

Feasibility And Safety of delaying nuTrition in Intensive Care Units

(FAST-ICU): statistical analysis plan for a multicentre, open-label, cluster-randomised cross-over non-inferiority trial.

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Protocol code	FAST-ICU V1.5
SAP version	Version 1.0
Date	4 September 2026
Trial registration	ISRCTN16339579
Framework	Confirmatory non-inferiority analysis for the primary endpoint
Primary endpoint	At least one hypoglycaemic episode (blood glucose <3.9 mmol/L) within 72 hours of ICU admission
Primary non-inferiority criterion	Upper bound of the two-sided 95% confidence interval for the risk difference < 0.05 and upper bound of the two-sided 95% confidence interval for the relative risk < 2.0
Primary analysis set	All eligible patients analysed according to the ICU policy assigned to the admission period

1. Administrative information

Full trial title	Feasibility And Safety of delaying nuTrition in Intensive Care Units (FAST-ICU)
Design	Multicentre, open-label, two-period, two-sequence cluster-randomised cross-over trial
Population	Adults admitted to participating ICUs
Intervention policy	Withhold enteral and parenteral nutrition and glucose-containing maintenance solutions for the first 72 hours after ICU admission; oral intake unrestricted; rescue glucose according to local policy
Control policy	Usual care for timing of nutrition initiation and glucose-containing maintenance solutions; rescue glucose according to local policy
Primary outcome window	0–72 hours from ICU admission
SAP purpose	To pre-specify the primary and secondary estimands, corresponding estimators, handling of missing data, sensitivity analyses, and interim safety monitoring
Relationship to protocol	This SAP expands and complements Protocol V1.5 sections 11–13 as the present SAP provides greater detail

2. Purpose and guiding principles

This document provides a prospective specification of the analyses to be undertaken for FAST-ICU. It is

intended to reduce analytical flexibility and ensure alignment between the trial objective and the statistical

methods.

This SAP prospectively specifies the estimands [1,2], estimators, handling of missing data, sensitivity analyses, and interim safety review for FAST-ICU. The primary endpoint will be analysed in a non-inferiority framework on the absolute risk difference scale. Secondary analyses are supportive and exploratory unless explicitly stated otherwise.

3. Trial objectives and hypotheses

3.1 Primary objective

To determine whether withholding artificial nutrition and glucose-containing maintenance solutions for the first 72 hours after ICU admission is non-inferior to standard care with respect to the risk of hypoglycaemia.

3.2 Secondary objectives

- To compare severe hypoglycaemia, glycaemic control metrics, insulin use, moderate hyponatraemia, refeeding-related biochemical abnormalities, need for organ support, length of stay, and mortality between treatment policies.
- To describe adherence to the assigned ICU policy and the frequency and pattern of clinically important protocol deviations and rescue treatments.
- To evaluate safety signals relevant to early withholding of calories and glucose-containing maintenance fluids.

3.3 Statistical hypotheses for the primary endpoint

Let risk difference (RD) denote the absolute risk difference for at least one hypoglycaemic episode within 72 hours under the intervention policy relative to the control policy, defined as intervention minus control.

Null hypothesis: $RD \geq 0.05$.

Alternative hypothesis: $RD < 0.05$.

Non-inferiority will be concluded if the upper bound of the two-sided 95% confidence interval for RD is below 0.05. This is equivalent to a one-sided type I error rate of 2.5%. In addition, non-inferiority will only be declared if the upper bound of the two-sided 95% confidence interval for the relative risk (intervention versus control) is below 2.0. This protects the conclusion against a clinically important relative increase in risk if the control event rate is lower than anticipated.

4. Trial design

FAST-ICU is a two-period, two-sequence cluster-randomised cross-over trial. Participating ICUs are randomised 1:1 to sequence AB (intervention then control) or BA (control then intervention). Each period lasts four weeks and is separated by a two- to four-week wash-out and training interval.

The design is cross-sectional: different patients contribute data in different periods. The treatment policy is applied at ICU level; outcomes are measured at patient level.

