



Open, multicentre, randomised controlled trial of cardiac output-guided haemodynamic therapy compared to usual care in patients undergoing emergency bowel surgery.

Short Title *FLO-ELA trial*

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1 GLOSSARY OF TERMS AND ABBREVIATIONS

AE	Adverse Event
ASA	American Society of Anesthesiologists
BP	Blood pressure
CEAC	Cost-Effectiveness Acceptability Curve
CI	Chief Investigator
DMEC	Data Monitoring & Ethics Committee
EPOCH	Enhanced Peri-Operative Care for High-risk patients trial
EQ-5D-3L	Euro-QoL 5-Dimension 3-level quality of life measure
GCS	Glasgow Coma Scale
GDHT	Goal directed haemodynamic therapy
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
HR	Heart rate
HSCIC	Health & Social Care Information Centre (now NHS Digital)
ICU	Intensive Care Unit
NELA	National Emergency Laparotomy Audit
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
NSSISD	NHS National Services Scotland Information Services Division
ONS	Office of National Statistics
OR	Odds Ratio
Participant	An individual who takes part in a clinical trial
PCTU	Pragmatic Clinical Trials Unit
PI	Principal Investigator
PIS	Participant Information Sheet
(P)-POSSUM	(Portsmouth modified)-Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QMUL	Queen Mary University London
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UHS	University Hospital Southampton

2 SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol (version 1.0, 26/01/2017), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current and applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Dr Mark Edwards

Chief Investigator Affiliation: University Hospital Southampton NHS Foundation Trust

Signature and date



26/01/2017

Statistician Agreement

The clinical study as detailed within this research protocol (version 1.0, 26/01/2017), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP and the current and applicable regulatory requirements.

Statistician name: Brennan Kahan

Signature and date:



26/01/2017

Principal Investigator Agreement

The clinical study as detailed within this research protocol (version 1.0, 26/01/2017), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current and applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator Name:

Principal Investigator Affiliation:

Signature and date:

3 SUMMARY

Short title	FLO-ELA trial
Methodology	Open, multi-centre, randomised controlled trial
Research sites	UK hospitals undertaking emergency bowel surgery and participating in the National Emergency Laparotomy Audit (NELA)
Objectives	To establish whether minimally invasive cardiac output monitoring to guide protocolised administration of intravenous fluid during and for up to six hours after major emergency bowel surgery will reduce the number of patients who die within 90 days of randomisation.
Number of patients	7646 patients (3823 per arm)
Inclusion criteria	Patients aged 50 years and over undergoing an expedited, urgent or emergency major abdominal procedure on the gastrointestinal tract eligible for inclusion within NELA.
Exclusion criteria	Refusal of patient consent, clinician refusal, abdominal procedure outside the scope of NELA, previous enrolment in the FLO-ELA trial, previous inclusion in the NELA audit within the same hospital admission, current participation in another clinical trial of a treatment with a similar biological mechanism.
Statistical analysis	<p>All analyses will be by modified intention-to-treat; patients will be analysed according to the treatment group to which they were randomised and all eligible patients for whom an outcome is available will be included in the analysis. Patients who were randomised in error (i.e. were ineligible at the time of randomisation) will be excluded from the analysis.</p> <p>Summary statistics, treatment effects, 95% confidence intervals, and p-values will be presented for primary, secondary and process outcomes. The primary outcome</p>

	(mortality within 90 days of randomisation) will be analysed using a mixed-effects logistic regression model with a random intercept for centre. The model will be adjusted for patient age, ASA score, urgency of surgery, and preoperative Glasgow coma score, systolic blood pressure, and heart rate. Secondary outcomes will be analysed using similar methods.
Proposed start date	01 May 2017
Proposed end date	01 January 2022
Study duration	57 months

4 INTRODUCTION

Emergency abdominal surgery on the gastrointestinal tract (laparotomy) is a common major surgical procedure performed for life-threatening abdominal conditions related to underlying cancer, infection or previous surgery. It is performed on over 30,000 patients in England and Wales each year (1,2) and has a particularly high burden of postoperative morbidity and mortality, with a 90-day postoperative mortality rate of 20% in those aged 50 and over. The critical need to improve the care of patients undergoing this procedure has been recognized by the establishment of a national audit of care and outcomes in this patient group and a number of national quality improvement initiatives (1,2). In a recent research priority setting exercise conducted by the Royal College of Anaesthetists and James Lind Alliance, research to improve outcomes for patients undergoing emergency surgery was chosen as one of the top ten priorities. This underlines the desire of clinicians, patients and the public to test treatments which may help improve outcomes for this group.

It is accepted that intra-venous fluids given during and after surgery have an important effect on patient outcomes, in particular following major gastrointestinal surgery. Yet they are commonly prescribed to subjective criteria leading to wide variation in clinical practice (3). One possible solution is the use of cardiac output monitoring to guide intra-venous fluid dosing as part of a haemodynamic therapy algorithm. This approach has been studied for many years and has been shown to modify inflammatory pathways, and improve tissue perfusion and oxygenation (4,5). A Cochrane review of this intervention was recently updated, incorporating the largest contemporary trial in this area to date (6). Complications were less frequent among patients treated according to a hemodynamic therapy algorithm (Intervention 488/1548 [31.5%] vs Controls 614/1476 [41.6%]; RR 0.77 [0.71-0.83]). The intervention was associated with a reduced incidence of post-operative infection (Intervention 182/836 patients [21.8%] vs Controls 201/790 patients [25.4%]; RR 0.81 [0.69-0.95]) and a reduced duration of hospital stay (mean reduction 0.79 days [0.62-0.96]). There was a non-significant reduction in mortality at longest follow-up (Intervention 267/3215 deaths [8.3%] vs Controls 327/3160 deaths [10.3%]; RR 0.86 [0.74-1.00]).

Despite this suggestion of benefit in elective surgery, these findings are not generalisable to patients undergoing emergency abdominal surgery (7). Patients requiring emergency bowel surgery have fundamental pathophysiological differences from elective patients. These include acute inflammation, sepsis, bleeding, and fluid disturbances which may be established before surgery even begins. They therefore have similarities with critically ill patients, in whom the evidence base for fluid resuscitation based on cardiac output monitoring is very uncertain (8–10). There is a lack of dedicated studies of this treatment in emergency surgical patients, with only one pilot study of a cardiac output-guided haemodynamic therapy algorithm exclusively in patients undergoing emergency laparotomy (11). Other studies included too few patients undergoing emergency surgery to allow subgroup analyses (12–15).

These data highlight the uncertainty surrounding the possible benefits of peri-operative haemodynamic therapy algorithms in emergency bowel surgery and the need for a definitive large multi-centre clinical trial to resolve this. The aim of this trial is to evaluate the effects of peri-operative haemodynamic therapy guided by cardiac output on the number of patients who die following major emergency bowel surgery.

5 TRIAL OBJECTIVES

5.1 Primary objective

To establish whether the use of minimally invasive cardiac output monitoring to guide protocolised administration of intra-venous fluid (goal-directed haemodynamic therapy, GDHT), for patients aged 50 and over undergoing emergency laparotomy will reduce mortality within 90 days of randomisation, when compared with usual care.

5.2 Primary outcome measure

Mortality within 90 days of randomisation

5.3 Secondary objectives

To determine whether GDHT reduces mortality one year after randomisation, and is cost-effective.

5.4 Secondary outcome measures

- Mortality within one year of randomisation

5.5 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
- Hospital readmission as an inpatient (overnight stay) within 90 days from randomisation

5.6 Health economic endpoints

- Mean cost of implementing the intervention and control treatments
- Mean cost of secondary care resource use within 90 days from randomisation
- QALY gain at 90 days from randomisation using EQ-5D-3L-derived utility scores at baseline and 90 day follow-up (estimated from preceding EPOCH trial data)

5.7 Assessment of primary and secondary outcomes

We will request hospital episode statistics and mortality data from NHS Digital (formerly HSCIC) for participants in England or equivalents for the devolved nations (NHS National Services Scotland Information Services Division, NSSISD, and Patient Episode Database for Wales, PEDW). Prospective consent for Office of National Statistics (ONS), Hospital Episode Statistics (HES) and devolved nation equivalent data linkage will be sought before enrolment into the trial. Mortality outcomes will be derived from ONS data (for England and Wales; via NSSISD for Scotland). Duration of hospital stay and critical

care stay (during the index hospital admission) will be derived from NELA data. Hospital readmissions will be derived from HES, NSSISD and PEDW data.

6 TRIAL METHODOLOGY

6.1 Study design

Open, multi-centre pragmatic randomised controlled trial with internal pilot.

6.2 Inclusion criteria

- Age 50 years and over
- Scheduled to undergo a surgical procedure which fulfils the criteria for entry into the National Emergency Laparotomy Audit (NELA), i.e. an expedited, urgent or emergency abdominal procedure on the gastrointestinal tract within the audit scope, including:
 - Procedures involving the stomach, small or large bowel, or rectum for conditions such as perforation, ischaemia, abdominal abscess, bleeding or obstruction.
 - Washout/evacuation of intra-peritoneal abscess (unless due to appendicitis or cholecystitis).
 - Bowel resection/repair due to incarcerated umbilical, inguinal and femoral hernias (but not hernia repair without bowel resection/repair).
 - Return to theatre for repair of substantial dehiscence of major abdominal wound (i.e. 'burst abdomen') or after patients underwent non-elective gastro-intestinal surgery.
- Patient has an NHS number

The term "emergency" laparotomy is defined in line with NELA and the National Confidential Enquiry into Peri-Operative Deaths (NCEPOD) 2004, to encompass the following categories: "immediate" surgery (required within two hours of the decision to operate), "urgent" surgery (required within 2-18 hours of the decision to operate) and "expedited" surgery (required within 18-24 hours of the decision to operate).

6.3 Exclusion criteria

- refusal of patient consent
- clinician refusal
- previous enrolment in the FLO-ELA trial
- previous inclusion in NELA within the current hospital admission
- current participation in another clinical trial of a treatment with a similar biological mechanism

- scheduled abdominal procedure outside the scope of NELA, including: elective procedures, uncomplicated appendectomy or cholecystectomy, non-elective hernia repair without bowel resection, vascular surgery, including abdominal aortic aneurysm repair, Caesarean section, obstetric laparotomies or gynaecological laparotomy, or laparotomy / laparoscopy for pathology caused by trauma.

