FLOELA

FLuid Optimisation in Emergency LAparotomy

Statistical Analysis Plan

Version: 4.0
Date: 31/05/2022

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1. **Administrative Information**

Trial registration number: ISRCTN registry - ISRCTN14729158

This SAP is based on protocol version 4.0 (date 27/04/2022)

SAP revision history

Changes from protocol version 1.0

- The protocol specified that the internal pilot outcomes include the representativeness of FLO-ELA patients' "pre-operative physiological markers" compared to NELA patients'. In this SAP we change "pre-operative physiological markers" to "preoperative NELA risk score (1)". This change was made to make the internal pilot outcomes match the internal pilot stop/go criteria.
- The protocol stated that we would use a preoperative risk score for the internal pilot stop/go criteria and for a subgroup analysis. This SAP clarifies that this is based on the preoperative NELA risk score.
- The protocol specified that subgroup analyses for age and the preoperative risk score would be carried out by dichotomising the subgroup variable and modelling an interaction between the treatment variable and the dichotomised subgroup variable. In this SAP we have changed the subgroup analysis for age and preoperative risk score so that they model an interaction between treatment and restricted cubic splines of the respective continuous variable. This approach should give more power to detect interactions between treatment and the subgroup variable of interest.

Changes from SAP version 1.0

- We added an additional subgroup analysis for gender (male vs. female)
- We updated the draft CONSORT diagram to include two additional reasons for why patients were excluded from the analysis (consent withdrawn for use of data, unable to link to mortality registry)
- We updated appendix 2 to clarify that outcomes would be set to missing if we were unable to link the patient to the relevant registry or database containing the outcome data

Changes from SAP version 2.0

- We updated the analysis plan to reflect new primary outcome; days alive and out of hospital within 90 days of randomisation (DAOH-90).
- We updated the sample size calculation in light of the new primary outcome
- We have changed the derivation of duration of stay in hospital so that it is now based on hospital episode statistic (HES) data.
- We have included a repeat of the primary analysis on a modified version of the primary outcome; "days at home" within 90 days of randomisation (DAH-90). This analysis will be carried out on a subset of patients for whom the requisite information is available in the

NELA dataset (has not been recorded since December 2019 and also subject to missing values). Results will be compared against those for the corresponding analysis on DAOH-90 (both for all data and for the subset described).

Changes from SAP version 3.0

- We have redefined the target population to include only participants who underwent surgery (in addition to pre-existing criteria for inclusion). In light of this modification, we have also included a sub-section within outcomes defining the main analysi/es in terms of an estimand framework.

- We have added analyses to look at the potential impact of the Covid-19 pandemic on treatment effect, quality of care and risk profile of participants being recruited into the study.

Protocol version	Updated SAP version no.	Section number changed	List of changes from previous version/protocol	Author of change	Date
V1.0	V1.0	n/a	See above	Gordon Forbes	24/07/2018
V1.0	V2.0	Section 6 (Subgroup analyses, Graphs) Appendix 2 Appendix 4	See above	Brennan Kahan	08/11/2019
V3.0	V3.0	Section 2 (Background and trial design) Section 3 (Trial outcome measures) Section 4 (Sample size calculation, randomisation procedure)		Neil Walker	25/06/2021

		Section 5 (General analysis principles, analysis of the primary outcome, analysis of the secondary outcomes, Analysis method to use if the main model fails to reach convergence. Added new section: Days at home analysis. Section 6 (References) Appendix 2, 3, 4 & 5.			
V 4.0		Section 2 (Background and trial design) Section 3 (Trial outcomes and measures) Section 5 (Analysis, General analysis principles, Graphs) Appendix 5 (Tables)		Neil Walker	16/05/2022

*If the SAP has been published, indicate which version.

Members of the writing committee

Gordon Forbes wrote Version 1.0 of the Statistical Analysis Plan, with input from Brennan Kahan, Mark Edwards. Version 3.0 was updated by Neil Walker, Mark Edwards and Kim May Lee. Version 4.0 contains updates from Mark Edwards, Neil Walker and Rachel Phillips with input from Brennan Kahan.

Timing of SAP revisions in relation to unblinding of data/results

Version 1.0 of the SAP was written and signed off before any contributors or members of the trial team had access to any trial data or to any trial results.

Version 2.0 of the SAP was updated and signed off after one statistician (GF) had access to a blinded dataset (i.e. a dataset with treatment allocation and any other variable which may unblind the statistician removed), but was updated and signed off before GF, ME, BK, or any other member of the trial team had access to unblinded data or any trial results split by treatment arm.

Similarly, at the time Versions 3.0 and 4.0 were signed off the trial statistician (NW) had had access to blinded extracts of data (for the purposes of DMEC report preparation), but neither NW or anyone else on the trial team had accessed unblinded data or had seen trial results split by treatment arm.

Handling of unblinded data for interim analysis (including analysis of internal pilot).

The trial statistician and senior statistician will remain blinded until the SAP is signed off, all follow up data is collected, and data cleaning has occurred. To maintain blinding for any interim reports (including the internal pilot) an independent statistician will prepare any information which requires knowledge of treatment allocations or involves data which would allow treatment allocations to be determined.

Remit of SAP

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported for the internal pilot and within the principal paper(s) of the FLO-ELA trial. This analysis plan does not cover the health economic analysis which will be detailed in a separate health economic analysis plan. Subsequent papers of a more exploratory nature (including those involving baseline data only) will not be bound by this strategy but will be expected to follow the broad principles laid down in it. Any exploratory, post hoc or unplanned analyses will be clearly identified in the respective study analysis report.

2. Background and trial design

Study objectives	**Primary Objective** To establish whether minimally invasive cardiac output monitoring to guide protocolised administration of intra-venous fluid during and for up to six hours after major emergency bowel surgery leads to an increase in the number of days alive and out of hospital within 90 days of randomisation.
Study design	Open, multi-centre, randomised controlled trial with internal pilot.
Setting	UK hospitals undertaking emergency bowel surgery. Hospitals in England and Wales must be participating in the National Emergency Laparotomy Audit (NELA)
Participants	**Inclusion Criteria** • Aged 50 years and over • Undergoing an expedited, urgent or emergency major abdominal procedure on the gastrointestinal tract eligible for inclusion within NELA. • Patient has an NHS number (England & Wales), CHI number (Scotland) or H&C number (Northern Ireland). **Exclusion Criteria** • Refusal of patient consent • Clinician refusal to randomise patient • Abdominal procedure outside the scope of NELA • Previous enrolment in the FLO-ELA trial • Previous inclusion in NELA audit within the same hospital admission • Current participation in another clinical trial of a treatment with a similar biological mechanism.
Interventions	**Intervention Group** Protocolised cardiac output-guided haemodynamic therapy during surgery, and for six hours after in patients admitted to an area capable of delivering this intervention. **Usual Care Group** Intravenous fluid administration without the use of cardiac output monitoring or protocol.
Primary outcome measure	Days alive and out of hospital within 90 days of randomisation

3. **Trial outcome measures**

Primary outcome measure

- Days alive and out of hospital within 90 days of randomisation (DAOH-90).

Secondary outcomes

- Mortality within 90 days of randomisation
- Mortality within 1 year of randomisation

Process Measures

- Duration of hospital stay (number of days from randomisation until hospital discharge).
- Duration of stay in a level 2 or level 3 critical care bed within the primary hospital admission post-randomisation.
- Hospital readmission as an inpatient (overnight stay) within 90 days from randomisation.

Estimand Framework

Inference on the primary and both secondary outcomes is complicated by the potential occurrence of inter-current events. Here we describe the estimand for this analysis, inter-current events identified *a priori* in relation to FLO-ELA and how we propose to account for these in analysis using the estimand framework.

