

Enhanced Peri-Operative Care for High-risk patients (EPOCH) Trial:

A stepped wedge cluster randomised trial of a quality improvement intervention for patients undergoing emergency laparotomy

Short title	<i>EPOCH Trial</i>
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1. GLOSSARY OF ABBREVIATIONS

CI	Chief Investigator
ELPQuIC	Emergency Laparotomy Quality Improvement programme
EPOCH	Enhanced Peri-Operative Care for High-risk patients Trial
HQIP	Healthcare Quality Improvement Partnership
JRMO	Joint Research Management Office
NELA	National Emergency Laparotomy Audit
NHS R&D	National Health Service Research & Development
NIGB	National Information Governance Board
PCTU	Pragmatic Clinical Trials Unit
PI	Principal Investigator
QI	Quality Improvement
RCS	Royal College of Surgeons of England
REC	Research Ethics Committee
SDV	Source Document Verification
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

2. SIGNATURE PAGE

Chief investigator agreement

The clinical study as detailed within this research protocol (**Version 1.0, dated 10th September 2013**), 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 applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief investigator name: Rupert Pearse

Chief investigator site: Barts Health NHS Trust

Signature 

Date: 10th September 2013

Principal investigator agreement

The clinical study as detailed within this research protocol (**Version 1.0, dated 10th September 2013**), 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 applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal investigator name:

Principal investigator site:

Signature:

Date:

Statistician agreement

The clinical study as detailed within this research protocol (**Version 1.0, dated 10th September 2013**), 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 applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Statistician name: Sally Kerry

Signature:

Date:

3. SUMMARY

Short title	EPOCH Trial
Methods	Multi-centre, stepped wedge cluster randomised trial
Research sites	90 NHS Trusts, grouped into 15 clusters, in the United Kingdom
Objective	To evaluate the effect of a quality improvement intervention to promote the implementation of an integrated peri-operative care pathway on survival at 90 days following emergency laparotomy
Number of patients	27,450 patients
Inclusion Criteria	Patients aged 40 years and over undergoing non-elective open abdominal surgery in participating hospitals will be eligible for inclusion in the data analysis. The following patients will be excluded: simple appendicectomy, gynaecological laparotomy, surgery related to organ transplant, laparotomy for traumatic injury, laparotomy to treat complications of recent elective surgery and patients whose data has previously been included in the trial.
Statistical analysis	The stepped wedge design is a matched design with before and after comparisons for each cluster randomised. 90-day mortality will be modelled using mixed effects logistic regression with random cluster (hospital) effects allowing inclusion of baseline risk factors. Secondary outcomes, 180-day mortality, hospital re-admission within 180 days and duration of hospital stay, will be analysed as time to event using a Cox proportional hazard's model.
Proposed Start Date	March 2014
Proposed End Date	April 2017
Study Duration	30 months

4. INTRODUCTION

More than one million adult patients undergo in-patient non-cardiac surgery in the National Health Service (NHS) each year with an estimated mortality of between 1.6% and 3.6%.¹⁻⁴ However, patients undergoing emergency surgery are exposed to a much greater risk of death. More than 150,000 high-risk patients undergo emergency surgery each year in the NHS, following which at least 90,000 patients develop complications resulting in over 20,000 deaths before hospital discharge.^{5,6} High-risk patients undergoing emergency surgery account for 10% of all in-patient surgical procedures but 65% of deaths. Patients who develop complications but survive, require in-hospital care for prolonged periods, suffering substantial reductions in functional independence and long-term survival.⁷ Recent data show that abdominal surgery and the need for surgery on an emergency basis are amongst the strongest factors associated with poor post-operative outcome.⁴⁻⁷ Around 35,000 patients present to NHS hospitals each year with precisely this pattern of risk and undergo a procedure known as 'emergency laparotomy'. This term describes a major surgical procedure to treat an acute and often life threatening problem with the gut or other abdominal organ. Around 180 patients undergo emergency laparotomy in a typical NHS hospital each year with a 90-day mortality of 25%.⁸ There is considerable heterogeneity in standards of care between hospitals, including wide variations in the involvement of senior surgeons and anaesthetists and post-operative admission to critical care, which are associated with important differences in mortality rates.⁸

In 2010 the Department of Health commissioned a Royal College of Surgeons of England (RCS) working group to develop an integrated care pathway which could improve the quality of care for patients undergoing emergency laparotomy.⁹ A key aspect of this brief was to develop a pathway which was resource neutral through allocation of resources to patients in greatest need, making widespread implementation more likely. The working group represented key stakeholder organisations and included three members of the EPOCH study group. An integrated care pathway was defined which represented an optimal standard of peri-operative care deliverable in all NHS hospitals. Examples of interventions included consultant led decision making and treatment, standards for diagnostic testing, structured post-operative surveillance, time limits for review of deteriorating patients and early admission to critical care. To date, there has been little systematic implementation of any component of the integrated care pathway.^{4,8} We have now completed a systematic review which has informed a Delphi consensus process to update the

RCS guideline and create a robust and evidence based modified RCS integrated care pathway (appendix).