A full list of NELA inclusion / exclusion criteria is included in Appendix 1. During the course of the trial the NELA Project Team may make minor modifications to the definitions of surgical cases included within the audit. In this circumstance the inclusion/exclusion criteria for FLO-ELA will be amended to ensure consistency with NELA.

6.4 Internal pilot

The FLO-ELA trial will incorporate an internal pilot in order to confirm predicted site enrolment, participant recruitment, representativeness of the participants recruited and compliance with the study protocol. The duration of the internal pilot will be the first 12 months of recruitment. During this time, it is anticipated that 100 sites will be activated, and approximately 1780 patients will have been randomised. Recruitment to FLO-ELA will continue during the internal pilot analysis. A report will be compiled at the end of the internal pilot phase, which will be discussed at a monitoring meeting with the funder.

6.4.1 Internal pilot outcomes:

- Number of sites open and having recruited first patient
- Number of patients randomised. This is anticipated to be approximately 1780 after 12 months. This figure allows for slower recruitment in the initial six months for each hospital (run-in phase).
- 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
 - pre-operative physiological markers.
- 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.

6.4.2 Internal pilot stop/go criteria:

Number of sites open and having recruited at least one patient

- *>90 sites open and having recruited first patient:* continue.
- *70-90 sites open and having recruited first patient:* review site selection and initiation procedures, provide further support.
- *<70 sites open and having recruited first patient:* discuss urgently with Trial Steering Committee and funder, considering all options including discontinuation.

Number of patients randomised (target 1780)

- *>80% of recruitment target achieved (>1426 patients):* continue.
- *50-80% of recruitment target achieved (890-1426 patients):* consider recruitment strategies (opening more centres, further training and support).
- *<50% of recruitment target achieved (<890 patients):* discuss urgently with TSC and funder, considering all options including discontinuation.

Adherence (intervention group)

- *>90%:* continue.
- *80-90%:* consider options such as re-training staff, providing further support, closing problem sites.
- *<80%:* discuss urgently with TSC and funder, considering all options including discontinuation.

Contamination (control group)

- *<10%:* continue.
- *10-20%:* consider options such as re-training staff, providing further support. Individual sites with contamination rates over 10% may be closed at the end of the pilot period.
- *>20%:* discuss urgently with TSC and funder, considering all options including discontinuation.

Representativeness of randomised patients compared all eligible patients in the NELA dataset

- *Small differences in all variables (<5 years difference in age, <10% difference in gender, <10% difference in pre-operative mortality risk score):* continue.
- *Large difference in one or more variables:* consider strategies to target specific groups.

A face-to-face workshop with hospital Principal Investigators will be held 15 months after recruitment begins to review contamination and adherence data and share best practice recruitment strategies.

7 TRIAL PROCEDURES

7.1 Recruitment and screening

Potential participants will be screened by clinical and research staff at the site having been identified from operating theatre lists and by communication with the relevant nursing and medical staff. Due to the randomisation at an individual level, participant consent is required. Most eligible patients will have capacity to consent (16,17). In the important minority who do not have capacity the Mental Capacity Act 2005 allows an alternative consent method (patients in England and Wales only) because:

- *The research is related to the impairing condition that causes the lack of capacity or to the treatment of those with that condition;* this is critical illness caused by an underlying condition needing urgent surgery.
- *The research cannot be undertaken as effectively with people who have the capacity to consent to participate.* Patients lacking capacity due to illness severity may be a subgroup with more to gain from optimal fluid management; excluding this subgroup would limit the representativeness of the overall FLO-ELA group and reduce the generalisability of the study findings to the ultimate target clinical group.
- *The research will serve to increase knowledge of the cause, treatment or care of people with the same or similar condition and that the risks to participants will be negligible, with no significant interference with their privacy or freedom of action.* We are testing the hypothesis that GDHT reduces mortality after surgery, demonstrating whether this intervention is beneficial to people with the same or similar conditions. The preceding literature suggests that the risk-benefit ratio is favourable (6). There will be no interference with privacy or freedom of action.

7.2 Informed consent

7.2.1 Consent by patients

In patients with capacity, an authorised member of the team (named on the Delegation Log and with GCP training) will be responsible for obtaining written informed consent. This process will include an explanation of the aims, methods, anticipated benefits and potential hazards of the trial and provision of a Patient Information Sheet accompanied by the relevant consent form. The Principal Investigator or designee will explain to all potential participants that they are free to refuse to enter the trial or to withdraw at any time during the trial, for any reason. Patients will be given an adequate amount of time to consider their participation in the trial. Within the time available before the patient proceeds to surgery the patient will be allowed to specify the time they wish to spend deliberating, and have a second consultation if they wish to consider and discuss again. Periods shorter than 24 hours to consider the trial will be necessary due to the emergency nature of the surgery, however the person seeking consent must be satisfied that the patient has fully retained, understood and deliberated on the information given.

Patients who are not entered into this trial should be recorded (including reason not entered) on the patient-screening log in the FLO-ELA Investigator Site File.

7.2.2 Consultation for patients lacking capacity to consent (England and Wales)

In cases where the patient lacks capacity to give informed consent and a Personal Consultee is available to advise on the presumed wishes of the patient, authorised staff will explain the FLO-ELA trial and provide a Consultee Patient Information Sheet. After checking that this has been understood, if the Personal Consultee agrees that the patient would want to participate, they will be asked to sign a Consultee Declaration Form. If the Personal Consultee is not present, agreement can be obtained by telephone, and a Consultee Telephone Agreement Form will be completed. If no Personal Consultee is available, a Nominated Consultee may be approached, agreement being addressed in the same manner as for the Personal Consultee.

A Personal Consultee is defined as someone who knows the person who lacks capacity in a personal capacity who is able to advise the researcher about the person who lacks capacity's wishes and feelings in relation to the project and whether they should join the research. A Nominated Consultee is defined as someone who is appointed by the researcher to advise the researcher about the person who lacks capacity's wishes and feelings in relation to the project and whether they should join the research. This may include a member of the care team or GP, as long as they have no connection with the research project.

7.2.3 Emergency consent for patients lacking capacity to consent (England and Wales)

Due to the emergency nature of the surgery, and the need to proceed with medical intervention – including fluid management – there may not be a Personal or Nominated Consultee available in a timely fashion. In other cases, a Personal Consultee may be available but the urgency of the surgery means there is inadequate time for the Consultee to receive trial information and to advise on the enrolment of the person who lacks capacity, particularly as clinical information must take priority. In these cases the authorised research team member will proceed with emergency consent using the process described in Section 32(9) of the Mental Capacity Act 2005. An independent doctor nominated by the local research team will be consulted - either in person or via telephone - and if they agree, the researcher will recruit the patient into the trial. An Emergency Consent form will be completed by the member of the research team seeking consent.

7.2.4 Retrospective consent (England and Wales)

If a patient subsequently recovers capacity to consent, retrospective consent will be sought. This process will use the same approach as with a first approach to patients with capacity. However, as the intervention period occurs while the patient is under anaesthesia and for only up to six hours after surgery, in almost all cases the study intervention will be completed before the patient regains capacity. In these cases consent will allow data use, but no other contact with the patient for trial interventions will

be required. Patients will not be informed of their treatment group allocation until after retrospective consent is obtained. Refusal of consent at this stage should be treated as a patient withdrawal from the study, see section: 7.10. Specific Retrospective Patient Information Sheets and Retrospective Consent Forms will be used. If however a site becomes aware that the patient has a pre-existing condition which means they would never regain sufficient capacity to give informed retrospective consent, agreement of a Personal or Nominated Consultee should be sought to use the patient's data.

7.3 Randomisation

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.

7.4 Trial treatment

The trial treatment period will commence at the start of general anaesthesia and continue for **six hours after the completion of surgery**. Eligible patients will be randomised to receive either cardiac-output guided haemodynamic therapy (intervention group), or usual care. Perioperative management for **all** patients during the trial treatment period will be in accordance with recommended guidance below.

7.4.1 Perioperative management for all patients

Care for all patients has been loosely defined to avoid extremes of clinical practice but also practice misalignment (18). All patients will receive standard measures to maintain oxygenation ($\text{SpO}_2 \geq 94\%$), haemoglobin ($>80 \text{ g/L}$), and core temperature (37°C). A list of recommended fluids that may be given will be provided in the Standard Operating Procedure (SOP) for the study treatment. These fluids have a composition recommended by NICE for their specific clinical indication, i.e. maintenance fluid requirements or plasma volume expansion (19). A recommended fluid will be administered to satisfy maintenance fluid requirements in line with NICE guidance (19). Additional fluid will be administered at the discretion of the clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate and base excess. Mean arterial pressure will be maintained between 60 and 100 mmHg using a vasopressor or vasodilator as required. If inotropes, vasoconstrictors or vasodilators are required, they should be provided by intravenous infusion rather than intermittent

bolus. Other aspects of perioperative care should be based on the best available evidence for this group (20,21), and the audit standards recommended by NELA (2).

7.4.2 Intervention group

The cardiac output-guided haemodynamic therapy intervention will commence with induction of anaesthesia and continue at least until the end of surgery. In patients receiving level 2/3 critical care after surgery, the intervention will continue for six hours after the end of surgery. This level of care may be delivered in intensive care units, high dependency units or post-anaesthetic care units (PACU). For patients with a clinical plan to be transferred to level 1 (ward) care after initial recovery from anaesthesia in the PACU, wherever possible the intervention should be delivered for six hours within the PACU before transfer. See Appendix 3 for definitions of levels of care. Cardiac output and stroke volume will be measured by cardiac output monitor. Clinicians may choose from a range of cardiac output monitors in established use which have been shown to track changes in cardiac stroke volume accurately. Please see the SOP for the study treatment for a recommended list. No more than 500ml of intra-venous fluid will be administered within the intervention period prior to commencing cardiac output monitoring. In addition to the maintenance fluid and blood products described previously, patients will receive 250ml fluid challenges with a solution selected from a recommended list (see: SOP for the study treatment) by the clinician as required in order to achieve a maximal value of stroke volume. The absence of fluid responsiveness will be defined as the absence of a sustained rise in stroke volume of at least 10% for 20 minutes or more, or by a stroke volume variation less than 5%. All other management decisions will be taken by clinical staff.