The estimand for the primary outcome (DAOH90) is the ratio of means of days alive and out of hospital within 90 days of randomisation between protocolised cardiac output-guided haemodynamic therapy vs. usual care (intravenous fluid administered without use of cardiac output monitoring), regardless of adherence or use of cardiac monitoring in the control arm, in participants aged ≥50 years who undergo emergency bowel surgery (see Table 1A).

Table 1A –Estimand for primary outcome (DAOH90)

Aspect	**Definition**
Target population:	Patients ≥50 years old who undergo emergency bowel surgery
Variable/endpoint:	Days Alive and Out of Hospital within 90 Days of Randomisation (DAOH90 = count of days alive and out of hospital within 90 days of randomisation where DAOH90 = 0 if patient dies within 90 days and DAOH = 90 – (days in hospital within 90 days of randomisation) if patient alive 90 days after randomisation)
Treatment conditions:	**Intervention Group -** Protocolised cardiac output-guided haemodynamic therapy during surgery, and for six hours after in patients admitted to an area capable of delivering this intervention.

	Usual Care Group - Intravenous fluid administration without the use of cardiac output monitoring or protocol.
Population level summary measure	Ratio of means (Intervention v usual care group).
Intercurrent events	**Strategy**
Surgery not received (applies to both treatment arms)	Principal stratum (of participants undergoing surgery)
Procedure modified after surgery begins such that no longer eligible for NELA (applies to both treatment arms)	Treatment policy
Receipt of cardiac output monitoring (control arm only)	Treatment policy
Failure to initiate cardiac output monitoring during/after surgery (intervention arm only)	Treatment policy
Cardiac output monitoring initiated but intervention algorithm not followed	Treatment policy

4. Sample size and randomisation

Sample Size Calculation

The original sample size calculation was based on a binary outcome (mortality within 90 days of randomisation) and predicated on an event rate in the control arm of 19%. It became clear during the course of recruitment that the initial target sample of 7,646 was (a) unattainable within the scheduled study period (b) unlikely to achieve the stated power of 90% due to a lower than expected event rate. It is anticipated that the revised primary outcome of DAOH-90 will achieve 90% power for a treatment effect size of comparable clinical importance with a smaller sample size, thus addressing both the above concerns.

<u>Parameters for new sample size calculation</u>

We first conducted a simulation in order to estimate an effect size for DAOH-90 commensurate with effect size in the original calculation on mortality within 90 days. Key parameters;

- overall 90-day mortality rate = 12.0% (this figure based on FLOELA data from report to DMEC in November 2019)

- relative risk difference (intervention v control) = 0.85. As per original sample size calculation.

- mean stay in hospital in Control arm = 15.93 days (this figure taken from summary NELA data on duration of hospital stay provided to FLOELA team, November 2020).

- reduction in mean hospital stay of 2 days (intervention v control). This estimate was based on a review of relevant literature (2-8).

These parameters give the following for the two treatment arms;

1. Control. 90-day mortality = 13.0%, mean duration of stay = 15.93 days
2. Intervention. 90-day mortality = 11.05%, mean duration of stay = 13.93 days

Calculation of DAOH-90

DAOH-90 was calculated in-simulation as follows.

1. 90-day mortality was simulated as a binary event using the designated treatment arm probability (13.0 % for Control, 11.05% for Intervention).
2. If 90-day mortality simulated as an event, this was treated as death within 90-days and DAOH-90 set to zero.
3. If 90-day mortality was simulated as a non-event, the case was taken to have survived beyond 90 days and duration of stay in hospital was simulated using the mean expectation for treatment arm (15.93 days for Control, 13.93 days for Intervention). In these cases, DAOH-90 = 90 days – duration of stay.

Treatment Effect at DAOH-90

Feeding the above values into simulation gave the following statistics for DAOH-90 in the respective treatment arms;

- Control; Mean = 64.5 days, S.D. = 28.0

- Intervention: Mean = 67.7 days, S.D. = 27.1

This equates to an expected mean difference of ~ 3.2 days (DAOH-90) between the treatment arms.

Final calculation

The above values were entered into a sample size calculation using Stata's "power twomeans" function. This allows for specification of group specific variances. As in the original calculation, power was fixed at 90% and Type I error rate at 5%.

Code used was as follows:

```
power twomeans 64.45 67.67 sd1(27.96) sd2(27.09) power(0.9)
```

This gives a sample size of 3,074. Correcting for anticipated 2% drop-out gives a revised sample size of 3,138 to estimate a 3.2 day difference in DAOH-90.

Randomisation procedure

After enrolment but before the start of surgery, participants will be centrally allocated to treatment groups in a 1:1 ratio by minimisation with a random component. The minimisation factors will be patient age (50-64 years, 65-79 years, and 80+ years) and ASA class (I, II, III, IV, and V). Randomisation will be performed as close as possible to the start of anaesthesia, typically when the patient arrives in the theatre suite for surgery. To enter a patient into the FLO-ELA trial, research staff at the site will log on to a secure web-based randomisation platform hosted by PCTU Queen Mary University of London and enter the patient's details to obtain a unique patient identification number and allocation to a treatment group. Allocation concealment will be used, ensuring that no one involved in study will be aware of the treatment allocation until after the patient has been randomised. Update: In September 2020, the platform for randomisation was switched to an external provider (Sealed Envelope) using the same minimisation procedure as described in the protocol.

Internal pilot

The FLO-ELA trial incorporates an internal pilot in order to confirm predicted site enrolment, patient recruitment, representativeness of the patients recruited, and compliance with the study protocol. Internal pilot outcomes will be assessed against stop/go criteria once the period of recruitment for the internal pilot is complete. The stop/go criteria are given in the trial protocol.

Internal Pilot outcome measures

- Number of sites open and having recruited first patient.
- Number of patients randomised.
- Adherence (intervention group): this is defined as a cardiac output monitor being used, and one or more cycles taken through the algorithm.
- Contamination (control group): this is defined as a cardiac output monitor being used for a patient in the control group.
- Representativeness of randomised patients compared with all eligible patients in the NELA dataset:
    - age
    - sex
    - NELA pre-operative risk score (1)
- Control arm event rate: the Data Monitoring and Ethics Committee will assess the 90-day mortality rate in the control arm to assess whether figures used in the sample size calculation are realistic. Only patients recruited during the first five months of recruitment will be included in this analysis; this is to provide enough time to complete data linkage. The trial team will remain blinded to this event rate.

Analysis of the internal pilot

We will report:

<u>Recruitment</u>

- The number of sites that have randomised at least one patient
- Total number of patients randomised to the trial

<u>Adherence to intervention</u>

- Proportion of patients in the intervention group where a cardiac output monitor is used and one or more cycles is taken through the algorithm
- Proportion of patients in the control group where a cardiac output monitor is used

Representativeness of FLO-ELA patients

- Mean age of FLO-ELA patients and eligible NELA patients. Difference in mean age and 95% confidence interval between patients enrolled in FLO-ELA and all eligible patients in the NELA data set.
- Proportion of females in FLO-ELA, proportion females in eligible NELA patients and difference in proportion of females and 95% confidence interval between patients enrolled in FLO-ELA and all eligible patients in the NELA data set.
- Mean of NELA risk score of FLO-ELA patients and eligible NELA patients. Difference in mean NELA risk score and 95% confidence interval between patients enrolled in FLO-ELA and all eligible patients in the NELA data set.

Patients in the NELA data set will be considered eligible if they are admitted to a hospital recruiting patients to FLO-ELA, aged 50 or over, and have date of admission between 08 September 2017 and 31 July 2018.

95% confidence intervals for differences in means and proportions will be calculated by treating the value from NELA as the population value (i.e. a constant) and assuming that the estimate from FLO-ELA is normally distributed.