Analyses will account for treatment, period, and clustering by ICU. Carryover is expected to be minimal because different patients contribute in different periods, a wash-out/training interval is planned, and the intervention acts only during the first 72 hours after ICU admission.

4.1 Randomisation

Randomisation will be performed using a restriction method [3] to achieve balance on two factors: number of beds and the proportion of admissions which are pre-planned. Sites will be stratified by the proportion of pre-planned admissions, into two levels, 25% or less vs above 25%. Sites will then be randomised to balance allocation to “intervention first” within each stratum. The allocations will be accepted or rejected based upon the difference in mean beds between the two arms. A difference greater than 4.5 will be rejected, and a new randomisation will be performed without resetting the seed. This threshold was selected to limit imbalance in unit size between the sequence groups, as bed count is a proxy for cluster size and case mix. Under 100 000 simulations 47.7% allocations were rejected; this was felt to leave an acceptable level of chance in the randomisation procedure. In the event of single trial sites enrolling in the study after the restricted randomisation process, a simple randomisation sequence will be generated and kept concealed from the investigators.

5. Analysis sets

5.1 Patient-level analysis sets

The primary treatment-policy estimand will be estimated using all eligible patients admitted during active study periods and analysed according to the ICU policy assigned to that period.

The secondary policy-concordant estimand will be estimated in the subset of patients meeting the prespecified policy-concordance criteria for the first 72 hours after ICU admission.

5.2 Cluster-period analysis set

For cluster-period sensitivity analyses, the dataset will contain one summary record per ICU and study period, including the number of analysed patients, the number with the outcome, treatment policy, period, and sequence.

6. Estimands and intercurrent events

6.1 Primary estimand

Population: all eligible adult ICU admissions during active study periods.

96 **Treatment conditions:** assignment to the ICU-level intervention policy versus control policy for the
97 admission period.

98 **Endpoint:** occurrence of at least one hypoglycaemic episode (blood glucose <3.9 mmol/L) within 72 hours
99 of ICU admission.

100 **Population-level summary:** participant-average marginal absolute risk difference, defined as intervention
101 minus control.

102 **Intercurrent-event strategy:** treatment-policy strategy for protocol deviations, rescue glucose
103 administration, clinician-initiated departures from the policy, and initiation of nutrition contrary to
104 allocation. These events are considered part of the policy effect being estimated because they are expected
105 in real-world implementation and are clinically relevant components of safety. Cases where nutrition is
106 delayed during control periods will be documented and reported, but not considered a protocol deviation as
107 this may reflect standard care. Truncating intercurrent events, defined as ICU discharge or death before 72
108 hours, will be handled using a while-alive and while-in-ICU strategy.

109 **6.2 Secondary estimand**

110 The secondary estimand for the primary endpoint addresses the effect of the allocated ICU policy under
111 policy-concordant implementation during the first 72 hours after ICU admission. It replaces a traditional
112 per-protocol analysis.

113 **Population:** eligible adult ICU admissions during active study periods whose management during the first
114 72 hours is concordant with the ICU policy assigned to that period according to prespecified adherence
115 criteria.

116 **Policy concordance in intervention periods:** no routine enteral nutrition, parenteral nutrition, or glucose-
117 containing maintenance solutions during the first 72 hours, except for prespecified rescue or clinician-
118 initiated safety measures documented as clinically indicated.

119 **Policy concordance in control periods:** management consistent with local usual care for initiation of
120 nutrition and use of glucose-containing maintenance solutions during the first 72 hours, without protocol-
121 imposed withholding of these measures.

122 **Additional target-population restriction:** patients who resume oral intake within 72 hours after ICU
123 admission, under either treatment policy, will not contribute to estimation of this secondary estimand,
124 because this estimand is intended to address policy-concordant implementation among patients who
125 continue to require ICU-directed nutritional and maintenance fluid management during that window.

126 **Endpoint:** occurrence of at least one hypoglycaemic episode (blood glucose <3.9 mmol/L) within 72 hours
127 of ICU admission.

128 **Population-level summary:** adjusted absolute risk difference.