Most opinion leaders agree there is an urgent need for a national project to improve survival for emergency laparotomy patients. However, there is uncertainty about how best to achieve such improvement. Some question the benefits of quality improvement initiatives, pointing to the lack of robust clinical evidence of effectiveness, both in terms of generic methodologies advocated to improve quality (e.g. quality collaboratives, Plan Do Study Act cycles), and the specific changes in patient care (e.g. care pathways). There are examples where a discrete quality improvement intervention was associated with improved clinical outcomes. The findings of an international cohort study of the use of surgical checklists suggested this simple intervention was associated with improved post-operative survival.¹⁰ Whilst this study had methodological limitations, the findings of a further investigation in Dutch hospitals also suggested surgical checklists were associated with improved patient outcomes.¹¹ In the UK, the positive findings of an implementation project to increase use of cardiac output monitoring during surgery have influenced guidelines from the National Institute for Health and Clinical Excellence (NICE).¹² These studies suggest beneficial effects for discrete interventions such as a checklist or clinical monitor but the evidence to support multi-intervention care pathways is less robust. The introduction of a single intervention is a very different proposition to the implementation of a complex integrated care pathway which requires behavioural change from a variety of healthcare practitioners. In the USA, the National Surgical Quality Improvement Program (NSQIP) was established to tackle poor patient outcomes. The success of this initiative is such that many private hospitals have also joined the programme. NSQIP has provided individual examples showing how the use of process and outcome data may inform quality improvement programmes designed to reduce morbidity, mortality and cost.¹³ The findings of a retrospective NSQIP study suggest team based training for operating theatre staff is associated with improved post-operative mortality.¹⁴ Data from the NHS Enhanced Recovery Partnership suggest improvements in outcome for patients undergoing elective colorectal surgery within a defined care pathway.¹⁵ This experience suggests that provision of robust data may promote implementation of quality measures but provides only weak clinical evidence to support the use of integrated care pathways in peri-operative care. For many the benefits of quality improvement initiatives are self-evident but others question the value of these projects. Common concerns include high cost, poor leadership, failure to engage clinicians and failure to sustain

process changes after the intervention has ended.¹⁶ Experience from more recent quality improvement initiatives has shown that these challenges can be overcome. However, doubts over the clinical effectiveness of quality improvement projects continue to limit the success of these initiatives. There is a clear need for robust clinical evidence to support or refute the use of this approach to improve clinical practice and, ultimately, patient outcome.

Prior to the RCS report, there was no defined care pathway for this patient group. As a result this has been implemented in a very small number of hospitals. The Emergency Laparotomy Quality Improvement Care Bundle programme (ELPQuIC) is a Health Foundation funded pilot study in four EPOCH Pathfinder Hospitals, which has provided a comprehensive theory of change both for the proposed quality improvement work and the integrated care pathway. The pathway is expected to improve quality of patient care whilst adverse effects are thought unlikely. Key stakeholder groups support this national project to implement the care pathway into routine practice. However, implementation of the integrated care pathway would have much greater impact if linked to high quality research demonstrating the effectiveness of doing so. The Healthcare Quality Improvement Partnership (HQIP) has commissioned a new National Emergency Laparotomy Audit (NELA),¹⁷ providing a unique opportunity to study the clinical effectiveness of a quality improvement project to implement an integrated peri-operative care pathway for emergency laparotomy patients. By providing a robust evidence base for quality improvement in peri-operative care, the findings of this work could accelerate implementation of care pathways for all categories of high-risk surgery with the potential for widespread improvements in survival affecting more than 170,000 NHS patients each year.³⁻⁶ We propose to conduct a large pragmatic clinical trial of the effectiveness of a quality improvement project to implement a modified version of the RCS integrated care pathway to improve patient outcomes following emergency laparotomy. Our aim is to provide the definitive evidence needed to inform practice in this area.

5. TRIAL OBJECTIVES

5.1 Primary objectives

1. To evaluate the effect of a quality improvement intervention to promote the implementation of an integrated peri-operative care pathway on survival at 90 days following emergency laparotomy
2. To assess the cost-effectiveness of the quality improvement intervention compared to ongoing clinical practice without the intervention
3. To evaluate the long-term effects of the intervention on standards of care and mortality following emergency laparotomy in participating hospitals

5.2 Primary outcome measures

All cause mortality at 90 days following surgery.

5.3 Secondary outcome measures

All cause mortality at 180 days following surgery, duration of hospital stay and hospital re-admission within 180 days of surgery. In six hospitals we will collect EQ-5D 3L and healthcare resource use data preoperatively, and at 90 and 180 days post surgery to perform a health economics analysis.

5.4 Process measures

1. Time to diagnostic imaging
2. Documented evaluation of mortality risk prior to surgery
3. Consultant surgeon present in operating theatre
4. Consultant anaesthetist present in operating theatre
5. Critical care admission (level 2 or 3)

6. METHODS

6.1 Inclusion criteria

Patients

All patients aged 40 years and over undergoing non-elective open abdominal surgery in participating hospitals during an 85 week period will be eligible for inclusion in the data analysis. The patient inclusion criteria are identical to those of the Healthcare Quality Improvement Partnership National Emergency Laparotomy Audit (HQIP-NELA) and the core EPOCH dataset will only include patient level data gathered by the audit.