90 day mortality in the control group will not be reported in the FLO-ELA internal pilot report but instead presented as part of the closed report to the FLO-ELA DMEC. We will include in the closed report to the FLO-ELA DMEC report the number and proportion of deaths within 90 days of randomisation in the control arm.

5. **Analysis**

Baseline characteristics

Baseline characteristics will be summarised for each treatment group by the mean and standard deviation or median and interquartile range for continuous variables, and the number and percent for categorical variables. Draft tables are given in Appendix 5.

General analysis principles

All eligible, randomised patients who went on to receive surgery and with a recorded outcome will be included in the analysis, and analysed according to the treatment group to which they were randomised (9). Patients with missing outcome data will be excluded from the analysis. Patients who are found post-randomisation to have been ineligible on any criteria for inclusion in the study will also be excluded from analysis. This will be individuals for whom any of the following applies:

- Aged below 50 on the date of randomisation
- Do not have an NHS, CHI or H&C number
- Previously found to have been enrolled in the FLO-ELA trial
- Previously found to have been enrolled in NELA within the same hospital admission
- Were not recruited to the trial in line with trial procedures
- Found to have been participating in another trial of a similar treatment with a similar biological mechanism at the time of randomisation.
- Information recorded pre randomisation indicates that the patient's planned procedure was not eligible for NELA.

We will retain in analysis participants whose ultimate surgical procedure is discovered post-randomisation to have been ineligible for NELA, as these individuals fall within the target population as defined in the estimand framework section.

Exclusions of patients randomised in error will not lead to bias in treatment effect estimates as the exclusions are based on pre-randomisation information which will not systematically differ between treatment arms.

Details on the data on which exclusions will be based are given in Appendix 1.

For the analysis of the primary and secondary outcomes, and all process measures, we will present the following information:

- The number of patients included in each analysis, by treatment arm
- A summary statistic of the outcome (e.g. number (%)), by treatment arm
- The estimated treatment effect
- A 95% confidence interval for the estimated treatment effect
- A two-sided p-value

For all analyses, a significance level of 5% will be used.

Estimator for primary estimand for DAOH90

The primary estimand will be estimated using a mixed effects negative binomial model. The analysis population will include all randomised participants except (i) those randomised in error (i.e. those who did not meet the eligibility criteria at the time of randomisation), as they fall outside the target population; and (ii) those who did not receive surgery (this is so that the estimate is based on the principal stratum strategy used to handle this intercurrent event). The former exclusion (participants randomised in error) is based on pre-randomisation information (i.e. failure to meet the eligibility criteria) and as such will be unbiased. The latter exclusion (participants who did not undergo surgery) will be unbiased for the principal stratum effect under the assumption that treatment group allocation does not affect whether participants undergo surgery or not (i.e. a participant in the intervention group who does not undergo surgery would also not receive surgery had they been allocated to the control, and *vice versa*). This assumption is justified on the basis that, in most cases, the relevant decision makers will be unaware of trial group allocation until surgery starts (i.e. at the point the decision is made). Further, the decision not to proceed with surgery has large health implications for the patient, and is only undertaken in response to a major change in the patient's clinical condition since surgery was initially planned, and it is implausible that such a fundamental change in patient care would be undertaken on the basis of the planned method of fluid delivery

Covariate adjustment

The primary analysis will be adjusted for the following covariates using fixed effects: the minimisation factors of patient age and ASA class (I, II, III, IV, and V) (10) , as well as urgency of surgery (Immediate, Urgent, and Expedited), Glasgow Coma Score (GCS), systolic blood pressure, and pulse rate (11), and a random intercept for the effect of hospital. Urgency of surgery and ASA class will be included as categorical variables, while patient age, GCS, systolic blood pressure, and pulse rate will be included as continuous variables. Patient age and GCS will be included assuming a linear association with the outcome, and systolic blood pressure and pulse rate will be included using restricted cubic splines with 3 knots (knots will be placed based on Harrell's recommended percentiles: 10^{th} percentile, 50^{th} percentile and 90^{th} percentile of covariate) (12, 13).

Missing Data

Missing data for baseline covariates to be included in the analysis model will be accounted for using mean imputation for continuous variables, and a missing indicator variable for categorical variables (14). Patients with missing outcome data will be excluded from the analysis. Subgroup analysis will only include patients who have complete data for the primary outcome and for the subgroup variable of interest.

Analysis and estimand of secondary outcomes: mortality within 90 days of randomisation and mortality within 1 year of randomisation.

The secondary outcomes (mortality within 90 days of randomisation and within 365 days of randomisation) will be analysed using a mixed-effects logistic regression model (15). The models will adjust for the set of covariates used in analysis of the primary outcome as specified in "Covariate adjustment" section above. The estimand for both secondary outcomes will be the odds ratio of mortality in the intervention relative to usual care arm in the same target population as defined for primary outcome analysis (see Table 1A).

Analysis of process measures

<u>Duration of hospital stay (number of days from randomisation until hospital discharge)</u>

Duration of hospital stay will be analysed using a competing-risk time-to-event model (16), which includes mortality as a competing risk for hospital discharge. The model will adjust for the set of covariates specified above. We note that this analysis assumes proportional hazards; we will not formally assess this assumption as simulation studies have shown that modifying the analysis approach based on a test for proportional hazards can lead to inflated type 1 error rates (17) (18).

For each treatment arm we will present median and interquartile range for length of hospital stay for patients who survived to hospital discharge. We will also present for each treatment arm the number and percentage of patients who survived until discharge from hospital, the number and percentage of patients who died whilst in hospital, and the number not discharged from hospital by end of trial.

<u>Hospital readmission as an inpatient (overnight stay) within 90 days from randomisation</u>

Hospital readmission as an inpatient will be analysed using a competing-risk time-to-event model (16), which includes mortality as a competing risk for hospital readmission. The model will adjust for the set of covariates specified above. As above, this analysis makes an assumption of proportional hazards.

For each treatment arm we will present median and interquartile range for time to readmission for patients who are readmitted to hospital. We will also present for each treatment arm the number and percentage of patients who died within 90 day of randomisation with no readmission to hospital, the number and percentage of patients who survived and were not admitted to hospital within 90 days of randomisation, and the number readmitted to hospital within 90 days.

<u>Duration of stay in a level 2 or level 3 critical care bed within the primary hospital admission</u>

Duration of stay in a level 2 or level 3 critical care bed will be analysed using a mixed-effects negative binomial regression model, with a random intercept for centre. The model will adjust for the set of covariates specified above.

Subgroup analyses

Subgroup analyses will be performed on the primary outcome (DAOH-90) to assess whether the effect of the intervention differs by:

- Urgency of surgery (Immediate vs. Urgent vs. Expedited)
- Age
- Indication for surgery (bowel perforation vs. bowel obstruction without perforation vs. other indications)
- NELA preoperative predicted risk score
- Gender (male vs. female)
- Pre / post onset of Covid pandemic (see Covid-19 Analyses section)
- Patient Covid status (see Covid-19 Analyses section)

For all subgroup analyses the presence of an interaction will be assessed using a Wald test to simultaneously test whether all interaction terms in the model are non-zero. The test will be considered significant at the 5% level.

For urgency of surgery, indication for surgery, gender, pre/post Covid-19 and Covid-19 status, the subgroup analysis will be performed using the same analysis model as for the primary outcome, adding the main effect for the subgroup variable as a categorical variable and the interaction term between the subgroup variable of interest and treatment arm. Within each level of each subgroup variable, we will report summary statistics of the outcome by treatment arm, a treatment effect and a 95% confidence interval.

For the continuous variables age and pre-operative risk score the subgroup analysis will be conducted by adding a restricted cubic spline and an interaction between treatment and the restricted cubic spline terms for the subgroup variable of interest to the primary analysis model. The restricted cubic spline will be fit using 3 knots with knot locations based on Harrell's recommended percentiles: 10^{th} percentile, 50^{th} percentile and 90^{th} percentile of covariate) (12, 13).