Intercurrent-event strategy: patients whose management is not concordant with the allocated policy during the first 72 hours will not contribute to estimation of this estimand. This estimand is supportive and addresses a different clinical question from the primary treatment-policy estimand. Truncating events will be handled using the same strategy as for the primary estimand.

6.3 Secondary outcome estimand framework

Unless otherwise specified, secondary outcomes will be evaluated under the same treatment-policy approach as the primary estimand, with the target population comprising all eligible patients admitted during active study periods. The endpoint and population-level summary measure will vary according to the outcome. For binary outcomes, the primary summary measure will generally be the absolute risk difference; relative measures may also be presented as supportive summaries where clinically helpful. For count outcomes, rate ratios or mean count differences will be used as appropriate. For continuous outcomes, the summary measure will generally be the mean difference.

6.4 Death as a truncating event

For the primary endpoint, death within 72 hours prevents any further observation of hypoglycaemic events. The endpoint is defined as whether at least one qualifying event occurred at any time within the 72-hour window. Patients who die within 72 hours without a recorded hypoglycaemic event will therefore contribute as 'no event' in the primary analysis. This is consistent with the primary treatment-policy estimand, which is based on observed events during the period the patient remained alive and under observation.

To assess whether unequal early truncation of observation could attenuate an apparent between-policy difference in hypoglycaemia, a prespecified sensitivity analysis will redefine the primary endpoint as the composite of at least one hypoglycaemic episode or death within 72 hours of ICU admission. This analysis will examine whether differential early death between policies could attenuate the observed between-policy difference in hypoglycaemia.

7. Outcome definitions

7.1 Primary outcome

Primary outcome: at least one blood glucose value <3.9 mmol/L recorded during the index ICU stay within 72 hours after ICU admission. All routinely recorded blood glucose measurements qualify, irrespective of sampling site. The thresholds of <3.9 mmol/L and <3.0 mmol/L correspond to level 1 and level 2 hypoglycaemia as defined by the International Hypoglycaemia Study Group [4].

7.2 Key safety outcomes

- Severe hypoglycaemia: at least one blood glucose value <3.0 mmol/L during ICU stay up to day 7; protocol-related serious adverse event defined as hypoglycaemia <3.0 mmol/L within the first 96 hours.
- Persistent or refractory hypoglycaemia: protocol-related serious adverse event defined as hypoglycaemia <3.9 mmol/L considered refractory to intravenous glucose within the first 96 hours, according to investigator adjudication and protocol definitions.
- Moderate hypernatraemia: sodium >150 mmol/L within the first 7 ICU days.
- Severe ICU-acquired hypernatraemia: protocol-related serious adverse event defined as sodium >155 mmol/L within the first 96 hours.
- Clinically manifested refeeding syndrome: protocol-related serious adverse event as defined in the protocol.

7.3 Other secondary outcomes

- ICU mortality, defined as death during the index ICU stay, and hospital mortality, defined as death during the index hospitalisation within 90 days after ICU admission; patients discharged alive, transferred to another institution, or still in hospital at day 90 are counted as survivors.
- ICU length of stay and hospital length of stay censored at 90 days.
- Number of severe hypoglycaemic events per patient during ICU stay up to day 7.
- Mean blood glucose concentration: arithmetic mean of all blood glucose measurements recorded during the first 7 ICU days or until ICU discharge, whichever occurs first.
- Proportion of blood glucose measurements in target range 4.4–10.0 mmol/L: number of glucose measurements within this range divided by the total number of glucose measurements recorded during the first 7 ICU days or until ICU discharge, whichever occurs first.
- Daily cumulative insulin use (units/day) during ICU stay up to day 7. Where hypoglycaemia occurs during continuous infusion, or within 12 hours after a subcutaneous bolus dose, the infusion rate at the time of the event or dose and drug (short- or long-acting insulin) received subcutaneously will be recorded to distinguish the events occurring under insulin administration from spontaneous hypoglycemia.
- Peak cumulative fluid balance during the first 7 ICU days: calculated as cumulative recorded fluid input minus cumulative recorded fluid output and expressed in litres.
- Refeeding hypophosphataemia: phosphate <0.65 mmol/L together with a decrease >0.16 mmol/L within 72 hours after initiation of feeding.
- Daily requirement for organ support therapies, including invasive or non-invasive mechanical ventilation, vasopressor therapy, renal replacement therapy and mechanical circulatory support, in ICU up to day 7.