7.4.3 Usual care group

Patients in the control group will be managed by clinical staff according to usual practice. As described in the guidance for the management of all patients, this will include 250ml fluid challenges with a recommended intra-venous fluid (see SOP for the study treatment) administered at the discretion of the clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate and base excess. If a specific haemodynamic end-point for fluid challenges is to be used, the most appropriate would usually be a sustained rise in central venous pressure of at least 2 mmHg for 20 minutes or more. Patients should not be randomised if the clinician intends to use cardiac output monitoring regardless of study group allocation; this is considered 'clinician refusal' and is a specific exclusion criteria. However, clinical staff are able to request cardiac output monitoring if this is required to inform the treatment of a patient who becomes critically ill (e.g. because of severe haemorrhage); in this situation a protocol deviation form will be completed.

7.5 Intervention algorithm

General haemodynamic measures (all patients)

1. Maintenance fluid (see SOP) at 1 ml/kg/hr
2. Transfuse blood to maintain haemoglobin >80 g/l
3. Clinician retains discretion to adjust therapy if concerned about risks of hypovolaemia or fluid overload
4. Mean arterial pressure 60-100 mmHg; SpO₂ ≥94%; temperature 37°C; heart rate <100 bpm

Administering fluid to a stroke volume end-point (intervention group)

1. 250ml fluid boluses to achieve a maximal value of stroke volume
2. Fluid challenges should not be continued in patients who are not fluid responsive in terms of a stroke volume increase
3. Fluid responsiveness is defined as a stroke volume increase ≥10%
4. If stroke volume decreases further fluid challenge(s) are indicated
5. Persistent stroke volume responsiveness suggests continued fluid loss
6. Fluid challenge is not recommended if stroke volume variation is <5%

What if blood or IV fluid is required regardless of stroke volume?

1. If blood products or additional fluid challenges are required, then stroke volume should still be monitored to identify any change in maximal stroke volume

7.6 Blinding and procedures to minimise bias

FLO-ELA is a pragmatic effectiveness trial of a treatment algorithm. It is not possible to conceal treatment allocation from all staff in trials of this type. Therefore, this trial will be open-label, and patients and the staff delivering the intervention will be unblinded. However, procedures will be put in place to minimise the possibility of bias arising because research staff become aware of trial group allocation. Clinicians will be instructed that the decision to admit a patient to critical care after surgery should be made on conventional clinical grounds before randomisation. Any changes to the planned level of care after surgery made after randomisation should also be based on clinical grounds and not trial group allocation. Confirmation of the primary and secondary outcomes is objective and automated through use of ONS/HES/NSSISD/PEDW data. Adjudication of Serious Adverse Events (SAEs) will be by the local Principal Investigator, who will be blinded to study group allocation.

Staff in hospitals participating in NELA are currently able to download a pseudo-anonymised NELA dataset for patients from their hospital that have been entered into NELA and have completed records. In order to prevent unauthorised local analysis, for hospitals participating in FLO-ELA, this dataset download will not indicate whether individual patients were recruited into FLO-ELA, and the data fields relating to the management of haemodynamic therapy, and the supplementary data fields used within FLO-ELA will not be included.

Research staff enrolling patients will not necessarily be blinded to previous allocations but the randomisation method used is not predictable so there is little risk of selection bias (22). The trial management group and the trial steering committee will not see results broken down by treatment arm during the trial. Final analysis will occur once all follow up data is collected, the final statistical analysis plan has been signed off and data cleaning has occurred. The independent data monitoring committee will see outcome results by treatment group but the report will be prepared by an independent statistician, not otherwise involved in the trial.

7.7 Data collection

Nearly all data described below is already collected for NELA and entered on to the secure online web portal by clinicians and staff already registered at sites. NELA data are entered by the range of clinicians caring for laparotomy patients, with each specialty entering data on their area of clinical care. Existing NELA leads at each hospital monitor data completeness, addressing any missing data and taking responsibility for completing and locking patient records. Data completeness is monitored routinely by the central NELA team and fed back to sites regularly as an audit standard. A small number of data fields will be added to the NELA web portal for FLO-ELA, only becoming activated for those patients who have been randomised. Clinicians will be asked to complete these data fields prospectively, as they currently do for NELA. Research nurses will check for data completeness and accuracy of the FLO-ELA

specific data fields after the intervention period. This will be monitored and actively managed throughout the trial. These data will then be linked to the ONS/HES/NSSISD/PEDW databases using patient identifiers to allow collation of outcome data including mortality and hospital readmission. The data sharing agreement – with a legal basis in individual patient consent - will be established with NHS Digital (formerly the Health & Social Care Information Centre, HSCIC) and devolved nation equivalent organisations prior to the start of patient recruitment.

7.7.1 Randomisation data

- NHS number*
- Date of birth*
- Gender*
- Postcode*
- NELA ID
- Checklist to ensure the patient meets the eligibility criteria
- Patient age
- ASA score
- Indication for planned surgery
- Centre ID (collected automatically during log-in to randomisation system)

*patient identifiers are collected to allow follow up of all randomised patients. See: section 7.10.

7.7.2 NELA dataset

The full list of data collected by NELA is in the Participant Manual available at <http://nela.org.uk/Audit-info-Documents#pt> and is included in Appendix 2.

Peri-operative data include: Date of birth, gender, date/time of hospital admission and other key aspects of pre-operative care, urgency and indication for surgery, patient risk scores and physiology markers, seniority of surgeon and anaesthetist during surgery, operative findings and procedure performed

Outcomes data include: Duration of stay in level 3 or level 2 bed and in hospital, vital status at discharge.

7.7.3 Supplementary data fields for FLO-ELA

Intervention patients:

Intra-operative:

- Cardiac output monitoring (COM): time started / monitor type
- Number of cycles through protocol (number of COM-guided fluid boluses given)
- Total volume of crystalloid, colloid, blood and blood product administered
- Inotrope/vasopressor administered – type and mode of administration (bolus / infusion)

In level 2/3 care during the six hours after surgery:

- Cardiac output monitoring (COM): time started and stopped / monitor type
- Number of cycles through protocol (number of COM-guided fluid boluses given)
- Total volume of crystalloid, colloid, blood and blood product administered
- Inotrope/vasopressor administered – type and mode of administration (bolus / infusion)
- Duration of trial intervention (if <6 hours, reason for early termination: transfer to level 1 care area / other)

Control group patients:

Intra-operative:

- Total volume of crystalloid, colloid, blood and blood product administered
- Inotrope/vasopressor administered – type and mode of administration (bolus / infusion)
- Cardiac output monitoring used in a control patient? If yes: time started and indication (patient deterioration / other reason)

In level 2/3 during the six hours after surgery:

- Total volume of crystalloid, colloid, blood and blood product administered
- Inotrope/vasopressor administered – type and mode of administration (bolus / infusion)
- Cardiac output monitoring used in a control patient? If yes: time started and indication (patient deterioration / other reason)
- Duration of trial intervention (if <6 hours, reason for early termination: transfer to level 1 care area / other)

7.7.4 Outcomes data from NHS Digital or devolved nation NHS datasets

- Mortality at 90 days and one year (via the ONS/NSSISD)
- Readmission to hospital as an inpatient (overnight stay) within 90 days of randomisation (HES/NSSISD/PEDW)

7.8 Predefined protocol deviations

- Failure to use cardiac output monitoring in an intervention group patient
- Failure to follow the haemodynamic algorithm (defined as at least one cycle of fluid bolus with measurement of stroke volume response) in an intervention group patient when a cardiac output monitor is being used.
- Use of cardiac output monitoring in a control group patient, including forms of monitoring based on stroke volume variation or pulse pressure variation only.

7.9 Follow-up procedures

Investigators will review a participant's medical record (paper or electronic) in order to check and complete NELA data entry. To collect data on the primary and secondary outcomes and enable the health economic analysis, we will request hospital episode statistics and mortality data from NHS Digital (formerly HSCIC) and equivalent devolved nation organisations. Prospective consent for ONS/HES/NSSISD/PEDW data linkage will be sought before enrolment into the trial.

7.10 Withdrawal of participants

All study participants are free to withdraw from the study at any time. In a small number of cases, after a patient has been randomised and the study intervention started, the patient may not ultimately undergo a surgical procedure in line with NELA inclusion criteria. This may be due to clinical deterioration before the start of surgery such that no surgery is performed, or to a change in the surgery performed. These patients are currently not included in the NELA dataset, and any data already entered to NELA is removed. These patients should also be withdrawn from the FLO-ELA trial, with clinical management reverting back to usual care. A participant withdrawal form will be completed for all participants withdrawn from the trial. However, ONS/HES data will still be collected for these patients, and they will be included in the final analysis on an intention to treat basis, unless a participant specifically asks for their data not to be included (see section 8).

7.11 End of study definition

The end of the study is defined as the point when the last patient has completed one year follow-up. The Data Monitoring and Ethics Committee (DMEC) will monitor safety data throughout the trial. Based on these results, they could recommend termination of the trial on safety grounds. They will report any concerns to the Trial Steering Committee (TSC), who will inform the Sponsor and take appropriate action, which may include stopping the trial, to address concerns about participant safety. The Research Ethics Committee will be informed in writing if the trial is suspended or terminated early.

7.12 Schedule of assessment

Event/Visit	Screening	Pre-op	Intra-op	24 hrs post-op	Hospital discharge	Post-op day 90	Post-op 365 days
Inclusion/exclusion criteria	x						
Informed consent	x						
NELA pre-operative data*		x					
Randomisation		x					
NELA intraoperative data*			x	x			
Fluid and inotropic therapy			x	x			
NELA postoperative data by medical notes review*				x	x		
NELA duration of hospital stay and days in critical care*					x		

SAE				X	X	X	X
Hospital readmissions (HES)						X	
Vital status (ONS)						X	X
End of trial form							X

****these data are already collected as routine care by medical teams for NELA***

8 STATISTICAL CONSIDERATIONS

8.1 Sample size calculation

Recent NELA data shows that in patients aged 50 or over, mortality 90 days after emergency laparotomy was 19.5% in 2014 and 18.8% in 2015. Meta-analysis of randomised trials of perioperative GDHT suggest a relative risk reduction in mortality at longest follow-up of ~15% (RR 0.86 [95%CI 0.74 – 1.0]) (6). This would be a clinically important effect to detect, as if the intervention became routine practice for all patients undergoing emergency laparotomy annually it could save several hundred lives each year.