For the analysis of treatment effect by age we will present treatment effects and 95% confidence intervals for participants aged 60, 70 and 80. We will summarise the number of deaths for those <65, 65-75 and >75. For the analysis of treatment effect by NELA risk score we will present treatment effects and 95% confidence intervals for participants with a risk of 2.5%, 7.5% and 25%. We will summarise the number of deaths for lower risk patients (NELA risk score <5%), high risk (NELA risk score 5% - 10%) and highest risk (NELA risk score > 10%).

For both the age subgroup analysis and the NELA risk score analysis we will present graphically treatment estimates for patients aged between the 10^{th} and 90^{th} centiles of the distribution observed in the FLO-ELA trial. We will not present estimates outside this range due to issues of sparse data and the impact that the restrictions on the splines model will have on the treatment estimates.

Covid-19 Analyses

We will carry out additional subgroup analyses to assess the potential impact of the Covid-19 pandemic on (i) treatment effect with respect to primary outcome of DAOH-90 (ii) quality of treatment delivery and the pre-surgical risk profile of FLOELA participants, details below.

The impact of Covid-19 on treatment effect will be assessed in two separate models. The first of these will include as fixed effects a binary pre/post Covid-pandemic onset indicator and the interaction between treatment group and the pre/post-Covid indicator. An individual will be considered to have been treated in the pre-pandemic onset phase if randomised prior to 30 January 2020 and in the post-Covid onset phase if randomised thereafter. For the second analysis, we will include as fixed effects Covid-19 status (negative[0], positive[1]) and the interaction between treatment group and Covid-19 status. Covid-19 status has been recorded in the NELA database from March 2020 onwards. "COVID positive" will be defined as a NELA response indicating COVID infection at any stage during the patient hospital admission (pre- or post-operative). "COVID negative" will be defined as all participants with confirmed negative COVID status throughout their hospital stay according to NELA. As defined, this analysis will be restricted to individuals whose Covid-19 status is recorded in the NELA database.

With respect to analysis of quality of delivery and surgical risk profile, treatment compliance rates (adherence and non-contamination) will be presented pre and post pandemic for all participants for whom this data available (not separated by treatment group). Similarly, mean NELA mortality risk score and NELA standard of care measures will be presented on all data pre and post pandemic. Individuals randomised prior to January 30th 2020 will be considered to have been treated "pre-pandemic" and those thereafter "post-pandemic". A cut-off date of 30th January 2020 was chosen as this was when Covid-19 was first confirmed to be present in the UK.

Days at home analysis

The revised primary outcome, DAOH-90, may be considered a proxy for days *at home* within 90 days (DAH-90). However, we will not have sufficiently detailed data to track individual pathway in terms of residence outside of hospital for everyone in the database.

In order to assess if inference on DAOH-90 may be extended to DAH-90, we will analyse data for a subset of FLOELA patients for whom post-discharge destination ("home" or "residence other than own home") is recorded. This was recorded as part of NELA audit up to December 2019, but not thereafter. DAH-90 will be calculated in the same way as DAOH-90, except that in instances where a patient is discharged to residence other than own home, DAH-90 will be set to zero. The primary analysis on DAOH-90 will be repeated with DAH-90 for patients with available data. This will be compared against results of the primary analysis on DAOH-90 for (i) all patients (ii) subset of patients on which DAH-90 analysis carried out.

The same overarching analysis strategy will be applied with respect to all sub-group analyses and for the days-at-home analysis as that described for the primary estimand (see estimand framework section).

Analysis method to use if the main model fails to reach convergence

If the analysis model for the primary analysis or any secondary analysis being carried out using mixed-effect models fails to converge the following strategy will be employed. If any other secondary analysis fails to converge covariates will be removed in the order specified below until the analysis converges:

	Change from previous strategy	Example Stata code
0	Primary analysis	`menbreg daoh_90 i.treat ///` `age i.asa_grade ///` `i.urg_surgery gcs ///` `sbp_spline* pulse_rate_spline* ///` `|| centre:`
1	Remove the random-effect for centre	`nbreg daoh_90 i.treat ///` `age i.asa_grade ///` `i.urg_surgery gcs ///`

		`sbp_spline* pulse_rate_spline*`
2	Adjust for systolic blood pressure (SBP) and pulse rate using single continuous variables	`nbreg daoh_90 i.treat /// age i.asa_grade /// i.urg_surgery gcs /// sbp pulse_rate`
3	Remove covariates in the following order. After each covariate is removed the model is run to see if convergence is reached: SBP, pulse rate, GCS, urgency of surgery, age, ASA grade.	`nbreg daoh_90 i.treat`

Other data summaries

Data on the clinical management of patients during the intervention period (characteristics of surgery, maintenance fluids and fluid boluses given, cardiac output monitor use) will be summarised for the periods during surgery and 6 hours after surgery for each treatment group by the mean and standard deviation or median and interquartile range for continuous variables, and the number and percent for categorical variables. Full details of data to be summarised is given Appendix 5, table 3.

Protocol Deviations

We will summarise by treatment group the number of protocol deviations, the type of protocol deviation whether it occurred during surgery only, after surgery only or both before and after surgery and the reason for the protocol deviation. For detail on how this information will be presented see tables 8-10 in appendix 5.

Safety analyses

For each treatment group we will report the total number of serious adverse events (SAEs) related to the FLO-ELA intervention and the number and percent of patients with at least one SAE related to the FLO-ELA intervention.

Graphs

We will present Kaplan-Meier plots displaying the survival curve for each treatment arm for mortality within 90 days of randomisation, mortality within 1 year of randomisation, time to hospital readmission, and time to discharge of primary admission. Presentations will include extended at-risk tables following the prescription described by Morris et al (19).

We will display treatment estimates and 95% confidence intervals from the subgroup analysis graphically. We will use a forest plot to show differences in treatment estimate for the categorical subgroup variables (u*rgency of surgery*, *indication for surgery*, and *gender*). For age and NELA risk score we will present treatment estimates and 95% confidence intervals across values from the 10th to 90th percentile of the respective subgroup variable.

Interim analyses

The data monitoring and ethics committee (DMEC) will review outcome data, safety data and recruitment data periodically during the trial. The DMEC will recommend that the trial be stopped early if:

i) There is overwhelming evidence that is likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management.

ii) It becomes evident no clear outcome will be obtained.

No formal stopping rules are in place and no adjustments to the primary analysis will be made to account for any interim analysis performed for the DMEC. To maintain blinding, all unblinded analysis for the DMEC will be performed by an independent statistician who is not otherwise involved in the trial.

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Appendix 1: Data used to determine post randomisation exclusions

The withdrawal CRF will be used to record patients randomised in error. For a patient to be considered randomised in error one of the following criteria must be met:

Reason for exclusion	Criteria that needs to be met
Aged below 50 on the date of randomisation	Age below 50 recorded in the withdrawal CRF
No NHS number	It is recorded that the patient has no NHS number in the withdrawal CRF.
Consent not provided in line with FLO-ELA consent procedures.	Withdrawal CRF indicates that consent was not taken.
Previously found to have been enrolled in the FLO-ELA trial	It is recorded that the patient was previously enrolled in FLO-ELA in the withdrawal CRF.
Previously found to have been enrolled in NELA within the same hospital admission	It is recorded that the patient was found to have been previously enrolled in NELA within the same hospital admission in the withdrawal CRF.
Found to have been participating in another trial of a similar treatment with a similar biological mechanism at the time of randomisation.	Chief investigator determines* that the other trial, named in the withdrawal CRF, meets the criteria for the patient to have been ineligible.
Information recorded pre randomisation indicates that the patients planned procedure was not eligible for NELA.	Chief Investigator determines that the free text information provided in the withdrawal CRF indicates that it should have been known prior to randomisation that the planned procedure was not eligible for the FLO-ELA trial.