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193 Feasibility of the intervention will be assessed using descriptive process measures, including protocol
194 deviations and the degree of treatment separation in patients eligible to receive the intervention (ie without
195 oral intake).

196 **8. General statistical principles**

197 All hypothesis tests will be two-sided unless otherwise stated. The primary non-inferiority decision will use a
198 two-sided 95% confidence interval and the associated one-sided 2.5% type I error rate.

199 Continuous variables will generally be summarised by mean (standard deviation) or median (interquartile
200 range), depending on distribution. Categorical variables will be summarised by counts and percentages.

201 No formal multiplicity adjustment is planned for secondary outcomes. Secondary analyses are exploratory
202 and will be interpreted primarily through effect estimates, confidence intervals, consistency across related
203 outcomes, and clinical plausibility.

204 All patient-level mixed-effects analyses will account for the cluster-randomised cross-over design by
205 incorporating fixed effects for treatment policy, study period and randomisation variables (pre-planned
206 admission stratum $\leq 25\%$ vs $> 25\%$, and ICU bed count), and a random intercept for ICU. The ICU random
207 intercept will account for correlation among patients within the same ICU across study periods.

208 The primary analysis will estimate the adjusted absolute risk difference across trial participants while
209 accounting for the hierarchical correlation of patients within ICUs. Because the number of ICUs is limited,
210 prespecified cluster-period sensitivity analyses will be performed using ICU-period summaries, with
211 sequence included as a model term, to assess robustness to model choice. The estimated within-period
212 and between-period intracluster correlations for the primary outcome will be reported, in line with the
213 CONSORT extension for cluster randomised cross-over trials [5].

214 In the event of convergence or singularity issues, alternative optimizers and convergence criteria will first be
215 considered. If the issue persists, the model will be simplified according to a prespecified hierarchy: (1)
216 alternative optimisers with increased iterations and, where applicable, quadrature points; (2) removal of
217 cluster-level covariates in fixed order, ICU bed count first, then admission stratum, with treatment policy
218 and period always retained; (3) a marginal model based on generalized estimating equations (GEEs) with an
219 independent, exchangeable, or autoregressive (in that order) working correlation matrix and cluster-robust
220 standard errors; (4) the weighted cluster-period analysis as the terminal fallback.

221 Statistical analyses will be conducted using validated statistical software. The primary analysis is planned in
222 R; package versions and an archived analysis environment will be documented before database lock.

223 Independent code review or replication of the primary analysis will be undertaken before final reporting.

224 **9. Baseline characteristics and trial conduct**

225 A CONSORT flow diagram adapted for a cluster-randomised cross-over trial will be prepared. This will
226 summarise:

- 227 • number of clusters assessed, randomised, and analysed by sequence;
- 228 • cluster-periods started and completed;
- 229 • patients screened, excluded, included, and analysed by treatment period;
- 230 • major protocol deviations and withdrawals of consent, if applicable.

231 Baseline characteristics will be summarised descriptively. Cluster-level characteristics will be described by
232 sequence where relevant; patient-level baseline characteristics will be described by treatment condition
233 and, where informative, by sequence-period cell.

- 234 • Age, sex, admission category, source of admission, body mass index, SAPS II, age-adjusted Charlson
235 Comorbidity Index, diabetes status, admission diagnosis category, and other baseline variables
236 recorded in the protocol.

237 No significance testing of baseline imbalances is planned.

238 **10. Adherence and protocol deviations**

239 Adherence summaries will be descriptive and will not redefine the primary estimand.

- 240 • In the intervention periods: proportion of patients receiving any enteral/parenteral nutrition within 72
241 hours; proportion receiving glucose-containing maintenance fluids; use of rescue glucose
- 242 • In the control periods: proportion of patients not receiving any enteral/parenteral nutrition or
243 maintenance glucose within 72 hours will be documented and reported; as this can reflect standard
244 care under specific clinical circumstances, it will not be classified as a protocol deviation.
- 245 • Frequency and reasons for documented protocol deviations.