With a 5% alpha level, 90% power, and assuming a 2% dropout rate and a 19% 90-day mortality rate in the usual care arm, we require 3823 patients in each arm (7646 total) to detect a risk ratio of 0.85 (equivalent to an absolute decrease from 19% to 16.15%) for the primary outcome.

8.2 Statistical analysis

The number of patients recruited and followed up will be recorded in a CONSORT flow chart. Baseline characteristics will be summarised by treatment group.

All analyses will be by modified intention-to-treat; patients will be analysed according to the treatment group to which they were randomised and all eligible patients for whom an outcome is available will be included in the analysis (23). Patients who were randomised in error (i.e. were ineligible at the time of randomisation) will be excluded from the analysis.

For each analysis we will present the number of patients included in the analysis, a summary measure of the outcome in each treatment group, treatment effect, 95% confidence interval and a two-side p-value. P-values <0.05 will be considered statistically significant.

The primary outcome (mortality within 90 days of randomisation) will be analysed using a mixed-effects logistic regression model, with a random-intercept for centre (24). The model will be adjusted for the minimisation factors of patient age and ASA class (I, II, III, IV, and V) (25), as well as the following prognostic baseline covariates: urgency of surgery (Immediate, Urgent, and Expedited), Glasgow Coma Score (GCS), systolic blood pressure and pulse rate (26). 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) (27,28). Missing baseline data will be handled using mean imputation for continuous variables, and a missing indicator variable for categorical variables (29). Secondary outcomes will be analysed using similar methods.

We will also conduct subgroup analysis of the primary outcome by urgency of surgery (Immediate vs. Urgent vs. Expedited), age (<70 vs. 70+), indication for surgery (bowel perforation vs. bowel obstruction without perforation vs. other indications) and a pre-operative predicted risk score, which will be determined, with a binary cut-off established for the subgroup analysis, before any of the data is viewed. Subgroup analysis will be undertaken by statistically testing for an interaction term. Subgroup specific estimates and 95% confidence intervals will also be reported. Any subgroup findings will be treated with caution and will be given less weight than the primary analysis.

8.3 Health economic analysis

The economic evaluation would adhere, as far as possible, to the most up to date NICE Guide to the Methods of Technology Appraisal to ensure that trial findings are informative for national-level policy considerations. The perspective will be limited to NHS secondary care, which will likely cover the main drivers of total care costs, including the initial hospital admission (including the treatment of complications) and subsequent hospital readmissions during the 90-day period. NELA will provide all relevant individual-level resource use information related to the initial hospital admission, including that related to implementation of the intervention. Electronic hospital resource use data (including inpatient, outpatient and critical care episodes) will be obtained from NHS Digital (or devolved nation equivalents) for the 90 day period post-randomisation to estimate total secondary care cost over the 90 day follow-up period. In addition, hospital data covering a period of 90 days pre-randomisation will be retrospectively obtained from NHS Digital (or equivalent) in order to carry out adjustments for baseline differences in mean cost between comparison groups.

Unit costs for each assessed resource use item will be collated from national sources (such as the NHS Reference Costs) where possible; adjustments and additional estimates will be obtained from published studies and expert opinion where needed. These will be applied to individual-level resource use to estimate individual-level costs.

Due to the lack of direct patient assessments in this trial, quality-adjusted life years (QALYs) will be estimated from EQ5D-3L assessments in the EPOCH trial using a mapping approach relevant to the available data (to be determined and established prior to an economic analysis plan being signed off). Broadly, this will involve estimating an EQ-5D-3L or tariff prediction model in the EPOCH data using relevant patient characteristics common to both studies, and applying that model to our study data to predict EQ-5D-3L or tariff values.

The comparison of resulting QALYs and costs will broadly follow the outcomes analyses (e.g. same comparison groups, intention-to-treat basis, adjustment for minimisation factors and other pre-specified covariates) but bootstrapped regression approaches (5000 replications) will be used to address the expected skewness in the data distributions.

The main economic analysis will be a cost-effectiveness analysis linking 90-day costs with the primary outcome, mortality within 90 days of surgery. The cost-effectiveness analysis will be presented in terms of incremental cost per death avoided at 90 days post-randomisation. A secondary economic analysis (since the QALY data are being estimated indirectly) will be a cost-utility analysis in terms of incremental cost per QALY gained at 90 days post randomisation. Incremental cost-effectiveness ratios will be calculated in cases when both incremental cost and outcome is positive or negative. In other cases, the proposed intervention will be considered either dominant (lower cost and higher outcome) or dominated (higher cost and lower outcome).

Uncertainty around cost-effectiveness/cost-utility will be analysed using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). CEACs will be constructed using the net benefit regression approach. For each cost-outcome combination that we will examine, we will calculate a series of net benefits for a range of relevant values that decision-makers may place upon outcome improvements (λ). (For QALYs the range is likely to be £0 to £50,000 to include the current value placed on QALY gains in decision-making by NICE). Net benefits will then be compared by trial arm using bootstrapped regressions (5000 replications; including relevant covariates) of trial arm upon net benefit. For each value of λ , the proportion of iterations indicating a higher net benefit for the intervention arm will be calculated and plotted as a CEAC.

One-way sensitivity analyses and Tornado diagrams will be used to examine the effect of structural and parametric assumptions on the results of the cost-effectiveness and cost-utility analyses. This includes uncertainty in published unit costs used to value resource use, intervention cost and the values of parameters used in the QALY mapping algorithm. All cost, outcome and unit cost data used for the economic evaluation will also be presented in a disaggregated format to facilitate interpretations from alternative perspectives.

8.4 Secondary studies

The use of FLO-ELA trial data for further secondary studies is encouraged. A prospective statistical analysis plan will be prepared for each secondary study before data analysis commences.

9 RESEARCH ETHICS

The PI will ensure that this trial is conducted in accordance with the Principles of the Declaration of Helsinki as amended in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington DC (2002), Tokyo (2004), Seoul (2008) and Fortaleza (2013) as described at the following internet site: <http://www.wma.net/en/30publications/10policies/b3/index.html>. The trial will fully adhere to the principles outlined in the Guidelines for Good Clinical Practice ICH Tripartite Guideline

(January 1997) and to the Mental Capacity Act 2005. The study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements. At sites, all accompanying material given to a potential participant will have undergone an independent Research Ethics Committee review. Full approval by the Research Ethics Committee will be obtained prior to starting the trial and fully documented by letter to the Chief Investigator naming the trial site, local PI (who may also be the Chief Investigator) and the date on which the ethics committee deemed the trial as permissible at that site. All members of the trial steering committee will declare conflicts of interest before joining the study group. These will be listed on any publications arising from the trial.

10 DATA HANDLING AND RECORD KEEPING

10.1 Confidentiality

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act (UK), NHS Caldicott Principles (UK), The Research Governance Framework for Health and Social Care (UK), and the conditions of Research Ethics Committee Approval, or corresponding legislation or approvals for a particular participating site. The patient's NHS Number, gender, date of birth and postcode will be collected at randomisation to allow tracing through national records. The personal data recorded on all documents will be regarded as confidential. The PI must maintain in strict confidence trial documents, which are to be held in the local hospital (e.g. patients' written consent forms). The PI must ensure the patient's confidentiality is maintained at all times. The Sponsor will ensure that all participating partner organisations will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. Representatives of the trial management team will require access to patient notes for quality assurance purposes and source data verification, but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete trial records, provided that patient confidentiality is protected.

10.2 Data storage

Data will be entered directly on to the secure NELA data entry web portal. Submitted data will be reviewed for completeness and consistency by authorised users within the study group. Submitted data will be stored securely against unauthorised manipulation and accidental loss since only authorised users at site, the Sponsor organisation, Queen Mary University of London or NELA (host of the data entry portal) will have access. Desktop security is maintained through user names and passwords. Data back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 1998 (UK).

10.3 Archiving

Each site will maintain and securely store an investigator site file. NELA and the PCTU (QMUL) will be responsible for archiving identifiable data. Data will be archived in accordance with local standards and procedures for quality and assurance. All other trial documentation and data will be archived by the Sponsor and PCTU in a purpose designed archive facility for twenty years in accordance with regulatory requirements. Access to these archives will be restricted to authorised personnel. Electronic data sets will be stored indefinitely.

10.4 Patient identifiable data

To facilitate linkage to national databases for the collection of follow-up data, patient identifiable data will be collected and entered on to the secure NELA data entry web portal and the randomisation system. Data will be stored and handled in accordance with the Data Protection Act 1998 (UK) or equivalent legislation for a particular country or site. In the event that patient identifiable data needs to be transferred between authorised users, this will occur by email from @nhs.net to @nhs.net.

11 PRODUCTS, DEVICES AND TECHNIQUES

11.1 Cardiac output-guided haemodynamic therapy

Cardiac output monitors are routinely used in secondary care. Investigators may only use commercially available cardiac output monitoring equipment shown to accurately track changes in cardiac stroke volume, from a list of devices in the intervention SOP. Please see the study intervention SOP for specific details of the intervention.

12 SAFETY REPORTING

12.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a subject to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities. However, FLO-ELA is a non-CTIMP trial, and all trial interventions are already in routine clinical use for patients undergoing emergency laparotomy surgery. Furthermore, adverse events are very common following emergency laparotomy. AEs will therefore not be collected for the FLO-ELA trial. The DMEC will monitor the safety of the intervention by reviewing in-hospital mortality rates and reported SAEs at intervals in both trial groups.

12.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as an untoward occurrence that:

- (a) results in death;
- (b) is life-threatening;
- (c) requires hospitalisation or prolongation of existing hospitalisation;
- (d) results in persistent or significant disability or incapacity;

An SAE occurring to a research participant should be reported to the sponsor where in the opinion of the Principal Investigator the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

The FLO-ELA trial is an investigation of a perioperative intervention. It is expected that patients undergoing emergency laparotomy surgery will suffer medical complications, with consequences up to and including death. Only complications considered by the local PI or delegated authority (blinded to study group allocation) to be *related to the use of study procedures* and not a typical complication of emergency bowel surgery should be reported as SAEs. Typical complications of emergency bowel surgery, which should not be reported as SAEs, are included in Appendix 4.

12.3 Notification and reporting of Serious Adverse Events

Serious Adverse Event (SAEs) that are considered to be 'related' and 'unexpected' are to be reported to the sponsor and the sponsor's representative within 72 hours of learning of the event. The event will be reviewed by the CI and if it meets the criteria for an SAE, will then be reported to the REC within 15 days of receipt of the SAE report.