* Where an assessment is required by the chief investigator this will be made blind to study allocation.

Appendix 2: Deriving outcomes

Primary Outcome

Days alive and out of Hospital within 90 days (DAOH-90).

The primary outcome will be calculated based on two separate measures (i) mortality within 90 days (ii) number of days spent in hospital within 90 days, according to the following steps:

- DAOH-90 = 0; if patient died within 90 days of randomisation
- DAOH-90 = 90 – (days in hospital within 90 days of randomisation); if patient alive 90 days after randomisation

This follows the prescription of e.g. Jerath et al. (20).

Date of death and 90-day mortality

Mortality within 90 days will be inferred with reference to date of death records, obtained from NHS-Digital based on a match of key patient identifiers. If no date of death is recorded by NHS-Digital, the patient will be considered to have survived. If the patient cannot be linked to the relevant registry (i.e. the FLO-ELA patient cannot be found on the relevant registry) then the date of death will be treated as unknown and mortality outcomes will be set to missing.

Mortality within 90 days of randomisation will be 'yes' (1) if date of death is recorded and is within 90 days of randomisation.

Mortality within 90 days of randomisation will be 'no' (0) if:

- No date of death is recorded
- Date of death is recorded, but is more than 90 days post-randomisation.

Mortality within 90 days of randomisation will be classified as missing if:

- The patient cannot be linked to the relevant registry
- Date of death is recorded as having occurred prior to date of randomisation (this may occur if there is an error in linking to the death register).
- The patient withdraws consent for use of data.

Days in Hospital within 90 days

This will be calculated from post-randomisation duration of stay in hospital in days. To this will be added the total number of days from readmission episodes within 90 days of randomisation. Dates for initial admission and discharge and subsequent readmission episodes within 90 days will be obtained from the Hospital Episode Statistics (HES) database managed by NHS-Digital, matching on key patient identifiers. If the patient cannot be linked to the HES database, then days in hospital will be treated as missing.

Linkage to NELA data on admission and discharge dates

Data on admission and discharge dates will also be available from the NELA database. The NELA dates will be used to calculate days in hospital in the event a patient cannot be matched to the HES database. In addition, a comparison will be made between dates of admission and discharge between the HES and NELA dates for each individual, where both available, to check for consistency. In the event of disagreement, assessment will be made as to which is the more realistic record on a case-by-case basis.

Secondary Outcomes

Mortality within 90 days and 1 year of randomisation

Mortality within 90 days will be calculated as described in previous section. Mortality within 1 year of randomisation will be defined similarly, but taken to 365 days after randomisation.

Process Measures

Duration of hospital stay (number of days from randomisation until hospital discharge)

This outcome will be derived from the dates of admissions and discharges from HES database. For this analysis, duration of stay refers to initial hospital admission only (readmissions not included). Definitions for variables in analysis as follows;

Discharge status

- Patients will be classified as discharged if there is a date of discharge in relation to the initial episode
- Patient will be classified as not discharged if there is no date of discharge in relation to initial episode
- Discharge event will be missing if no match is made to HES database and thus no dates available for this patient.

Died prior to discharge

- Patients will be classified as dead if
  i) There is a date of death and no date of discharge in relation to initial episode
- Patient will be classified as alive if
  i) There is no date of death (and patient successfully matched to date of death registry) OR

   ii) There is a date of death but this falls after the date of discharge in relation to initial episode
- Died prior to discharge will be missing if:
   i) Either date of death data or discharge date in relation to initial episode not found from matching to NHS-Digital data
   ii) Dates do not follow logical sequence (date of death preceding date of discharge)

time_to_discharge_event

- For patients who are discharged, time to discharge event will be calculated by subtracting the patient's randomisation date from the discharge date in relation to initial episode.
- For patients who died in hospital, time to discharge will be calculated by subtracting their randomisation date from their date of death.
- For patients who are recorded as still in hospital, the time to discharge will be calculated as the time between date of data extract from HES and date of randomisation.

<u>Duration of stay in a level 2 or level 3 critical care bed within the primary hospital admission</u>

- Duration of stay in a level 2 or level 3 critical care bed will be the response to NELA Q7.4
- If the duration of stay in level 2 or level 3 critical care bed reported in NELA exceeds the number of days from randomisation to date of death (including both day of death and day of randomisation) then duration of stay in a level 2 or level 3 critical care bed will be equal to the from randomisation to date of death (inclusive) [duration of critical care stay = min(NELA Q7.4, date of death – date of randomisation +1)]
- Duration of stay in a level 2 or level 3 critical care bed will be missing if the response to NELA Q7.4 is missing, or if the patient cannot be linked to NELA.

<u>Hospital readmission as an inpatient (overnight stay) within 90 days from randomisation</u>

This outcome will be defined by three variables derived from HES data on hospital admissions, *readmitted*, *died_prior_to_readmit*, and *time_to_readmission_event*. Patients will be considered missing if the patient cannot be linked to the HES database.

readmitted

- *readmitted* will equal "readmission" if a hospital inpatient hospital admission is recorded in the HES data and:
    - Date of admission is after date of discharge for primary admission
    - Date of admission is within 90 days of randomisation

    - Date of discharge for readmission is different to date of admission or no date of discharge recorded (i.e. admission is overnight)
- *readmitted* will be "no readmission" if either no hospital admission is recorded in the HES data OR for any recorded hospital admission one of the following holds:
    - Date of admission is before date of discharge for primary admission
    - Date of admission is not within 90 days of randomisation
    - Date of discharge is the same as date of admission (i.e. not an overnight stay)

died_prior_to_readmit

- *died_prior_to_readmit* will be "dead" if date of death is prior to 90 days and prior to any overnight hospital readmissions being recorded.
- Patients will be classified as alive if patient is alive at 90 days or an overnight hospital admission is recorded prior to date of death.

If an admission is recorded in the HES data after date of death then the patient will be considered missing for this outcome.

time_to_readmission_event will be:

- The number of days between randomisation and date of readmission if patient is readmitted
- Number of days between randomisation and date of death if patient dies before being readmitted
- 90 days if no readmission or death is recorded.

Appendix 3: Example STATA code for analysis

Note variable names in analysis data set may be different to those given in the code below.

Internal Pilot

<u>Calculating confidence intervals for differences in means and proportions</u>

```
scalar female_popultion = xx // the proportion of females in the NELA population
gen female_diff = female - female_population
ci means feamale_diff
```

Creating splines for use in all analysis

```
mkspline sbp_spline = sbp, cubic nknots(3)
mkspline pulse_rate_spline = pulse_rate, cubic nknots(3)
```

Primary outcome

<u>Days alive and out of hospital within 90 days of randomisation</u>

```
menbreg daoh_90 i.treat ///
       age i.asa_grade ///
       i.urg_surgery gcs ///
       sbp_spline* pulse_rate_spline* ///      || centre:
```

Secondary outcome

<u>Mortality within 90 days and 1 year of randomisation</u>

```
melogit mortality_90  i.treat ///
       age i.asa_grade ///
       i.urg_surgery gcs ///
       sbp_spline* pulse_rate_spline* ///
       || centre:



melogit mortality_365  i.treat ///
       age i.asa_grade ///
       i.urg_surgery gcs ///
       sbp_spline* pulse_rate_spline* ///
       || centre:
```

Process measures

<u>Duration of hospital stay</u>

```
stset time_to_discharge_event, failure(discharge)
stcrreg  i.treat ///
       age i.asa_grade ///
       i.urg_surgery gcs ///
       sbp_spline* pulse_rate_spline* ///
       ,compete(died_prior_ to_discharge)
```