246 **11. Primary analysis**

247 **11.1 Main estimator**

248 The primary analysis will estimate the adjusted absolute risk difference for the binary primary outcome at
249 patient level, including treatment policy and period in the model and accounting for clustering by ICU. The
250 primary analysis model will be a mixed-effects logistic regression with fixed effects for treatment policy,
251 period, pre-planned admission stratum ($\leq 25\%$ vs $>25\%$), and ICU bed count (both as recorded at
252 randomisation), and a random intercept for ICU. After fitting the model, adjusted risks under each policy will
253 be estimated by averaging model-based predicted probabilities under each policy over all analysed

patients. The difference between these adjusted risks will be reported as the adjusted absolute risk difference. This corresponds to a patient-average (individual-average) treatment effect.

The primary result will be the patient-average marginal absolute risk difference and its two-sided 95% confidence interval, based on standard errors calculated using automatic differentiation and Laplace approximation [6]. Non-inferiority will be concluded if the upper limit of the confidence interval is below 5 percentage points. In addition, non-inferiority will be concluded only if the upper bound of the two-sided 95% confidence interval for the adjusted relative risk (intervention versus control) is below 2.0. This dual criterion ensures that the fixed absolute margin cannot support a conclusion of non-inferiority when the control event rate is lower than anticipated and the relative increase in risk is clinically important.

11.2 Sensitivity analyses for the primary endpoint

Cluster-period aggregated analysis: supportive analysis of ICU-period event proportions, using one summary record per ICU-period. The event proportion will be analysed with fixed effects for treatment policy, period and sequence, and a random intercept for ICU to account for pairing of the two study periods within each ICU. The analysis will be performed twice: weighted by the number of analysed patients per ICU-period, targeting the patient-average effect, and unweighted, targeting the ICU-average effect.

Secondary policy-concordant estimand analysis: the same model structure as the primary analysis, applied to patients meeting the prespecified policy-concordance criteria.

Composite truncation sensitivity analysis: redefining the primary endpoint as hypoglycaemia or death within 72 hours.

Glucose-target interaction analysis: mixed-effects logistic regression using the same model structure as the primary analysis, with ICU glucose-target included as a fixed effect and a treatment-policy-by-glucose-target interaction term added to assess whether the treatment effect differs according to the ICU's usual glucose target range; this analysis is supportive and exploratory. Glucose-target categories will be defined by the threshold to start insulin therapy (>6.1 , >8.3 or >10 mmol/L).

12. Analysis of secondary outcomes

Unless otherwise specified, patient-level regression models for secondary outcomes will include fixed effects for treatment policy, study period, pre-planned admission stratum ($\leq 25\%$ vs $>25\%$) and ICU bed count, and a random intercept for ICU.

12.1 Binary outcomes

Binary secondary outcomes will be analysed using patient-level mixed-effects logistic regression. Results will be reported as adjusted absolute risk differences with 95% confidence intervals. Relative measures may also be presented as supportive summaries, where clinically helpful.

286 **12.2 Continuous outcomes**

287 Continuous outcomes will be analysed using linear mixed-effects models. If strong non-normality materially
288 affects model fit, an alternative transformation, generalized linear mixed models or non-parametric
289 summary analysis will be reported as supportive.

290 **12.3 Count outcomes**

291 Count outcomes, including the number of severe hypoglycaemic episodes per patient, will be analysed
292 using count-data mixed-effects regression models. Model family will be chosen based on the distribution of
293 the outcome variable. Effect estimates will be presented as rate ratios where appropriate.

294 **12.4 Length-of-stay outcomes**

295 ICU and hospital length of stay will be summarised descriptively by treatment policy using medians and
296 interquartile ranges. Time to discharge alive from the ICU and from hospital will be analysed using
297 competing risks methods, with death before discharge treated as a competing event. Cumulative incidence
298 functions will be estimated by treatment policy. Treatment effects will be estimated using Fine-Gray
299 regression, including fixed effects for treatment policy, study period and the variables used for restricted
300 randomisation. Clustering within ICUs will be accounted for in the variance estimation.