Hospital sites and clusters

Participating hospitals must undertake a significant volume of emergency laparotomies, participate in the National Emergency Laparotomy Audit, nominate specialty leads from surgery, anaesthesia and critical care, and secure the support from their NHS Trust Board to participate in the EPOCH study. Hospitals which already use an integrated care pathway to maintain standards of care for this patient group will be excluded. Clusters will be organised geographically with specific attention to the rotation of clinical staff and patient referral patterns between hospitals to minimise contamination of pre-intervention hospitals.

6.2 Exclusion criteria

The following patients will be excluded: simple appendicectomy, gynaecological laparotomy, surgery related to organ transplant, laparotomy for traumatic injury, laparotomy to treat complications of recent elective surgery and patients whose data has previously been included in the EPOCH trial.

6.3 Study design

Multi-centre, stepped wedge cluster randomised trial conducted in at least 90 NHS hospitals over an 85 week period, divided into 17 time period of 5 weeks. Hospitals will be grouped into fifteen clusters of six on a geographical basis. The quality improvement intervention will commence in one cluster each five week step from the 2nd to the 16th time period, with the order of clusters determined by computer based randomisation. The stepped wedge design allows delivery of the intervention at an organisational level with evaluation of outcome measures at a patient level. Structuring the quality improvement intervention through a staged activation of sites in a random order provides important methodological advantages. The design allows us to control adoption bias and adjust for time-based changes in the background level of patient care in the statistical analysis. A key strength of the stepped wedge design is that we can offer the quality improvement project to every site which takes part.

6.4 Trial intervention

The dissemination of new healthcare practices is not a linear process. Scientific evidence is only one element influencing the change process. The EPOCH trial intervention is therefore comprised of two major components:

6.4.1 Integrated care pathway

We have now completed a systematic review which has informed a Delphi consensus process to update the RCS guideline and create a robust and evidence based modified EPOCH integrated care pathway (appendix).

6.4.2 Quality improvement (QI) methods

An evidence based QI package will be used to change the practice and culture of care for this patient group, engendering the belief that survival can be improved by providing a model of optimal care (integrated care pathway) with the methods to implement it. Hospitals will be linked in clusters on a geographical basis, facilitating adoption by building on local and regional relationships and minimising bias due to natural workforce movements between hospitals. Each hospital will nominate at least one champion from each stakeholder discipline (surgery, anaesthesia and critical care). These champions, supported by their NHS Trust board and guided by the EPOCH QI team, will lead a hospital wide improvement project to implement the care pathway. Exposure will start in each participating hospital as they are activated to the intervention. Over the trial period, approximately half the patients in all centres will receive care in hospitals exposed to the QI intervention. Whether the intervention leads to care provided in accordance with the integrated care pathway will be identified through the collection of the relevant process measures.

The major features of the QI methodology are:

- *Engaging frontline staff and executive leaders* providing evidence that change is required and proposing the trial intervention as a solution
- *Reframing the high mortality associated with this patient group as a 'social problem'* that requires both technical and non-technical interventions to create effective change
- *Using data for quality improvement* with feedback of process measure data to frontline teams
- *Training in basic QI skills* enabling local champions to lead their teams through implementation
- *Creating a community of practice* through meetings and web-based forums

QI Educational meetings for champions

Around the time of activation, hospital staff will attend a half day cluster group meeting led by the EPOCH QI team. This will develop the knowledge, skills and attitudes required to effect change. Attendance will include the champions from each stakeholder discipline but other frontline staff and NHS trust board members are encouraged to attend. Five weeks before the meeting, champions will identify their 'change teams' and develop a presentation entitled 'Where we are now' including baseline data, local challenges and ideas for improvement to share at the regional cluster meeting. These QI educational meetings will have four distinct aims:

A) Raise awareness of poor outcomes & propose a technical solution

- Describe epidemiology, clinical outcomes and challenges for clinicians
- Use filmed patient stories to present patient perspective of need for change
- Introduce the integrated care pathway as a real opportunity to improve patient outcomes
- Describe the study process measures and explain their importance
- Use driver diagrams to help teams understand the basis for change and where to target QI activities

B) Introduce quality improvement to maximise opportunities to improve outcomes

Local champions will be trained in basic QI methodology supported by on-line resources and materials, to include:

- Basic process mapping and segmentation techniques to help teams understand how the care pathway will function in the context of their hospital. Plan-Do-Study-Act (PDSA) cycles to allow observation of incremental changes in key areas identified through process mapping and segmentation activity
- Time series audit data (run-charts) to present trends in process measures over time helping teams to monitor their progress and identify which implementation activities are effective and which are not

C) Create excitement about the project and start building a community of practice

- Promote a multi-disciplinary team approach and foster a culture of belonging to the project by the use of highly visible promotional materials Encourage and facilitate sharing of good practice through meetings and web-based forums
- Encourage local patient and public input and provide resources to facilitate this

D) Plan for commencement of QI activities

- Provide high quality educational materials (including patient story films, paper and internet-based learning materials) for champions to disseminate to local staff
- Setting local implementation milestones with each team e.g. frontline staff meetings, process mapping sessions

The EPOCH team will use information and advertising to maintain the visibility of the project to staff in centres following implementation. Local investigators will be contacted on a regular basis and provided with feedback on process and outcome measures. Advice and support will be provided by the EPOCH quality improvement team and through the on-line community of practice hosted on the EPOCH website.