12.4 Reporting a Serious Adverse Event

The local PI or delegated authority will be blinded to study group allocation and will review any reported events to ensure that they meet the criteria for an SAE. Individual sites will notify the co-ordinating centre in that country of an SAE by emailing a scanned copy of the supplementary SAE report form to the national co-ordinator. An SAE log should be maintained at site to record the details of the SAE and its review until resolution. SAEs will be reported within 72 hours and will be forwarded to the sponsor via the co-ordinating centre.

12.5 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of trial participants from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However,

it is the responsibility of the CI to inform the sponsor and Research Ethics Committee of this event in writing, setting out the reasons for the urgent safety measures and the plan for further action, within three days. The sponsor must be sent a copy of the correspondence with regards to this matter.

12.6 Annual safety reporting

The CI will send the annual progress report to the REC and to the sponsor starting 12 months after the date of the favourable opinion..

12.7 Overview of the safety reporting responsibilities

The CI/PI has the overall oversight responsibility. The CI/PI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

13 MONITORING & AUDITING

The Sponsor and PCTU will have oversight of the trial conduct at each site. The trial team will take day-to-day responsibility for ensuring compliance with the requirements of GCP in terms of quality control and quality assurance of the data collected as well as safety reporting. The FLO-ELA Trial Management Group will communicate closely with individual sites and the Sponsor's representatives to ensure these processes are effective. A Data Monitoring and Ethics Committee (DMEC) will be appointed (see section 14.3).

The PCTU quality assurance manager will conduct a study risk assessment in collaboration with the CI. Based on the risk assessment, an appropriate study monitoring and auditing plan will be produced according to PCTU SOPs. Any changes to the monitoring plan must be agreed by the PCTU QA manager and C.I.

13.1 Monitoring the safety and wellbeing of trial participants

The Research and Development departments at each trial site should perform regular audits of research practice. Systems are in place to ensure that all PIs and designees are able to demonstrate that they are qualified by education, training or experience to fulfill their roles and that procedures are in place that assures the quality of every aspect of the trial. The intervention will last less than 12 hours in most cases, therefore it is extremely unlikely that new safety information will arise during the intervention period. Nonetheless should this situation arise, participants will be informed and asked if they wish to discontinue the intervention. If the subjects wish to continue in the trial they will be formally asked to sign a revised approved patient information sheet and consent form. Early termination of trial in response to safety issues will be addressed via the DMEC. Day to day management and monitoring of individual sites will be undertaken via the Trial Management Group composed of the Chief Investigator and supporting staff. They will meet on a regular basis to discuss trial issues.

13.2 *Monitoring the safety of investigators*

Each site has health and safety policies for employees. All personnel should ensure that they adhere to health and safety regulations relating to their area of work. The PI will ensure that all personnel have been trained appropriately to undertake their specific tasks. The trial team will complete GCP and consent training prior to start up.

14 TRIAL MANAGEMENT & COMMITTEES

14.1 *Trial management group*

Day-to-day trial management will be co-ordinated by a trial management group consisting of the Chief Investigator, their support staff and members of the PCTU.

14.2 *Trial steering committee*

The Trial Steering Committee will be formed in accordance with NIHR guidance. It will oversee the trial and will consist of:

- several independent clinicians, statistician and trialists
- lay representation
- co-investigators
- an independent Chair

Meetings will be held at regular intervals determined by need but not less than once a year. The TSC will take responsibility for:

- approving the final trial protocol;
- major decisions such as a need to change the protocol for any reason;
- monitoring and supervising the progress of the trial;
- reviewing relevant information from other sources;
- considering recommendations from the DMEC and
- informing and advising on all aspects of the trial

14.3 *Data monitoring and ethics committee*

The Data Monitoring and Ethics Committee (DMEC) will be formed in accordance with NIHR guidance. It is independent of the trial team and comprises of two clinicians with experience in undertaking clinical trials and a statistician. The committee will agree conduct and remit, which will include the early termination process. During the period of recruitment into the trial the DMEC will monitor safety data and routinely meet to assess safety analyses. The trial will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile. The DMEC functions primarily as a check for safety by

reviewing SAEs and in-hospital mortality.

15 FINANCE AND FUNDING

The FLO-ELA trial will be funded by the National Institute for Health Research (UK).

16 SPONSORSHIP & INDEMNITY

University Hospital Southampton NHS Foundation Trust will act as Sponsor and provide no fault insurance.

17 PUBLICATION

Data arising from this research will be made available to the scientific community in a timely and responsible manner. A detailed scientific report will be submitted to a widely accessible scientific journal on behalf of the FLO-ELA Trial Steering Committee. The TSC will agree the membership of a writing committee, which will take primary responsibility for final data analysis and writing of the scientific report. All members of the writing committee will comply with internationally agreed requirements for authorship and will approve the final manuscript prior to submission. Please see FLO-ELA trial publication charter for further details.

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Appendix 1: NELA Inclusion & Exclusion Criteria

NELA Inclusion Criteria

NELA will enrol the patients treated in England or Wales who meet the following criteria:

- aged 18 years and over
- have an NHS number
- who undergo an expedited, urgent or emergency (NCEPOD definitions) abdominal procedure on the gastrointestinal tract

This will include:

- Open, laparoscopic, or laparoscopically-assisted procedures
- Procedures involving the stomach, small or large bowel, or rectum for conditions such as perforation, ischaemia, abdominal abscess, bleeding or obstruction
- Washout/evacuation of intra-peritoneal abscess (unless due to appendicitis or cholecystitis - excluded, see below)
- Washout/evacuation of intra-peritoneal haematoma
- Bowel resection/repair due to incarcerated incisional, umbilical, inguinal and femoral hernias (but not hernia repair without bowel resection/repair) E.g. large incisional hernia repair with bowel resection.
- Bowel resection/repair due to obstructing/incarcerated incisional hernias provided the presentation and findings were acute. This will include large incisional hernia repair with division of adhesions.
- Laparotomy/laparoscopy with inoperable pathology (e.g. peritoneal/hepatic metastases)
- Laparoscopic/open adhesiolysis
- Return to theatre for repair of substantial dehiscence of major abdominal wound (i.e. "burst abdomen")
- Any reoperation/return to theatre meeting the criteria above is included, such as;
 - patients returning to theatre for ischaemic bowel following elective or emergency aortic aneurysm surgery, or for ischaemic bowel following cardiac surgery
 - patients requiring non-elective GI surgery following prior gynaecological surgery

If multiple procedures are performed on different anatomical sites within the abdominal/pelvic cavity, the patient would be included if the major procedure is general surgical. E.g.

- Non-elective colonic resection with hysterectomy for a fistulating colonic cancer would be included as the bowel resection is the major procedure
- However bowel resection at the same time as emergency abdominal aortic aneurysm repair would not be included as the aneurysm repair is the major procedure

- Any reoperation/return to theatre meeting the criteria above is included, such as;
 - patients returning to theatre for ischaemic bowel following elective or emergency aortic aneurysm surgery, or for ischaemic bowel following cardiac surgery
 - patients requiring any of the above non-elective GI procedures following prior gynaecological surgery
 - patients returning to theatre for post-operative complications (e.g. bleeding, sepsis) following prior urological/renal surgery (except transplant)
 - patients requiring any of the above non-elective GI procedures as a return to theatre following any other elective or emergency procedure (even if the original procedure would have been excluded)

The above criteria are not exhaustive. Any intra-abdominal procedure not identifiable within the exclusion criteria should be included.

NELA Exclusion Criteria

Patients with the following characteristics will be excluded from NELA:

1. Patients under 18
2. Do not have an NHS number
3. Elective laparotomy / laparoscopy
4. Diagnostic laparotomy/laparoscopy where no subsequent procedure is performed (NB, if no procedure is performed because of inoperable pathology, then include)
5. Appendicectomy +/- drainage of localised collection unless the procedure is incidental to a non-elective procedure on the GI tract
6. Cholecystectomy +/- drainage of localised collection unless the procedure is incidental to a non-elective procedure on the GI tract (All surgery involving the appendix or gallbladder, including any surgery relating to complications such as abscess or bile leak is excluded. The only exception to this is if carried out as an incidental procedure to a more major procedure. We acknowledge that there might be extreme cases of peritoneal contamination, but total exclusion avoids subjective judgement calls about severity of contamination.)
7. Non-elective hernia repair without bowel resection
8. Minor abdominal wound dehiscence unless this causes bowel complications requiring resection
9. Non-elective formation of a colostomy or ileostomy as either a trephine or a laparoscopic procedure (NB: if a midline laparotomy is performed, with the primary procedure being formation of a stoma then this should be included)
10. Vascular surgery, including abdominal aortic aneurysm repair (NB: resection of ischaemic bowel as a separate visit to theatre following abdominal aortic aneurysm repair is included)
11. Caesarean section or obstetric laparotomies

12. Gynaecological laparotomy (However bowel resection performed as a non-elective procedure for obstruction due to gynaecological cancer would be included)
13. Ruptured ectopic pregnancy, or pelvic abscesses due to pelvic inflammatory disease
14. Laparotomy/laparoscopy for pathology caused by blunt or penetrating trauma
15. All surgery relating to organ transplantation (including returns to theatre for any reason following transplant surgery)
16. Surgery relating to sclerosing peritonitis
17. Surgery for removal of dialysis catheters
18. Laparotomy/laparoscopy for oesophageal pathology
19. Laparotomy/laparoscopy for pathology of the spleen, renal tract, kidneys, liver, gall bladder and biliary tree, pancreas or urinary tract

Appendix 2: NELA data entry

1.	Demographics and Admission	Format	Notes
1.1	NHS Number		
1.2	Pseudo-anonymisation		Computer generated
1.3	Local patient id/hospital number		
1.4	Date of birth		
	Age on arrival		Age will automatically be calculated on web tool
1.5	Sex	•Male / •Female	
1.6	Forename		
1.7	Surname		
1.8	Postcode		
1.9	Date and time patient admitted to this hospital		Admission time is 1st presentation to hospital/A&E. If the GP out of hours centre is based at the hospital A&E, then use time care was transferred from GP to the hospital. I.e. Admission time is intended to reflect the time at which the patient's care became the responsibility of the hospital.
1.10	What was the nature of this admission?	•Elective / •Non-elective	
1.10b	If non-elective, what was the initial route of admission/assessment?	<ul style="list-style-type: none"> ○ Assessed initially in Emergency Department ○ Assessed initially in "front of house" acute surgical assessment unit ○ Direct referral to ward by GP 	
1.11	Which specialty was this patient first admitted under?	<ul style="list-style-type: none"> ○ General surgery ○ General medicine ○ Gastroenterology ○ Elderly Care ○ Other 	Do not use "other" if the patient spent a period of observation under Emergency Medicine
1.12	Residence before this hospital admission	<ul style="list-style-type: none"> ○ Own home/sheltered housing ○ Residential care ○ Nursing care ○ Unknown 	