301 **12.5 Daily organ support outcomes**

302 Daily organ support outcomes up to day 7 in ICU will be summarised descriptively by treatment policy.
303 Supportive comparative analyses may be performed for clinically important summary measures, such as
304 any use of organ support during the first 7 days.

305 **12.6 Mortality outcomes**

306 ICU mortality and hospital mortality up to 90 days will be analysed using patient-level binary-outcome
307 models accounting for treatment policy, period, and ICU clustering.

308 All secondary analyses will be analysed under a superiority framework; these analyses are exploratory and
309 will be interpreted using effect estimates and 95% confidence intervals. No claim of efficacy or safety
310 superiority will rely on nominal p-values alone.

311 **13. Missing data**

312 The amount and pattern of missing data will be described for all outcomes.

13.1 Primary outcome

If missingness in the primary endpoint exceeds 5%, or differs by more than 5% between treatment policies, the robustness of the primary analysis will be assessed using extreme-case sensitivity analyses. Incomplete ascertainment will be defined as one or more study/eCRF days within the first 72 hours with no recorded blood glucose measurement while the patient remains alive and in the ICU, unless hypoglycaemia has already been documented. In the conservative scenario for non-inferiority, incompletely ascertained outcomes will be assigned as hypoglycaemia in the intervention group and no hypoglycaemia in the control group; the reverse assignment will also be examined.

13.2 Secondary outcomes

For secondary outcomes, missingness will be summarised by policy. No imputational analyses will be performed.

13.3 Withdrawals and consent issues

If local regulations require post-admission consent for data use and consent is later withdrawn, no further data collection will occur. Data already collected before withdrawal will be retained or removed according to the applicable ethics approval and legal requirements. The resulting impact on missing data will be described.

14. Subgroup analyses

Subgroup analyses are supportive and hypothesis generating. The primary endpoint will be examined in the following prespecified subgroups:

- diabetes history present versus absent (defined by ICD-10 codes E08–E11 or E13, or an HbA1c concentration $\geq 6.5\%$);
- SAPS II >33 versus ≤ 33 ;
- baseline corticosteroid exposure present versus absent.

Each subgroup analysis will be implemented by adding a treatment-by-subgroup interaction term to the primary model. Results will be presented as subgroup-specific effect estimates with 95% confidence intervals and interaction p-values. No subgroup claim will be considered confirmatory.

15. Sample size and relationship to the planning assumptions

The enrolment target for the trial is planned using the primary endpoint of at least one hypoglycaemic episode within 72 hours after ICU admission. The planning assumptions are an expected control-group event rate of 10%, an absolute non-inferiority margin of 5 percentage points, one-sided type I error of 2.5%,

and a two-period cluster-randomised cross-over design with approximately equal cluster-period sizes. The planning work assumes approximately 72 participants per ICU per period, corresponding to a design target of approximately 15 ICUs (30 ICU-periods) and an overall sample size of about 2,160 participants. The planned number of clusters and mean cluster-period size were selected to demonstrate non-inferiority with approximately 86% to 94% power across an assumed intracluster correlation coefficient range of 0.01 to 0.04 and assumed cluster auto-correlation of 0.8.

16. Interim analyses and DSMB review

16.1 General principle

The interim review is intended to support patient safety monitoring by the DSMB. It is not planned as a formal efficacy analysis and will not be used for early declaration of non-inferiority or superiority. The remit, membership, data access and reporting arrangements of the DSMB are defined in the DSMB Charter.

16.2 Timing

The interim DSMB review will take place after approximately 30-40% of data accrual is complete, corresponding to ~3/4 of the first cluster-period at all sites.