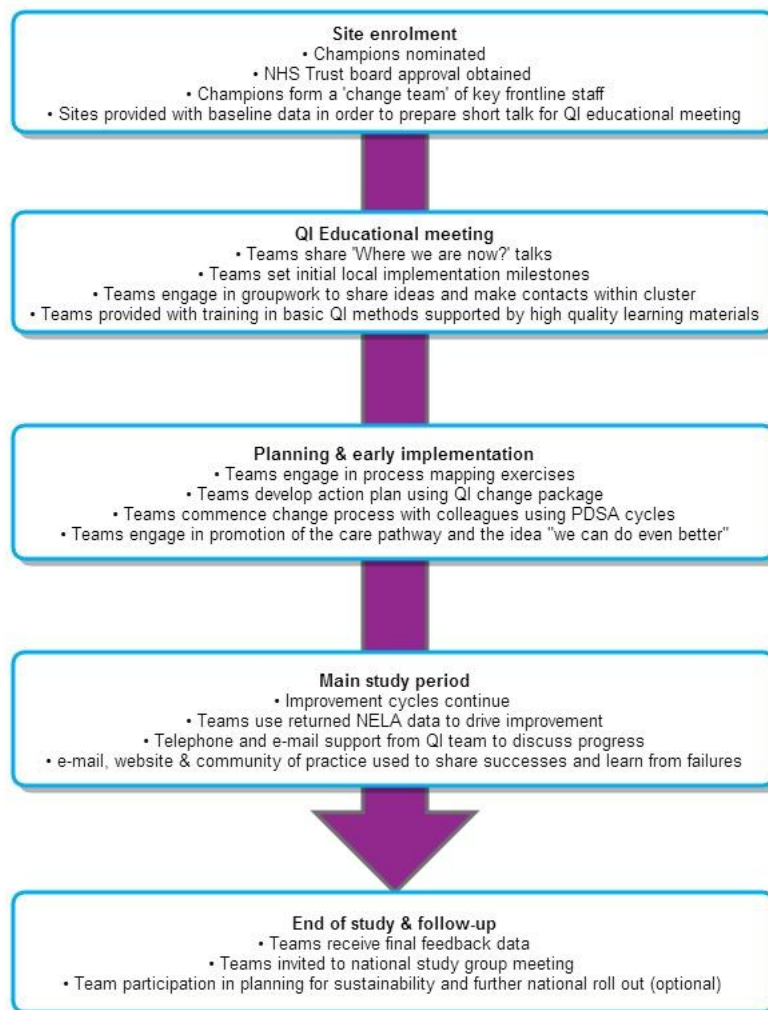


Figure 1. EPOCH quality improvement intervention from the perspective of participating hospitals

7. STUDY PROCEDURES

7.1 Informed Consent

The trial intervention is at an institutional level and individual patient consent will not be sought. Data will be captured by the direct care team through the NHS National Emergency Laparotomy Audit and anonymised before transfer to the EPOCH team. The exception will be the six hospitals which collect additional data required for the health economics analysis. Patients will give written informed consent to provide quality of life data (see section 7.4). By definition, patients will undergo surgery on an emergency basis and we expect that some will lack capacity to give or withhold consent. In these instances, we will consult with relatives or friends to advise on the potential participant's wishes regarding the project and whether she or he would be content to take part. The relative or friend will be termed the personal consultee or guardian / welfare attorney. Once the patient has regained capacity, consent to remain in the study will be sought from them at the earliest opportunity.

7.2 Randomisation

An independent statistician will randomise the clusters and keep randomisation records prior to the beginning of the data collection. Simple randomisation will be used to randomise one cluster of hospitals to receive the intervention in each of the fifteen time periods 2 to 16. Local investigators will be notified 12 weeks in advance of the start date for the quality improvement project at their hospital.