2	Pre-op	Format	Notes
If the patient is returning to theatre as an emergency following previous elective surgery, all answers should relate to the emergency laparotomy, not the previous elective surgery.			
2.1	Date and time first seen by consultant surgeon following admission with acute abdomen. If under care of a non-surgical specialty, this should be the time 1 st seen after referral to general surgeons..	Date _____(DD/MM/YYYY) <ul style="list-style-type: none"> ○ Date not known Time _____(HH:MM) <ul style="list-style-type: none"> ○ Time not known ○ Not Seen 	For acute general surgical admissions, please detail the first consultant surgical review following admission. For inpatients referred to the surgical team by different specialities, please detail the first consultant surgical review following referral. For patients having emergency surgery as a complication of elective surgery, please use the time that the decision was made that they needed surgery for 2.1 & 2.2. In reality, Qu 2.1

			will be redundant for these patients as they will be highlighted by the fact that they were originally an elective admission (Qu1.10), and complication of previous surgery within the same admission (Qu 5.1).
2.2	Date and time that the decision was made to operate <i>If this is unavailable please enter date and time that this patient was first booked for theatre for emergency laparotomy</i>	Date _____(DD/MM/YYYY) ○ Date not known Time _____(HH:MM) ○ Time not known	If the time is unknown for “decision made”, but date and time known for “booking”, please provide full details of the latter. If only date is known for both fields, please provide date for “decision made”.
2.2i	Which date and time is recorded?	○ Decision to operate ○ First booked for theatre	
2.3	Consultant responsible for surgical care at the time the patient was booked for surgery (this may be different to the operating consultant)	(Local pick list of names with GMC number)	If a consultant is being entered for the first time, please tick on the 'Consultant not on list' box and manually enter the name and GMC number. Once these have been entered, the consultant will appear on the drop down list in call cases going forward
2.4	Was there consultant surgeon input into the decision to operate?	○ Yes, consultant reviewed patient at time of decision* ○ Yes, following discussion with junior team member # ○ Decision made by junior team member without consultant input ○ Unknown	*can refer to situations where e.g. decision is made on consultant ward round pending CT results, which then confirms need for surgery # refers to situations where consultant has not seen patient but has been discussed with consultant
2.5	NO LONGER REQUIRED	NO LONGER REQUIRED	
2.6	NO LONGER REQUIRED	NO LONGER REQUIRED	
2.7	Was an abdominal CT scan performed in the pre-operative period as part of the diagnostic work-up?	○ No ○ Yes ○ Unknown	
2.7a	If performed, how was this CT reported pre-operatively?	○ In-house consultant ○ In-house Registrar ○ Outsourced service ○ Not reported pre-operatively ○ Unknown	If CT is reported by a registrar and validated by a consultant before surgery, select “in-house consultant”. If not validated by a consultant before surgery, select “registrar”)
2.7b	Was there a pre-operative discussion between the radiologist and the requesting team about the CT findings?	○ Yes ○ No ○ Unknown	
2.7c	Was there a discrepancy between the CT report and surgical findings that altered or delayed either the diagnosis or surgical management?	○ Yes ○ No ○ Unknown	

2.8a	Consultant Anaesthetist involvement in planning perioperative care	<ul style="list-style-type: none"> ○ Yes – seen by consultant anaesthetist in person ○ Yes – discussion between consultant anaesthetist & other team member (of any specialty) ○ No consultant anaesthetist input before surgery ○ Unknown 	This can include pre-operative assessment, discussion about decisions and risks/benefits or surgery, or need for critical care
2.8b	Intensive care involvement in planning perioperative care	<ul style="list-style-type: none"> ○ Yes – seen by consultant intensivist in person ○ Yes – discussion between consultant intensivist & other team member (of any specialty) ○ Seen by or discussion with junior ITU team member only ○ No intensive care input before surgery ○ Unknown 	This can include pre-operative assessment, discussion about decisions and risks/benefits or surgery, or need for critical care
2.9	NO LONGER REQUIRED	NO LONGER REQUIRED	
2.10	What was the date and time of the first dose of antibiotics following presentation to hospital?	<ul style="list-style-type: none"> ○ In theatre, or Date _____(DD/MM/YYYY) ○ Date not known Time _____(HH:MM) ○ Time not known ○ Not Administered 	Only relevant for non-elective admissions
2.11a	Was sepsis suspected on admission?	<ul style="list-style-type: none"> ○ Yes ○ No ○ Unknown 	
2.11b	Was sepsis suspected at the time the decision for surgery was made?	<ul style="list-style-type: none"> ○ Yes ○ No ○ Unknown 	
2.12	Was the patient assessed by a specialist from Elderly Medicine in the pre-operative period?	<ul style="list-style-type: none"> ○ Yes ○ No ○ Unknown 	Can include physician or nurse specialist

3	Pre-op Risk stratification	Format	Notes
3.1	Prior to surgery, what was the risk of death for the patient that was entered into medical record?	<ul style="list-style-type: none"> ○ lower (<5%) ○ high (5-10%) ○ highest (>10%) ○ Not documented 	<p>For information, wording of relevant standard: "An assessment of mortality risk should be made explicit to the patient and recorded clearly on the consent form and in the medical record."</p> <p>If both percentage predicted mortality AND risk category are documented, please select the highest risk option</p>
3.2	If documented, how was this assessment of risk made? (Please select all that apply)	<ul style="list-style-type: none"> ○ Risk prediction tool (e.g. P-POSSUM) ○ Clinical Judgement ○ Surgical APGAR ○ Physiological criteria ○ Other e.g. hospital policy 	<p>Formal assessments of risk; this includes risk stratification tools (such as ASA) and prediction models (such as APACHE and POSSUM systems).</p> <p>Clinical judgement; refers to the categorisation or estimation of risk, based on</p>

			clinical acumen and experience. Physiological criteria; either use of physiological variables in isolation (eg lactate) or incorporated into tools such as the early warning score (i.e. not incorporated into a risk stratification tool or prediction model as above)
3.3	What was the ASA score?	<input type="radio"/> 1: No systemic disease <input type="radio"/> 2: Mild systemic disease <input type="radio"/> 3: Severe systemic disease, not life-threatening <input type="radio"/> 4: Severe, life-threatening <input type="radio"/> 5: Moribund patient	
3.4	What was the most recent pre-operative value for serum Creatinine (micromol/l)	<input type="radio"/> _____ <input type="radio"/> Not performed	Please enter values closest to time of booking for theatre
3.5	What was the most recent pre-operative value for blood lactate – may be arterial or venous (mmol/l)	<input type="radio"/> _____ <input type="radio"/> Not performed	Please enter values closest to time of booking for theatre. Only one decimal point required.
3.5i	What was the highest CRP in the pre-operative period (mg/l)?	<input type="radio"/> _____ <input type="radio"/> Not performed	
3.5ii	What was the lowest albumin in the pre-operative period (g/l)?	<input type="radio"/> _____ <input type="radio"/> Not performed	
	P-POSSUM calculation		
	For questions 3.6 to 3.22 please enter values closest to time of booking for theatre in order to calculate P-POSSUM. Answers should reflect chronic <i>and</i> acute pathophysiology. in order to calculate		
3.6	Serum Sodium concentration (mmol/l)		
3.7	Serum Potassium concentration (mmol/l)		
3.8	Serum Urea concentration (mmol/l)		
3.9	Serum Haemoglobin concentration (g/dl)		Units must be in g/l. If results are presented as g/dl in your institution, the value should be multiplied by 10 to convert to g/l.
3.10	Serum White cell count ($\times 10^9 / l$)		
3.11	Pulse rate(bpm)		
3.12	Systolic blood pressure (mmHg)		
3.13	Glasgow coma scale		
3.14	Select an option that best describes this patient's ECG	<input type="radio"/> No abnormalities <input type="radio"/> AF rate 60-90 <input type="radio"/> AF rate >90/ any other	If no investigation have been performed AND there is no clinical detail available, please select "no abnormality"

		abnormal rhythm/paced rhythm/ >5VE/min/ Q, ST or T wave abnormalities	
3.15	Select an option that best describes this patient's cardiac signs and chest xray appearance	<ul style="list-style-type: none"> ○ No failure ○ Diuretic, digoxin, antianginal or antihypertensive therapy ○ Peripheral oedema, warfarin Therapy or CXR: borderline cardiomegaly ○ Raised jugular venous pressure or CXR: cardiomegaly 	<p>If CXR findings are worse than clinical findings, (or vice versa) please use worst score.</p> <p>If no investigation have been performed AND there is no clinical detail available, please select "no abnormality"</p>
3.16	Select an option that best describes this patient's respiratory history and chest xray appearance	<ul style="list-style-type: none"> ○ No dyspnoea ○ Dyspnoea on exertion or CXR: mild COAD ○ Dyspnoea limiting exertion to < 1 Flight or CXR: moderate COAD ○ Dyspnoea at rest/rate > 30 at rest or CXR: fibrosis or consolidation 	<p>If CXR findings are worse than clinical findings, (or vice versa) please use worst score.</p> <p>If no investigation have been performed AND there is no clinical detail available, please select "no abnormality"</p>
3.16a	Patient was ventilated prior to emergency laparotomy	<ul style="list-style-type: none"> ○ Yes ○ No 	This is intended to identify those patients who are intubated and ventilated prior to laparotomy, e.g. ITU patients
		<i>Online web tool will automatically calculate Physiology severity score</i>	
3.17	Select the operative severity of the intended surgical intervention (see help box for examples)	<ul style="list-style-type: none"> ○ Major ○ Major+ 	<p>Major+:</p> <p>All colonic resections (excluding colostomy alone)</p> <p>All gastrectomy (but not repair perforated or bleeding ulcer) Small bowel tumour resection</p> <p>Re-operations for ongoing sepsis or bleeding</p> <p>Laparostomy</p> <p>Intestinal bypass</p> <p>Major</p> <p>All other procedures including: Stoma formation</p> <p>Small bowel resection Division adhesions</p> <p>Repair perforated or bleeding ulcer</p>
3.18	Including this operation, how many operations has the patient had in the 30 day period prior to this procedure?	<ul style="list-style-type: none"> ○ 1 ○ 2 ○ >2 	<p>Do not "unbundle" procedures. Examples of single procedure:</p> <ul style="list-style-type: none"> • Hartmann's procedure (this should not be "unbundled" as 2 procedures -sigmoid colectomy and end colostomy). • Colonic resection with washout of a localised abscess would also be 1 procedure.