16.3 Data reviewed by the DSMB

The DSMB will have unblinded access to data to review recruitment, adherence to study policies, major protocol deviations, and key safety outcomes, including:

- severe hypoglycaemia
- persistent or refractory hypoglycaemia
- moderate and severe hypernatraemia
- clinically manifested refeeding syndrome
- serious adverse events considered related to the study policy

16.4 Prespecified stopping guidance for safety

Based on the interim safety review, the DSMB may recommend continuation without change, protocol modification, temporary suspension, or trial termination. Particular attention will be given to any clinically important excess of severe hypoglycaemia, persistent hypoglycaemia, severe hypernatraemia, refeeding syndrome, or other serious adverse events plausibly related to the intervention policy.

16.5 Documentation

Any DSMB recommendations and resulting protocol changes will be documented and described in the final trial report.

373 **17. Quality assurance and validation**

374 Data will be captured in REDCap. The database will undergo programmed range, consistency, and logical
375 checks before lock.

376 The primary analysis dataset and code will undergo independent review or replication. Any discrepancies
377 between independently generated primary results will be resolved before finalisation of the statistical
378 report.

379 **18. Planned tables and figures**

- 380 • Table 1. Cluster and patient baseline characteristics.
- 381 • Table 2. Adherence and protocol deviations by treatment policy.
- 382 • Table 3. Primary endpoint analysis (main and sensitivity analyses).
- 383 • Table 4. Secondary efficacy and safety outcomes.
- 384 • Table 5. Serious adverse events and protocol-related safety events.
- 385 • Figure 1. CONSORT flow diagram for CRXO design.
- 386 • Figure 2. Forest plot of subgroup analyses for the primary endpoint.

387 **19. Deviations from this SAP**

388 Any revisions to the SAP will be uploaded to the clinical trials registry with an updated version history, date
389 and a description of the changes. Deviations from this SAP made after database lock or after access to
390 unblinded results will be described and justified in the final report and, where relevant, in the trial
391 publication.

392 **Appendix A. Methodological basis used in drafting this SAP**

393 This draft was informed by Protocol V1.5, the ICH E9(R1) estimand addendum, the BMJ estimands primer,
394 the 2025 CONSORT extension for cluster-randomised cross-over trials, the EMA draft guideline on non-
395 inferiority and equivalence comparisons [7], and the Trials SAP guidelines protocol for an extension to
396 cluster randomized trials [8]

397

398 **References**

- 399 1. Committee for Medicinal Products for Human Use. ICH E9(R1) addendum on estimands and
400 sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.
401 EMA/CHMP/ICH/436221/2017. Amsterdam: European Medicines Agency; 2020.
- 402 2. Kahan BC, Hindley J, Edwards M, Cro S, Morris TP. The estimands framework: a primer on the ICH
403 E9(R1) addendum. *BMJ*. 2024;384:e076316. doi:10.1136/bmj-2023-076316.
- 404 3. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54
405 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes
406 Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2017
407 Jan;40(1):155-157. doi: 10.2337/dc16-2215.
- 408 4. Raab GM, Butcher I. Balance in cluster randomized trials. *Stat Med* 2001;20:351-365
- 409 5. McKenzie JE, Taljaard M, Hemming K, Arnup SJ, Giraudeau B, Eldridge S, Hooper R, Kahan BC, Li T,
410 Moher D, Turner EL, Grimshaw JM, Forbes AB. Reporting of cluster randomised crossover trials:
411 extension of the CONSORT 2010 statement with explanation and elaboration. *BMJ*.
412 2025;388:e080472. doi:10.1136/bmj-2024-080472.
- 413 6. Kristensen K, Nielsen A, Berg CW, Skaug H, Bell BM (2016). "TMB: Automatic Differentiation and
414 Laplace Approximation." *Journal of Statistical Software*, **70**(5), 1–21. doi:10.18637/jss.v070.i05.
- 415 7. Committee for Medicinal Products for Human Use / Methodology Working Party. Guideline on non-
416 inferiority and equivalence comparisons in clinical trials. Draft. EMA/301654/2025. Amsterdam:
417 European Medicines Agency; 24 Oct 2025.
- 418 8. Hemming K, Thompson JY, Hooper RL, et al. Guidelines for the content of statistical analysis plans
419 in clinical trials: protocol for an extension to cluster randomized trials. *Trials*. 2025;26:72.
420 doi:10.1186/s13063-025-08756-3.