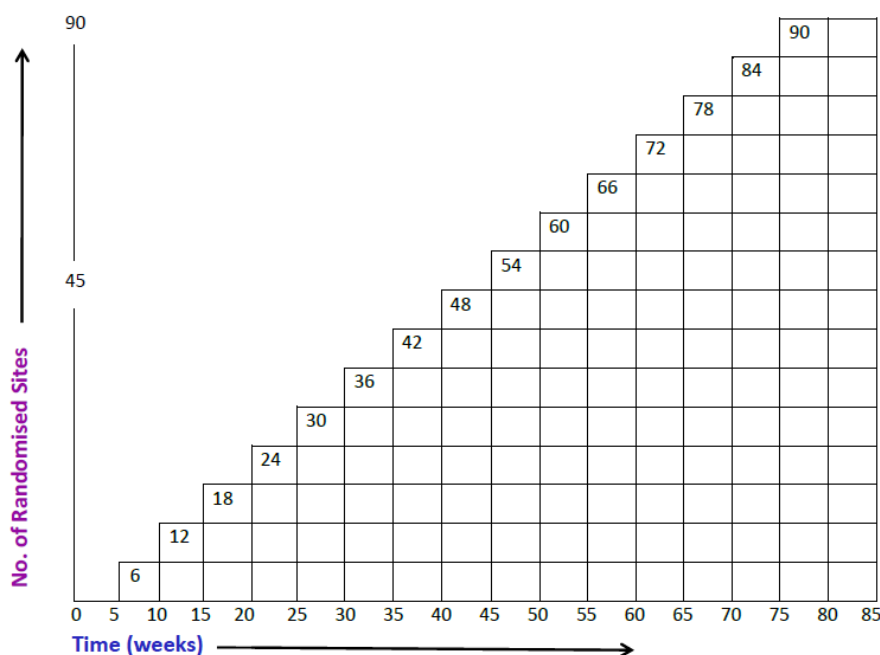


Figure 2. Cluster randomisation diagram

7.3 Data collection

Patient level data will be collected and collated by the National Emergency Laparotomy Audit in all participating hospitals from the beginning of the intervention period. Before the randomisation period commences, investigators will be trained to use a secure internet based data entry system to collect pre-operative, intraoperative process data on individual patients. This data will then be linked to the Office for National Statistics and Hospital Episodes Statistics databases using patient identifiers to allow collation of outcome data including mortality and hospital readmission. The EPOCH and HQIP-NELA teams will work together to ensure complete data on all eligible patients.

Data to be collected at different stages:

Pre operative data: Age, Sex, American Society of Anesthesiologists (ASA) Score, Co-morbid disease, Date of hospital admission, Admitting specialty, Time and date of decision to perform surgery, Time to diagnostic imaging (usually computed tomography scan of the abdomen), Documented mortality risk before surgery (Y/N).

Intra-operative data: Urgency of surgery, Duration, time and date of surgery, Grades of most senior surgeon and anaesthetist present in theatre, Surgical procedure performed, Underlying pathology.

180-day follow-up: Critical care admission, Duration of hospital stay, Hospital readmission and mortality.

Health economics: In six hospitals, EQ-5D 3L and healthcare resource use will be collected pre-operatively and at 90 and 180 days (telephone) post surgery. Staff resources associated with the quality improvement intervention. These hospitals will be amongst those which commence the quality improvement intervention midway through the trial period.

7.4 Data management for NELA hospitals not included in EPOCH

Hospitals that participate in NELA but are not included amongst those which participate in the EPOCH quality improvement project will form a reference group for the EPOCH trial. These sites will not receive any support or advice regarding quality improvement from the EPOCH team during the trial period. Quality improvement for all NELA participants is planned for the latter part of the NELA programme and will be informed by results from the EPOCH study. The EPOCH reference groups will

only have access to their own internal process measure data and other information provided by NELA. This will include newsletters that provide information on levels of participation in NELA, and various general messages to improve case-ascertainment and data completeness. Towards the end of the EPOCH intervention period, NELA will commence publication of annual reports containing process and outcome data for each hospital. These will provide comparative information to other NHS hospitals. NELA will also make general recommendations to NHS trusts for improvements in practice. NELA leads in individual hospitals will be able to download their local data from the data collection web tool. Throughout, the NELA team will provide support to hospitals by responding to hospital queries about the audit results and data collection processes.

7.5 Subject withdrawal

Subject withdrawal is not applicable to the main project. Patients who wish to withdraw from the quality of life data collection will be asked for permission for the EPOCH group to retain existing data. All data will be destroyed and the patient withdrawn from this part of the trial if requested.

7.6 End of study definition

The end of the study is defined as the end of the 180-day follow-up of the last patient undergoing surgery within the 85-week trial period. Data analysis shall follow this.

8. STATISTICAL CONSIDERATIONS

8.1 Sample size calculation

Prospectively collected data from the recently published Emergency Laparotomy Network study in 35 NHS hospitals closely match our inclusion/exclusion criteria and describe a median of 184 eligible patients aged ≥ 40 years per hospital per year (range 32-736) with a 30-day mortality rate of 16.4%⁸. Data from the Hospital Episodes Statistics database for the year ending April 2011 gives the average 30-day mortality as 17% (10th centile 13% – 90th centile 22%) and the average 90-day mortality as 25% (10th centile 20% – 90th centile 31%). These data have been used to estimate the baseline mortality rate and between hospital coefficient of variation. Power calculations are based on the methodology proposed by Hussey & Hughes,¹⁸ for an analysis with fixed time effects and random cluster effects, modified to exclude data collected during the five week period in which the intervention commences in individual hospitals. The trial will be conducted in at least **90 NHS hospitals** over a period of **85 weeks** during which time we expect to receive data describing **27,540**