			<p>Examples of 2 procedures:</p> <ul style="list-style-type: none"> • Primary colonic anastomosis with a defunctioning ileostomy. • Colonic resection and extensive division of adhesions. • Colonic resection and small bowel repair. <p>Example of >2 procedures: Hartmann's procedure with resection of small bowel with insertion of tube gastrostomy</p>
3.19	Based on your clinical experience of the intended surgery, please estimate the likely <i>intraoperative</i> blood loss (ml)	<ul style="list-style-type: none"> ○ <100 ○ 101-500 ○ 501-999 ○ ≥1000 	Based on your clinical experience, please do your best to estimate the likely volume of intraoperative blood loss.
3.20	Please select a value that best describes the likely degree of peritoneal soiling	<ul style="list-style-type: none"> ○ None ○ Serous fluid ○ Localised pus ○ Free bowel content, pus or blood 	Based on available radiological imaging and your clinical experience, please do your best to estimate the likely degree of peritoneal soiling.
3.21	What severity of malignancy is anticipated to be present?	<ul style="list-style-type: none"> ○ None ○ Primary only ○ Nodal metastases ○ Distant metastases 	Based on available radiological imaging and your clinical experience, please do your best to estimate the extent of intra- abdominal malignancy.
3.22	Please select urgency of surgical intervention (see help notes for additional information, including equivalent Possum categories)	<ul style="list-style-type: none"> ○ 3. Expedited (>18 hours) ○ 2B. Urgent (6-18 hours) ○ 2A. Urgent (2-6 hours) ○ 1. Immediate (<2 hours) 	<p>Based on your clinical experience this should be the maximum time that a patient could reasonably wait for surgery. These classifications are based on NCEPOD and Surviving Sepsis. The equivalent POSSUM categories are also shown.</p> <p>Examples:</p> <p>POSSUM: Emergency (resuscitation of > 2h possible)</p> <p>3. Expedited (>18 hours): No SIRS or sepsis e.g. developing large bowel obstruction</p> <p>2B. Urgent (6-18 hours): Sepsis e.g. localised abscess or obstructed hernia</p> <p>2A. Urgent (2-6 hours): Severe sepsis e.g. intestinal perforation</p> <p>POSSUM: Emergency (immediate surgery <2h needed)</p> <p>1. Immediate (<2 hours): Life threatening haemorrhage and septic shock e.g. profuse GI bleed or pan-intestinal ischaemia</p>
		Online web tool will automatically calculate	

		<i>Operative severity score</i>	
3.23	Pre-op P-POSSUM predicted mortality	Calculated_____	This value will be calculated automatically
3.24	Pre-op POSSUM predicted morbidity	Calculated_____	This value will be calculated automatically
3.25	Not all P-POSSUM investigations available	○	Please select if any of the above investigations are unavailable. This will allow you to save the form with missing data
3.26	Estimated mortality using NELA risk adjustment model	○ Calculated_____	Figure only provided if all data available

4	Intra-op	Format	Notes
4.1	Date and time of entry in to operating theatre/anaesthetic room (not theatre suite)	Date_____ (DD/MM/YYYY) Time_____ (HH:MM) ○ Timenotknown	Please enter the date/time at which the patient enters the anaesthetic room OR operating theatre (for patients anaesthetised in theatre), whichever comes first.
4.2	Senior surgeon grade	○ Consultant ○ Post-CCT fellow ○ SAS grade ○ Research Fellow / Clinical Fellow ○ Specialty trainee / registrar ○ Core trainee / SHO ○ Other	This can include surgeon supervising in theatre but not necessarily scrubbed
4.2a	Consultant present/supervising: Name/GMC/specialty of operating or supervising consultant	(Please select consultant - Online) _____	If consultant not present, enter name of supervising consultant
4.3	Senior anaesthetist present in theatre	○ Consultant ○ Post-CCT fellow ○ SAS grade ○ Research Fellow / Clinical Fellow ○ Specialty trainee / registrar ○ Core trainee / SHO ○ Other	
4.3a	Consultant present (or supervising): Name/GMC of anaesthetist	(Please select consultant - Online) _____	If consultant not present, enter name of supervising consultant
4.4	How did you provide goal directed fluid therapy?	○ Not provided ○ Dynamic index e.g. Stroke volume, PPV, SVV ○ Static index e.g. CVP ○ Other, e.g. bioimpedance	PPV – pulse pressure variability SVV – stroke volume variability CVP – central venous pressure

	THIS QUESTION REPLACED AS DESCRIBED IN MAIN PROTOCOL FOR FLO-ELA PATIENTS		
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5	Procedure	Format	Notes
	Is this the first surgical procedure of this admission, or a complication of previous surgery within the same admission?	<ul style="list-style-type: none"> ○ First surgical procedure after admission ○ Surgery for complication of previous surgical procedure within the same admission 	
5.2	What is the indication for surgery? (Please select all that apply)	<ul style="list-style-type: none"> ○ Peritonitis ○ Perforation ○ Abdominal abscess ○ Anastomotic leak ○ Intestinal fistula ○ Phlegmon ○ Pneumoperitoneum ○ Necrosis ○ Sepsis ○ Small bowel obstruction ○ Large bowel obstruction ○ Volvulus ○ Internal hernia ○ Pseudo-obstruction ○ Intussusception ○ Incarcerated hernia ○ Obstructing incisional hernia ○ Haemorrhage ○ Ischaemia ○ Colitis ○ Abdominal wound dehiscence ○ Abdominal compartment syndrome ○ Acidosis ○ Iatrogenic injury ○ Foreign body ○ Planned relook 	
5.3.a	Main procedure	<ul style="list-style-type: none"> ○ Peptic ulcer – suture or repair of perforation ○ Peptic ulcer – oversew of bleed ○ Gastrectomy: partial or total ○ Gastric surgery - other ○ Small bowel resection ○ Resection of Meckel's diverticulum ○ Colectomy: left (including sigmoid colectomy and anterior resection) ○ Colectomy: right (including ileocaecal resection) ○ Colectomy: subtotal or 	<p>Please note that, in accordance with NELA inclusion criteria, primary and additional procedure options vary</p> <p>Please see inclusion/exclusion criteria under the “support” tab on this data collection website. They can also be downloaded from http://www.nela.org.uk/NELA_Docs</p>

		<ul style="list-style-type: none"> panproctocolectomy ○ Hartmann's procedure ○ Colorectal resection - other ○ Abdominal wall closure following dehiscence ○ Abdominal wall reconstruction ○ Adhesiolysis ○ Reduction of volvulus ○ Enterotomy ○ Stricturoplasty ○ Drainage of abscess/collection ○ Evacuation of haematoma ○ Debridement ○ Exploratory/relook laparotomy only ○ Haemostasis ○ Intestinal bypass ○ Laparostomy formation ○ Repair of intestinal perforation ○ Repair or revision of anastomosis ○ Repair of intestinal fistula ○ Resection of other intra-abdominal tumour(s) ○ Defunctioning stoma via midline laparotomy ○ Revision of stoma via midline laparotomy ○ Large incisional hernia repair with bowel resection ○ Large incisional hernia repair with division of adhesions ○ Washout only ○ Removal of foreign body ○ Not amenable to surgery 	
5.3.b	Second procedure (at same laparotomy)	<ul style="list-style-type: none"> ○ Peptic ulcer – suture or repair of perforation ○ Peptic ulcer – oversew of bleed ○ Gastrectomy: partial or total ○ Gastric surgery - other ○ Small bowel resection ○ Resection of Meckel's diverticulum ○ Colectomy: left (including sigmoid colectomy and anterior resection) ○ Colectomy: right (including ileocaecal resection) ○ Colectomy: subtotal or panproctocolectomy ○ Hartmann's procedure ○ Colorectal resection – other ○ Splenectomy ○ Abdominal wall closure following dehiscence ○ Abdominal wall reconstruction ○ Abdominal hernia repair 	
5.3.c	Third procedure (at same laparotomy)		

		<ul style="list-style-type: none"> ○ Adhesiolysis ○ Reduction of volvulus ○ Enterotomy ○ Stricturoplasty ○ Drainage of abscess/collection ○ Evacuation of haematoma ○ Debridement ○ Haemostasis ○ Intestinal bypass ○ Laparostomy formation ○ Repair of intestinal perforation ○ Repair or revision of anastomosis ○ Repair of intestinal fistula ○ Resection of other intra-abdominal tumour(s) ○ Defunctioning stoma via midline laparotomy ○ Revision of stoma via midline laparotomy ○ Large incisional hernia repair with bowel resection ○ Large incisional hernia repair with division of adhesions Removal of foreign body 	
5.4	Procedure approach	<ul style="list-style-type: none"> ○ Open ○ Laparoscopic ○ Laparoscopic assisted ○ Laparoscopic converted to open 	
5.5	<p>Operative findings: (Please select all that apply) If unsure whether this patient is eligible for NELA please refer to help box</p>	<ul style="list-style-type: none"> ○ Abscess ○ Anastomotic leak ○ Perforation – peptic ulcer ○ Perforation – small bowel/colonic ○ Diverticulitis ○ Intestinal fistula ○ Adhesions ○ Incarcerated hernia ○ Volvulus ○ Internal hernia ○ Intussusception ○ Stricture ○ Pseudo-obstruction ○ Gallstone ileus ○ Meckel's diverticulum ○ Malignancy – localised ○ Malignancy – disseminated ○ Colorectal cancer ○ Gastric cancer ○ Haemorrhage – peptic ulcer ○ Haemorrhage – postoperative ○ Ulcerative colitis ○ Other colitis ○ Crohn's disease ○ Abdominal compartment syndrome ○ Intestinal ischaemia ○ Necrotising fasciitis ○ Foreign body 	<p>Operative findings are intended to be best guess. There may be instances where the operative findings are such that, had these findings been known prior to surgery, the patient would not have been included in the audit. However since they have now had a laparotomy, they are still included. This is why there appear to be some findings/procedures that are under the exclusion criteria.</p>

