlier complete-case-only statements.