patients undergoing emergency laparotomy. For a baseline 90-day mortality of 25%, between hospital coefficient of variation of 0.15, constant case-load (18 patients per 5 weeks per hospital) and assuming independent hospital effects, the study would achieve 92% power to detect a 12% relative risk reduction in mortality from 25% to 22% (two-sided $p < 0.05$). This calculation is insensitive to the coefficient of variation but sensitive to the effect size. In practice, power may be reduced by correlation between hospitals within clusters and by variation in case-load between hospitals. The worst case scenario is one where each of the 15 clusters functions effectively as a single large hospital, reducing the power to 83%. This figure incorporates an adjustment for variable case-load from the pilot data. Thus the power of the study to detect a 12% relative risk reduction lies between 83% and 92%.

8.2 Statistical analysis

This will be conducted on an intention-to-treat basis i.e. all patients recorded in the data base during the 85-week period will be included, and considered exposed to the intervention according to randomisation regardless of when the intervention was actually implemented. The intervention start date for each cluster will be fixed regardless of whether implementation proceeds on time. The stepped wedge design is in effect a matched design with before and after comparisons for each cluster randomised. The primary outcome will be 90-day mortality. Overall differences in 90-day mortality rates between pre- and post-intervention periods will be reported. In the primary analysis, 90-day mortality will be modelled using mixed effects logistic regression with random cluster (hospital) effects allowing inclusion of baseline risk factors such as co-morbid disease and ASA score and adjustment for a fixed time effect between 5-week periods. Patients will be excluded during the five week period immediately after randomisation. Baseline data collected from the first time period will be tabulated by order of implementation, grouping the clusters into three groups of five clusters. This will include 90-day mortality, mean age, sex, admitting specialty, ASA score and five stated process measures (see above). We will examine the adequacy of our randomisation and include any hospital level variable unbalanced at baseline in our final model. The patient level covariates included will be finalised in a statistical analysis plan prior to analysts becoming unblinded to randomisation group. Secondary outcomes will be 180-day mortality, hospital re-admission within 180 days and duration of hospital stay. The latter will be analysed as time to event using a Cox proportional hazard's model with fixed and random effects. Process measures will be analysed in the same way using either logistic or Cox proportional hazards. Total in-patient days will be analysed using a mixed effects regression model after

transforming the data to allow for non-normality if necessary. Between-hospital differences will be described using percentiles. In supplementary analyses, the development of the intervention effect within hospitals over time (learning effect) will be investigated, as will possible intervention by cluster interactions. It is not anticipated that clusters will withdraw from data collection but in this instance, the primary analysis will include only hospitals that have collected data across the whole time period and secondary analysis will use multiple imputation of missing data. No interim analyses are planned.

8.3 Health economic analysis

The health economics analysis will assess whether implementing the quality improvement intervention is likely to be cost-effective on average and whether this varies between low and high mortality groups. The intervention may have effects that impact on quality and duration of life beyond the trial follow-up period. The cost-effectiveness analysis will therefore take the form of a decision model with 90-day mortality as an input in terms of treatment effectiveness. A Markov or semi-Markov decision analytic model will be used with 90-day and 180-day mortality generated from the trial as key inputs. The risk of mortality will be estimated from trial data using parametric survival regression to facilitate analysis of low and high mortality sub-groups. This model will also allow extrapolation beyond the trial follow-up period based on available external evidence. Other states in the model will relate to subsequent non fatal events.

Perspective

The analysis will take an NHS and PSS perspective, consistent with that used by NICE. The time horizon of the cost-effectiveness analysis will be the life expectancy of the patient. Discounting will be conducted at current recommended rates (currently 3.5% per annum on both costs and effects).

Effectiveness

Effectiveness of the intervention will be defined by any differences in mortality and will be used as a parameter input into the model.

Resource use

Resource use associated with the quality improvement intervention and will be captured using pre-designed questionnaires. These questionnaires will capture details about the input of the quality improvement team as well as additional

consultant level personnel in attendance during surgery. Resource use associated with in-patient admissions, outpatient attendances and critical care admissions will be estimated using HES and NELA. Additional resource use in primary and community settings will be estimated from the patient questionnaires sent to the subsample of patients.

Unit costs

Unit costs will be estimated from published literature, NHS and government sources, including NHS Reference costs and Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care, to generate a total cost per trial participant for the relevant resource use.

Subgroup and sensitivity analysis

Sub-group analysis will establish whether cost effectiveness varies between low and high mortality groups. Probabilistic sensitivity analyses will be conducted to characterise the uncertainty around the adoption decision (depicted using Cost-Effectiveness Acceptability Curves) and to assess the potential and value of further research in this area. Sensitivity analyses will determine the robustness of the results by altering certain assumptions.

Sources of data for model inputs

Clinical trial

The evidence generated by the clinical trial will be used estimate parameters for the decision analytic economic model. The effect of the intervention on mortality will be a key input into the model, though other estimates from published literature will also be used.