<u>Number of critical care free days up to 30 days from randomisation</u>

```
menbreg crit_care_free  i.treat ///
       age i.asa_grade ///
       i.urg_surgery gcs ///
       sbp_spline* pulse_rate_spline* ///
       || centre:
```

Hospital readmission as an inpatient (overnight stay) within 90 days from randomisation

```
stset time_to_readmission_event, failure(readmit)
stcrreg  i.treat ///
       age i.asa_grade ///
       i.urg_surgery gcs ///
       sbp_spline* pulse_rate_spline* ///
       ,compete(death_readmit)
```

Subgroup analysis

Example of subgroup analysis for a categorical variable: urgency of surgery

```
*fitting model including interaction term
menbreg daoh_90 i.treat i.treat#i.urg_surgery ///
       age i.asa_grade ///
       i.urg_surgery gcs ///
       sbp_spline* pulse_rate_spline* ///      || centre:


*Obtaining treatment effects for subgroup
*Urgency surgery coded 1,2,3. The treatment effect for group 1 will be given by the
*coefficient for treat in the output from fitting the model.

lincom 1.treat + 1.treat#2.urg_surgery, eform // treatment estimate for group 2
lincom 1.treat + 1.treat#3.urg_surgery, eform // treatment estimate for group 3


*performing Wald test for interaction
test 2.urg_surgery 3.urg_surgery
```

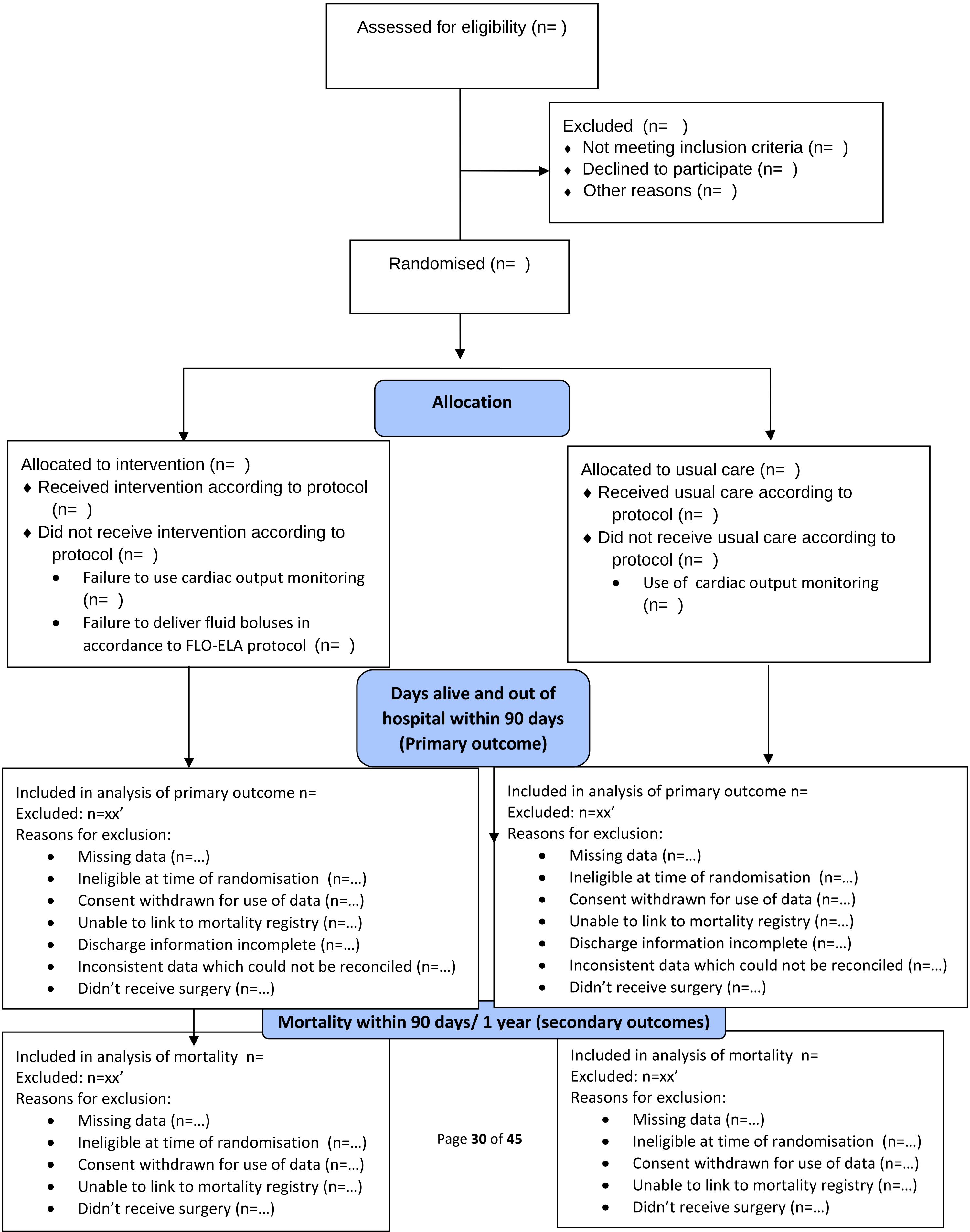
Example of subgroup analysis for a continuous variable: age

```
mkspline age_spline = age, cubic nknots(3)  displayknots
mat KNOTS = r(knots) // saving knot locations in a matrix

menbreg daoh_90 i.treat##c.age_spline* ///
       age i.asa_grade ///
       i.urg_surgery gcs ///
       sbp_spline* pulse_rate_spline* ///
       || centre: // fitting analysis model


test 1.treat#c.age_spline1 1.treat#c.age_spline2 // Testing for interaction

*calculating treatment estimate for patients age 60. Treatment effects at other
ages will be analogous.

local age = 60

*Calculating the value of the second spline variable. This is done using the
formula from the STATA 14 help file for mkspline\methods and formulas.

local age_spline = (max((`age'-KNOTS[1,1])^3, 0) ///
       - (KNOTS[1,3]-KNOTS[1,2])^-1 ///
       *(max((`age'-KNOTS[1,2])^3,0)*(KNOTS[1,3]-KNOTS[1,1]) ///
       - max((`age'-KNOTS[1,3])^3,0)*(KNOTS[1,2]-KNOTS[1,1]))) ///
       /(KNOTS[1,3]-KNOTS[1,1])^2
```

```
lincom _b[1.treat] + `age'*_b[1.treat#c.age_spline1]+
`age_spline'*_b[1.treat#c.age_spline2], eform

*Calculating treatment estimates and confidence intervals at different ages.

mat define V = e(V) // extracting variance/covariance matirx

*local macros which store the rows of the covariance matrix for the beta
coefficients required to estimate treatment effects for different ages. CHECK
THESE. These will vary according to the order covariates are entered to the model

local treat_row = 2
local sp1_int_row = 6
local sp2_int_row = 8

*generate variable containing log odds ratio for treatment estimate at different
ages
gen treat_beta = _b[1.treat] ///
        + age_spline1*_b[1.treat#c.age_spline1] ///
       + age_spline2*_b[1.treat#c.age_spline2]

gen treat_or = exp(treat_beta) // odds ratio for treatment effect at different ages

*Calculating the standard error for the treatment effect at different ages.
gen treat_se = sqrt(V[`treat_row',`treat_row'] ///
        +  age_spline1^2*V[`sp1_int_row',`sp1_int_row'] ///
        + age_spline2^2*V[`sp2_int_row',`sp2_int_row'] ///
       +2*( age_spline1*V[`sp1_int_row',`treat_row'] ///
        + age_spline2*V[`sp2_int_row',`treat_row'] ///
        + age_spline1*age_spline2*V[`sp2_int_row',`sp1_int_row']))

*Upper and lower confidence limits
gen ll = exp(treat_beta - treat_se*invnorm(0.975))
gen ul = exp(treat_beta + treat_se*invnorm(0.975))

*10th and 90th percentile of age are the knot locations for knot 1 and 3
local pc10 = KNOTS[1,1]
local pc90 = KNOTS[1,3]

sort age
*Plotting graph
twoway line treat_or age if age > `pc10' & age < `pc90' ///
              || line ul age if age > `pc10' & age < `pc90' ///
              || line ll age if age > `pc10' & age < `pc90' ///
              , yline(1, lpattern(dash) lcolor(black)) xscale(range(`pc10' `pc90'))
```