		<ul style="list-style-type: none"> ○ Stoma complications ○ Abdominal wound dehiscence ○ Normal intra-abdominal findings 	
5.6	Please describe the peritoneal contamination present (select all that apply)	<ul style="list-style-type: none"> ○ None or reactive serous fluid only ○ Free gas from perforation +/- minimal contamination ○ Pus ○ Bile ○ Gastro-duodenal contents ○ Small bowel contents ○ Faeculent fluid ○ Faeces ○ Blood/haematoma 	
5.7	Please indicate if the contamination was;	<ul style="list-style-type: none"> ○ Localised to a single quadrant of the abdomen ○ More extensive / generalised 	

6	Post-op Risk stratification	Format	Notes
6.1	At the end of surgery, what risk of death was the patient documented as having?	<ul style="list-style-type: none"> ○ Lower (<5%) ○ High (5-10%) ○ Highest (>10%) ○ Not documented 	
6.2	How was this assessment of risk made? (Please select all that apply)	<ul style="list-style-type: none"> ○ Risk prediction tool (e.g. P-POSSUM) ○ Clinical Judgement ○ Surgical APGAR score ○ Physiological criteria ○ Other, e.g. hospital policy 	<p>Formal assessments of risk; this includes risk stratification tools (such as ASA) and prediction models (such as APACHE and POSSUM systems).</p> <p>Clinical judgement; refers to the categorisation or estimation of risk, based on clinical acumen and experience.</p> <p>Physiological criteria; either use of physiological variables in isolation or incorporated into tools such as the early warning score (i.e. not incorporated into a risk stratification tool or prediction model as above)</p>
6.3	Blood lactate – may be arterial or venous (mmol/l)	<hr/> <ul style="list-style-type: none"> ○ Not performed 	Or within 30 minutes of the end of surgery.
	Post-operative P-POSSUM calculation <i>Q 6.4-6.14 no longer included from Year 4 specification</i>		
	Physiology severity score:	(Automatically calculated)	
6.15	What was the operative severity? (see help box for examples)	<ul style="list-style-type: none"> ○ Major ○ Major+ 	Major+: All colonic resections (excluding colostomy alone) All gastrectomy (but not repair

			<p>perforated or bleeding ulcer) Small bowel tumour resection Re-operations for ongoing sepsis or bleeding Laparostomy Intestinal bypass Major All other procedures including: Stoma formation Small bowel resection Division adhesions Repair perforated or bleeding ulcer</p>
6.16	Including this operation, how many operations has the patient had in the 30 day period prior to this procedure?	<ul style="list-style-type: none"> ○ 1 ○ 2 ○ >2 	<p>Do not “unbundle” procedures. Examples of single procedure:</p> <ul style="list-style-type: none"> • Hartmann’s procedure (this should not be “unbundled” as 2 procedures -sigmoid colectomy and end colostomy). • Colonic resection with washout of a localised abscess would also be 1 procedure. <p>Examples of 2 procedures:</p> <ul style="list-style-type: none"> • Primary colonic anastomosis with a defunctioning ileostomy. • Colonic resection and extensive division of adhesions. • Colonic resection and small bowel repair. <p>Example of >2 procedures:</p> <ul style="list-style-type: none"> • Hartmann’s procedure with resection of small bowel with insertion of tube gastrostomy
6.17	Please select this patient’s measured intraoperative blood loss (ml)	<ul style="list-style-type: none"> ○ <100 ○ 101-500 ○ 501-1000 ○ >1000 	If measured blood loss is unavailable, please estimate
6.18	Please select the option that best describes this patient’s degree of peritoneal soiling	<ul style="list-style-type: none"> ○ None ○ Serious fluid ○ Local pus ○ Free bowel content, pus or blood 	
6.19	What was the level of malignancy based on surgical findings	<ul style="list-style-type: none"> ○ None ○ Primary only ○ Nodal metastases ○ Distant metastases 	
6.20	What is the NCEPOD urgency?	<ul style="list-style-type: none"> ○ 3. Expedited (>18 hours) 	Based on your clinical experience

	<i>(see help notes for additional information, including equivalent Possum categories)</i>	<ul style="list-style-type: none"> ○ 2B. Urgent (6-18 hours) ○ 2A. Urgent (2-6 hours) ○ 1. Immediate (<2 hours) 	<p>this should be the maximum time that a patient could reasonably wait for surgery. These classifications are based on NCEPOD and Surviving Sepsis. The equivalent POSSUM categories are also shown.</p> <p>Examples:</p> <p>POSSUM: Emergency (resuscitation of > 2h possible)</p> <p>3. Expedited (>18 hours): No SIRS or sepsis e.g. developing large bowel obstruction</p> <p>2B. Urgent (6-18 hours): Sepsis e.g. localised abscess or obstructed hernia</p> <p>2A. Urgent (2-6 hours): Severe sepsis e.g. intestinal perforation</p> <p>POSSUM: Emergency (immediate surgery <2h needed)</p> <p>1. Immediate (<2 hours): Life threatening haemorrhage and septic shock e.g. profuse GI bleed or pan-intestinal ischaemia</p>
	<i>Online web tool will automatically calculate Operative severity score</i>		
6.21	Post-op P-POSSUM predicted mortality :	Calculated _____	This value will be calculated automatically
6.22	Post-op POSSUM predicted morbidity :	Calculated _____	This value will be calculated automatically
6.23	Not all P-POSSUM investigations available	○	Please select if any of the above investigations are unavailable. This will allow you to save the form with missing data
6.24	Where did the patient go for continued post-operative care following surgery?	<ul style="list-style-type: none"> ○ Ward ○ Critical Care (includes Level 2 HDU or Level 3 ICU) ○ Other enhanced care area (e.g. PACU) ○ Died prior to discharge from theatre complex 	
6.24a	At the end of surgery, was the decision made to place the patient on an end of life pathway?	<ul style="list-style-type: none"> ○ Yes ○ No 	This is intended to identify those patients whose pathology, at the time of surgery, was such that only supportive treatment was warranted.
6.26	Estimated mortality using NELA risk adjustment model <i>(Figure only provided if all data available)</i>	Calculated _____	

7	Post-op	Format	Notes
7.1	Total length of post-operative critical care stay (rounded up to whole days) <i>Includes both ICU and HDU stay -see help box for additional information. Do not include LOS in PACU/other enhanced recovery area</i>	<hr/> Number required	Each day, or part day, counts as 1 day. Hence: a. Admitted and discharged on same day = 1 day b. Admitted on Monday, discharged on Tues = 2 days c. Admitted on Monday, discharged on Wed = 3 days. Values should reflect actual discharge, rather than when medically fit for discharge.
7.3	Was the patient assessed by a specialist from Elderly Medicine in the post-operative period?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	Can include physician or nurse specialist
7.4	Within this admission, did the patient have an unplanned return to theatre in the post-operative period following their initial emergency laparotomy?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	Do not include planned returns for e.g. closure of abdomen
7.4a	What was the main indication for the return to theatre	<input type="radio"/> Anastomotic leak <input type="radio"/> Abscess <input type="radio"/> Bleeding or Haematoma <input type="radio"/> Decompression of abdominal compartment syndrome <input type="radio"/> Bowel obstruction <input type="radio"/> Abdominal wall dehiscence <input type="radio"/> Accidental damage to bowel or other organ <input type="radio"/> Stoma viability or retraction <input type="radio"/> Other <input type="radio"/> Unknown	Only one option to be chosen
7.5	Did the patient have an unplanned move from the ward to a higher level of care within 7 days of surgery? (do not include moves from HDU to ITU, or escalation from other enhanced area/PACU)	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	This refers to within 7 days of their emergency laparotomy, not any prior surgery.
7.6	NO LONGER REQUIRED	NO LONGER REQUIRED	
7.7	Status at discharge	<input type="radio"/> Dead <input type="radio"/> Alive <input type="radio"/> Still in hospital at 60 days	'Still in hospital at 60 days' option to be used when approaching an audit deadline by which all incomplete cases need to be locked
7.8	Date discharged from hospital	<hr/> (DD/MM/YYYY) Date required	Date of discharge, NOT date fit for discharge.

7.9	Discharge destination	<ul style="list-style-type: none"> ○ Own home/sheltered housing ○ Residential care ○ Nursing care ○ Unknown 	
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Appendix 3 - Level of care after surgery

The level of care should be defined according to the care the patient received rather than the location. For example, a patient receiving level 2 care in a level 3 area should be recorded as receiving level 2 care.

1. Critical care level 3: includes advanced organ support e.g. invasive ventilation, renal replacement therapy.
2. Critical care level 2: may include advanced cardiorespiratory monitoring (e.g. invasive arterial / central venous monitoring) and basic organ support (e.g. non-invasive ventilation, inotropic/vasoactive drug administration).
3. Post-anaesthetic care unit: care within a designated area for the patients in the immediate recovery from anaesthesia. May deliver care at levels 1 to 3.

Surgical ward (level 0/1): normal ward care without level 2 or 3 capabilities.

Appendix 4 – Typical complications of emergency laparotomy

The following are recognised complications of emergency laparotomy surgery, which may have clinical severity up to and including disability and death.

Acute kidney injury
Acute Respiratory Distress Syndrome (ARDS)
Anaphylaxis
Anastamotic breakdown
Bowel infarction
Cardiac arrhythmia
Cardiac arrest
Cardiogenic pulmonary oedema
Deep vein thrombosis
Delirium or acute psychosis
Electrolyte imbalance
Gastrointestinal or other postoperative bleed
Infection, source uncertain
Laboratory confirmed bloodstream infection
Multi-organ dysfunction syndrome
Myocardial infarction
Myocardial injury after non-cardiac surgery
Pneumonia
Paralytic ileus
Perforated viscus
Postoperative haemorrhage
Pulmonary embolism
Stroke
Surgical site infection (superficial, deep or organ/space)
Urinary tract infection

Appendix 5 – Protocol version history

Protocol:		Amendments:		
Version no.	Date	Amendment no.	Protocol section (no./title)	Summary of main changes from previous version
1.0	26/01/2017	N/A	N/A	N/A