Patient sub-sample

EQ5D data will be collected for a subsample of patients. These data will be collected pre-surgery and at 90 days and 180 days after surgery and will be based on all patients in the six identified hospitals. This will give an estimate of the health related quality of life (HRQoL) weights that could be used in the model. For example, the HRQoL weight for an individual who has undergone laparotomy without complications is likely to be different from an individual undergoing the same procedure but who also experiences complications. Similarly, the resource use of these individuals is likely to differ.

Quality-Adjusted Life Years (QALYs)

QALYs over the patients' lifetime will be used as the primary outcome measure of the cost-effectiveness analysis. This will involve taking the within-trial mortality data to estimate differential mean survival duration over the period of trial follow-up. This will be quality-adjusted on the basis of EQ5D data collected in the sub-sample and allowing for non-fatal clinical events experienced in the two trial arms. A long-term extrapolation will be undertaken to estimate QALYs over a patient's expected lifetime. This will involve the use of parametric survival modelling together with relevant clinical and epidemiological data on patients' long-term life expectancy given their age, recovery from high-risk an abdominal surgery and whether or not they have experienced non-fatal clinical events following surgery.

9. ETHICS

Approval will be sought from a Research Ethics Committee and the National Information Governance Board (NIGB). Principal investigators at each site will ensure that the study is carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care and its subsequent amendments as applicable and applicable legal and regulatory requirements.

9.1 Risks and burdens

The risks and burdens to patients as a consequence of this research are minimal. The main ethical issue is the use of anonymised patient level data provided by NELA without patient consent. In view of this additional approvals will be sought from the National Information Governance Board by the NELA and EPOCH trial groups.

10. SAFETY CONSIDERATIONS:

There are no safety issues relating to the EPOCH Trial. There is no risk of harm to either patients or investigators.

11. DATA HANDLING AND RECORD KEEPING

11.1 Confidentiality

All data collected, processed and stored for the purposes of the project will remain confidential at all times and comply with GCP guidelines and the principles of the Data Protection Act 1998. NELA data collection sheets will be stored securely in a locked cupboard and handled by NHS audit and clinical staff familiar with handling personal data and with good clinical practice. All data will be anonymised by NELA prior to transfer to the EPOCH study group. Identifiable data will not be available

centrally but only in the centre where the patient was recruited. Health economics data will include identifiable data and will be handled according to the same principles but transferred directly from the hospitals involved to the PCTU using a secure internet based data entry system. Desktop and laptop security will be maintained through user names and frequently updated passwords and back up procedures are in place. All local investigators will undergo Good Clinical Practice (GCP) training. GCP training certificates will be stored in local site files and a copy of all investigators certificates will be kept in the trial master file. Trial records will be stored in an approved repository for 20 years following the end of the trial.

11.2 Record retention and archiving

Each site will maintain and securely store an investigator site file. Paper copies of the health economics data being collected by six sites will be stored at each local site. NELA will be responsible for archiving identifiable data. Data will be archived in accordance with local standards and procedures for quality and assurance.

12. SAFETY REPORTING

The trial involves negligible risks to patients or investigators and adverse events will not be monitored or reported.

13. MONITORING & AUDITING

The Pragmatic Clinical Trials Unit (PCTU) Quality Assurance (QA) manager will conduct a risk assessment of the EPOCH study to determine the level of monitoring and auditing required. Monitoring plan will be drafted explaining the nature, frequency and intensity of trial monitoring as determined by the PCTU risk assessment. Trial monitoring will include source data verification checks on informed consent forms and site eligibility for participation. The monitoring reports will be completed by the PCTU Monitor and reviewed by PCTU QA Manager and all findings will be followed up according to the trial monitoring reports. The finalised monitoring reports will be sent to the sponsor for review. The PCTU QA Manager will also carry out triggered audits as determined by risk assessment or through findings identified in the monitoring reports. A random sample of cases will be monitored at source when site visits are performed. The documents to be verified will be randomly selected. Any major discrepancies found at a site visit would trigger a more extensive audit of trial data at the site involved. In addition, the sponsor may also carry out an audit throughout the duration of the trial.

14. TRIAL COMMITTEES

14.1 Trial management group

The EPOCH trial will be managed by the PCTU at Queen Mary's University of London. Day to day conduct of the trial will be led by the trial management group which will meet at least once every two months. The group will include trial co-ordinators, a trial statistician, data manager and quality assurance manager, and will be chaired by Rupert Pearse (CI). The quality improvement group, chaired by Carol Peden, will lead the QI intervention and associated educational strategy. Dr Pearse will take overall responsibility for all aspects of trial management.

14.2 Trial steering committee

The trial steering committee will be appointed in accordance with NIHR guidance with an independent chairperson, a statistician, lay representation and two independent members from the advisory group and will meet at least once a year. There is no role for a Data Monitoring Committee.

14.3 EPOCH advisory group

To maintain effective links with stakeholder organisations, an advisory group has been formed with representation from Royal colleges, specialist societies, UKCRN, NCEPOD and NHS trusts. The advisory group will be chaired by Mr Iain Anderson.