Appendix 4: Consort diagram

Information for CONSORT flow diagram



Appendix 5: Tables

Table 1 – Results of internal Pilot

Recruitment			
No. sites recruited			
No. patients recruited			
Adherence to trial interventions			
Adherence (intervention patients): Cardiac output monitor used, and one or more cycles taken through the algorithm (intervention patients)			
Contamination (control group): Cardiac output monitor used			
Patient characteristics	**FLO-ELA N=xx**	**NELA N=yy**	**Difference (95% CI)**
Age (years) – mean (sd)			
Females – no. %			
NELA risk score – mean (sd)			

Table 2 - Baseline table

Data are mean (SD) unless otherwise specified

	Summary measure		**Missing data**	
	Intervention (n=…)	**Usual care no. (%)**	**Intervention no. (%)**	**Usual care (n=…)**
Demographics and admissions				
Age (years)				
Female – no (%)				
Weight (kg)				
Height (cm)				
Body mass index (kg/m^2)				
Nature of admission				
Elective				
Non-elective				
Pre-op Characteristics				
Indication for surgery – no. (%)				
Bowel obstruction without perforation				
Bowel perforation				
Other indications				
ASA Grade – no. (%)				
I: No systemic disease				
II: Mild systemic disease				

III: Severe systemic disease, not life threatening				
IV: Severe life threatening				
V: Moribund patient				
Serum creatinine (micromol/l)				
Blood lactate (mmol/l)				
Lowest albumin in pre-op period (g/l)				
Serum sodium (mmol/l)				
Serum potassium (mmol/l)				
Serum Urea (g/l)				
Serum haemoglobin (g/l)				
Serum White cell count (x10^9/l)				
Pulse rate (bpm)				
Systolic blood pressure (mmHg)				
Glasgow coma scale				
Urgency of surgery – no (%)				
Expedited (>18 hours)				
Urgent (6-18 hours)				
Urgent (2-6 hours)				
Immediate (<2 hours)				
Pre-op POSSUM predicted mortality				
Pre-op POSSUM predicted morbidity				
Estimated mortality using NELA risk adjustment model				

Table 3 - Clinical management of patients during intervention period
Data are mean (SD) unless otherwise specified

	Summary measure		Missing data	
	Intervention (n=…)	**Usual care no. (%)**	**Intervention (n=…)**	**Usual care no. (%)**
Characteristics of surgery				
Primary operative procedure – no. (%)				
Adhesiolysis				
Colectomy*				
Hartmann's procedure				
Stoma formation				
Peptic ulcer suture or repair of perforation				
Drainage of abscess / collection				
Washout only				
Other				
*includes right or left hemicolectomy, subtotal or panproctocolectomy				
Measured or estimated intra-operative blood loss (ml) – no. (%)				
<100				
101-500				
501-1000				
>1000				
Degree of peritoneal soiling – no. (%)				
None				
Serous fluid				
Localised pus				
Free bowel content, pus or blood				
Surgical technique – no. (%)				
Open surgical technique				
Laparoscopic or laparoscopic assisted technique				
Laparoscopic converted to open				
Duration of surgery - median (IQR), min				
Time spent in post-anaesthesia care unit at end of surgery – median (IQR)				
Level of care following surgery – no. (%)				
Critical care level 3 or 3				
Other enhanced care eg. PACU				
Surgical ward				

Died prior to discharge from theatre complex				
Maintenance fluids during surgery				
Maintenance fluid during surgery – no. (%)				
5% dextrose				
4% dextrose with 0.18% NaCl (+/-KCl)				
5% dextrose with 0.45% NaCl (+/-KCl)				
'Balanced' crystalloid				
0.9% sodium chloride				
Other				
Total maintenance fluid volume given during surgery (ml)				
Fluid boluses during surgery				
'Balanced' Crystalloid (ml)				
0.9% Sodium Chloride (ml)				
Gelatin-based colloid (ml)				
Albumin (ml)				
Red blood cells (ml)				
Other blood product (ml)				
Cardiac output monitor use during surgery				
Cardiac output monitor used – no. (%)				
Deltex Oesophageal Doppler				
Edwards FloTrac/EV1000/Hemoshpere				
LiDCO Rapid				
LiDCO Plus				
Not used				
Maintenance fluids 6 hours after surgery				
Maintenance fluid during surgery – no. (%)				
5% dextrose				
4% dextrose with 0.18% NaCl (+/-KCl)				
5% dextrose with 0.45% NaCl (+/-KCl)				
'Balanced' crystalloid				
0.9% sodium chloride				
Other				
Total maintenance fluid volume given during surgery (ml)				

Fluid boluses 6 hours after surgery				
'Balanced' Crystalloid (ml)				
0.9% Sodium Chloride (ml)				
Gelatin-based colloid (ml)				
Albumin (ml)				
Red blood cells (ml)				
Other blood product (ml)				
Cardiac output monitor use 6 hours after surgery				
Cardiac output monitor used – no. (%)				
Deltex Oesophageal Doppler				
Edwards FloTrac/EV1000/Hemosphere				
LiDCO Rapid				
LiDCO Plus				
Not used				

Table 4 – Care received in line with NELA recommendations

Data are no. (%)

	Summary measure		Missing data	
	Intervention (n=…)	**Usual care (n=…)**	**Intervention no. (%)**	**Usual care no. (%)**
CT scan reported before surgery				
Risk of death documented pre-operatively				
Arrival in theatre within a timescale appropriate to urgency				
Preoperative review by a consultant surgeon and consultant anaesthetist when preoperative risk of death > 5%				
Consultant surgeon and consultant anaesthetist both present in theatre when preoperative risk of death ≥5%.				
Consultant surgeon present in theatre when preoperative risk of death ≥5%				
Consultant anaesthetist present in theatre when preoperative risk of death ≥5%				
Admission directly to critical care after surgery when preoprative risk of death >10% (or >5% after 2018)				
Assessment by a care for the older person specialist for patients aged 70 years and over (or revised definition after 2018).				

Table 5 - Main results for analysis of primary and secondary outcomes

	Number included in analysis		Summary measure			
	Intervention no. (%)	Usual Care no. (%)	Intervention	Usual Care	Treatment effect / Rate ratio / Odds ratio (95% CI)	p-value
Days alive and out of hospital within 90 days						
Mortality within 90 days of randomisation						
Mortality within 1 year of randomisation						

Table 6 - Results for analysis of process measures

	Number included in analysis		Summary measure			
	Intervention no. (%)	Usual Care no. (%)	Intervention	Usual Care	Treatment effect (95% CI)	p-value
Duration of hospital stay for* survivors – median (IQR)						
Survived to hospital discharge – no. (%)	n/a	n/a			n/a	n/a
Not discharged by end of trial – no. (%)	n/a	n/a			n/a	n/a
Died in hospital – no. (%)	n/a	n/a			n/a	n/a
Duration of stay in a level 2 or level 3 critical care bed within the primary hospital admission** – mean (SD)						
Time to hospital readmission as an inpatient (overnight stay) within 90 days from randomisation* – median (IQR)						
Readmitted to hospital within 90 days – no. (%)	n/a	n/a			n/a	n/a
Survived to 90 days with no readmission – no. (%)	n/a	n/a			n/a	n/a
Died prior to 90 days and prior to any readmission – no. (%)	n/a	n/a			n/a	n/a