15. FINANCE AND FUNDING

The EPOCH Trial is funded solely by the National Institute for Health Research Health Services and Delivery research panel.

16. INDEMNITY

The EPOCH trial is sponsored by Queen Mary's University of London.

17. DISSEMINATION OF RESEARCH FINDINGS

Our findings will be widely disseminated to the NHS community at regional, national and international meetings in a timely manner. We will provide specific reports for healthcare policy makers, frontline NHS staff and patients.

18. REFERENCES

1. *Quality and performance in the NHS: NHS Performance Indicators*: NHS Executive;2000.
2. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet*. 2008;372(9633):139-144.
3. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet*. 2012;380(9847):1059-1065.
4. Findlay G, Goodwin A, Protopappa K, Smith N, Mason M. *Knowing the Risk; A review of the peri-operative care of surgical patients*. London: National Confidential Enquiry into Patient Outcome and Death;2011.
5. Pearse RM, Harrison DA, James P, et al. Identification and characterisation of the high-risk surgical population in the United Kingdom. *Crit Care*. 2006;10(3):R81.
6. Jhanji S, Thomas B, Ely A, Watson D, Hinds CJ, Pearse RM. Mortality and utilisation of critical care resources amongst high-risk surgical patients in a large NHS trust. *Anaesthesia*. 2008;63(7):695-700.
7. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*. 2005;242(3):326-341.
8. Saunders DI, Murray D, Pichel AC, Varley S, Peden CJ. Variations in mortality after emergency laparotomy: the first report of the UK Emergency Laparotomy Network. *Br J Anaesth*. 2012;109(3):368-375.
9. Anderson I, Eddlestone J, Lees N, et al. *The Higher Risk General Surgical Patient - Towards Improved Care for a Forgotten Group*. London: Royal College of Surgeons of England;2011.
10. Haynes AB, Weiser TG, Berry WR, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. *N Engl J Med*. 2009;360(5):491-499.
11. de Vries EN, Prins HA, Crolla RM, et al. Effect of a comprehensive surgical safety system on patient outcomes. *N Engl J Med*. 2010;363(20):1928-1937.
12. Kuper M, Gold SJ, Callow C, et al. Intraoperative fluid management guided by oesophageal Doppler monitoring. *BMJ*. 2011;342:d3016.
13. Rowell KS, Turrentine FE, Hutter MM, Khuri SF, Henderson WG. Use of national surgical quality improvement program data as a catalyst for quality improvement. *J Am Coll Surg*. 2007;204(6):1293-1300.
14. Neily J, Mills PD, Young-Xu Y, et al. Association between implementation of a medical team training program and surgical mortality. *JAMA*. 2010;304(15):1693-1700.
15. Mythen M, Horgan A. *Fulfilling the potential*. London: Enhanced Recovery Partnership;2012.
16. Dixon-Woods M, McNicol S, Martin G. *Overcoming challenges to improving quality: Lessons from the Health Foundation's improvement programme evaluations and relevant literature*. London: Social Science Applied to Healthcare Improvement Research (SAPPHIRE) Group, University of Leicester;2012.
17. <http://www.hqip.org.uk/emergency-laparotomy-audit-specification-development/>.
18. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials*. 2007;28(2):182-191.

19. APPENDIX: EPOCH integrated Care Pathway

Before surgery

- Consultant led decision making
- Computed tomography imaging within two hours of decision to perform test
- Early goal directed therapy for patients with severe sepsis/septic shock
- Analgesia within one hour of first medical assessment
- Antibiotic therapy within one hour of first medical assessment
- Correction of coagulopathy
- Maintain normothermia
- Active glucose management
- Documented mortality risk estimate
- Provided patient and relatives with oral and written information about treatment

During surgery

- Surgery within six hours of decision to operate
- Consultant delivered surgery and anaesthesia
- WHO checklist
- Early antibiotic therapy (unless inappropriate)
- Fluid therapy guided by cardiac output monitoring
- Low tidal volume protective ventilation
- Maintain normothermia
- Active glucose management
- Prescribe post-operative analgesia
- Prescribe post-operative nausea & vomiting prophylaxis
- Prescribe post-operative venous thromboembolism prophylaxis
- End of surgery risk evaluation
- Measure arterial blood gases and serum lactate
- Confirm full reversal of neuromuscular blockade
- Document core temperature
- Re-evaluate mortality risk estimate

After surgery

- Admission to critical care within six hours of surgery
- Analgesia: early review by acute pain team
- Continued antibiotic therapy where indicated with microbiology review

- Prophylaxis for post-operative nausea & vomiting
- Venous thromboembolism prophylaxis
- Maintain normothermia
- Active glucose management
- Daily haematology & biochemistry until mortality risk is low (senior opinion)
- Nutrition: early dietician review with consideration of benefits of enteral feeding
- Chest physiotherapy review on day one after surgery
- Critical Care Outreach review on standard ward with use of Early Warning Scores