*Treatment effect is a hazard ratio

**Treatment effect is a rate ratio, which is based on the ratio of mean length of stay in level 2 or 3 critical care

Table 7 - Results for subgroup analysis of primary outcome

	Number included in the analysis		Summary			
	Intervention no.	**Usual Care no.**	**Intervention no. (%)**	**Usual Care no. (%)**	**Treatment effect (95% CI)**	**p-value (interaction)**
Urgency of surgery						
Immediate						
Urgent						
Expedited						
Indication for surgery						
Bowel perforation						
Bowel obstruction without perforation						
Other indications						
Preoperative NELA risk score						
Highest (> 10%)[1]						
High (5%-10%)[2]						
Low (< 5%)[3]						
Age (years)						
>75[4]						
65-70[5]						
<65[6]						
Pre or post Covid-19 pandemic						
Pre (< 30 Jan 2020)						
Post (≥30 Jan 2020)						
Covid-19 Status						
Negative						
Positive						

[1] Treatment estimate given for participant with NELA risk score of 25%
[2] Treatment estimate given for participant with NELA risk score of 7.5%
[3] Treatment estimate given for participant with NELA risk score of 2.5%
[4] Treatment estimate given for participant aged 80
[5] Treatment estimate given for participant aged 70
[6] Treatment estimate given for participant aged 60

Table 8 - Serious adverse events related to the FLO-ELA trial procedures

	Summary measure	
	Intervention (n=…)	**Usual care (n=…)**
Number of serious adverse events – no.		
Number of patients experiencing one or more serious adverse events – no. (%)		

Table 9 – Adherence and contamination* (n [%])

	Adherence	**Contamination**
Intervention group	xxx/xxx (xx%)	NA
Control group	NA	xxx/xxx (xx%)

* Adherence is defined in the intervention group as a cardiac output monitor is used and one or more cycles is taken through the algorithm. Contamination is defined in the control group by use of a cardiac output monitor.

Table 10 – Details of adherence and contamination

	During surgery – no (%)	**After surgery – no (%)**
Intervention group		
Cardiac output monitor used and 1 or more fluid boluses received according to FLO-ELA algorithm		
Cardiac output monitor used but no fluid boluses given in line with FLO-ELA algorithm		
Did not receive cardiac output monitoring		
Control group		
Did not receive cardiac output monitoring		
Received cardiac output monitoring		

Table 11 – Reasons for non-adherence or contamination. Denominators are the total number of non-adherence or contamination in the respective group.

	Intervention N=	**Usual care N=**
Clinician decision		
Equipment related		
Communication error		
Other		

Table 12 – Measures on standard of treatment delivery and risk profile of participants summarised before and after pandemic (before = participants randomised prior to January 30th 2020, after = participants randomised on or after January 30th 2020).

	Pre-Covid	**Post-Covid**
	n/N (%)	**n/N (%)**
Compliance rates		
Adherence		
Contamination		
Standard of care		
CT scan reported before surgery		
Risk of death documented pre-operatively		
Arrival in theatre within a timescale appropriate to urgency		
Preoperative review by a consultant surgeon and consultant anaesthetist when preoperative risk of death > 5%		
Consultant surgeon and consultant anaesthetist both present in theatre when preoperative risk of death ≥5%.		
Consultant surgeon present in theatre when preoperative risk of death ≥5%		
Consultant anaesthetist present in theatre when preoperative risk of death ≥5%		

Admission directly to critical care after surgery when preoprative risk of death >10% (or >5% after 2018)		
Assessment by a care for the older person specialist for patients aged 70 years and over (or revised definition after 2018).		
Pre-operative NELA risk score		
Highest (> 10%)		
High (5%-10%)		
Low (< 5%)		

Appendix 6: Deriving the NELA preoperative risk score

The NELA methodology for deriving the NELA risk score is given in the NELA technical document "Development of the risk adjustment model July 2016" (1). The formula for deriving the NELA pre-operative risk score, given in "NELA Risk model formula", is reproduced below:

The two documents can be downloaded from https://www.nela.org.uk/reports and were accessed on 06/07/2018.

Centred variables		KEY ln = natural log	
Age_cent	= Age – 64	Creatinine_cent	= ln(Creatinine) - 4
Pulse_cent	= Pulse - 91	Urea_cent	= ln(Urea) - 1.9
SystolicBP_cent	= Systolic BP – 127	Potassium_cent	= Potassium - 4
Sodium_cent	= Sodium - 123	WBC_cent	= WBC - 13

Category definitions

Respiratory[2] = Dyspnoea on exertion or CXR
Respiratory[3] = Dyspnoea limiting exertion & at rest
Cardiac[2] = Diuretic, digoxin, antihypertensive therapy
Cardiac[3] = Peripheral oedema, warfarin therapy or CXR
Cardiac[4] = Raised jugular venous pressure or CXR

CALCULATE for all patients

PartA = 0.03200 x Female
+ 0.08938 x Cardiac[2] + 0.3259647 x Cardiac[3] + 0.24444 x Cardiac[4]
– 0.11484 x Urgency[6-18hrs] + 0.01322 x Urgency[2-6hrs] + 0.42474 x Urgency[<2hrs]
+ 0.16550 x AF rate[60-90] +0.21009 x AF rate[>90 / abnormal rhythm]
– 0.30646 x Operations[n=2] – 0.31247 x Operations[n>2]
+ 0.14551 x Operative severity[Major+] + 0.01149 x Blood loss[101-500ml]
+ 0.04770 x Blood loss[501-999ml] – 0.12317 x Blood loss[≥1000ml]
+ 0.19592 x Soiling[Serous fluid] – 0.00964 x Soiling[Localised pus]
+ 0.35131 x Soiling[Free bowel content, pus or blood]
+ 0.09954 x Malignancy[Primary only] + 0.44169 x Malignancy[Nodal metastases]
+ 1.17612 x Malignancy[Distant metastases]
+ 0.60558 x Glasgow coma score[9-12] + 0.82952 x Glasgow coma score[3-8]
+ 0.01170 x Pulse_cent – 0.0001129 x Pulse_cent2
– 0.00782 x SystolicBP_cent + 0.0001201 x SystolicBP_cent2
– 0.25180 x Creatinine_cent + 0.2250538 x Creatinine_cent2
– 0.11405 x Potassium_cent + 0.2394057 x Potassium_cent2
+ 0.32310 x Urea_cent – 0.0406424 x Urea_cent2
– 0.00062 x WBC_cent + 0.0009041 x WBC_cent2
– 0.00082 x Sodium_cent3 + 0.0002584 x [Sodium_cent3 x ln(Sodium_cent)]

For patients with ASA	Calculate Log odds of 30 day mortality as:
1-2	Log (odds) = PartA -4.11832 + 0.0556509 x Age_cent + 0.0003635 x Age_cent2 + 0.7285072 x Respiratory[2] + 1.251223 x Respiratory[3]
3	Log (odds) = PartA -4.11832 + 0.8959784 + (0.0556509-0.0163981) x Age_cent + (0.0003635 - 0.0002042) x Age_cent2 + (0.7285072 - 0.382044) x Respiratory[2] + (1.251223 - 0.597705) x Respiratory[3]
4	Log (odds) = PartA -4.11832 + 1.822416 + (0.0556509-0.0253105) x Age_cent + (0.0003635 - 0.0000425) x Age_cent2 + (0.7285072 - 0.5330661) x Respiratory[2] + (1.251223 - 0.8656163) x Respiratory[3]
5	Log (odds) = PartA -4.11832 + 2.8656163 + (0.0556509 - 0.0270848) x Age_cent + (0.0003635 - 0.0002982) x Age_cent2 + (0.7285072 - 0.8290239) x Respiratory[2] + (1.251223 - 1.107162) x Respiratory[3]