Enhanced Peri-Operative Care for High-risk patients (EPOCH) Trial: A stepped wedge randomised cluster trial of a quality improvement intervention for patients undergoing emergency laparotomy

Summary

Each year, more than one million adults undergo in-patient non-cardiac surgery in the NHS with an overall mortality between 1.6% and 3.6%. Deaths are most frequent amongst high-risk patients undergoing emergency surgery. The key factors associated with poor patient outcomes following emergency surgery are advancing age, co-existing medical disease and abdominal surgery. Around 35,000 patients present to NHS hospitals each year with precisely this pattern of risk and undergo a procedure termed 'emergency laparotomy' - major surgery to treat an acute life threatening problem within the abdomen. Both standards of patient care and mortality following this procedure vary widely between NHS hospitals indicating a need for quality improvement interventions to improve survival. A working group led by the Royal College of Surgeons has developed an integrated care pathway which may significantly improve quality of care for this patient group. Pathway interventions include consultant led treatment, timely surgery and planned admission to critical care. Some hospitals already meet some of these standards but there are few examples of systematic implementation of the entire care pathway. Many opinion leaders support the use of quality improvement projects to promote implementation but others question this approach which is not well supported by clinical evidence. This uncertainty affects the care of all high-risk surgical patients. We propose a randomised stepped wedge cluster trial of a quality improvement intervention to implement an integrated care pathway in patients scheduled for emergency laparotomy in 90 NHS hospitals to confirm the effect on survival at 90 days after surgery. This will provide a robust evidence base for quality improvement which will inform the treatment of 170,000 NHS high-risk surgical patients each year.

Background

The clinical problem: In the NHS, more than one million adult patients undergo in-patient non-cardiac surgery 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 were associated with important differences in mortality rates (8).

Improving the quality of care for patients undergoing emergency laparotomy: 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 an ongoing Delphi consensus process to revise and refine the RCS integrated care pathway creating a robust evidence based intervention (appendix 1).

The challenge of quality improvement in peri-operative care: 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. Collaboratives, PDSA 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 colo-rectal 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.

Why is this research needed now? 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, with which we have been collaborating with to undertake a ***feasibility pilot project*** (page 18). The pathway is expected to improve quality of patient care whilst adverse effects are thought unlikely and the key stakeholder groups now support our proposal for a 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 activities of various groups with a related interest in improving surgical outcomes have made this an ideal time for such a project. A large European epidemiological study led by the lead applicant has confirmed the importance of preventable deaths after surgery, stimulating widespread discussion of this issue (3). An NCEPOD report has made specific recommendations for improved care of the high-risk surgical patient (4), and the Healthcare Quality Improvement Partnership (HQIP) has commissioned a new National Emergency Laparotomy Audit (NELA) led by two of the applicants (17). These factors have created 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 an integrated care pathway to improve patient outcomes following emergency laparotomy. We have formed a highly experienced research team with expertise particularly suited to this project allowing us to provide the definitive evidence needed to inform practice in this key area.

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 conduct an ethnographic evaluation of the process of quality improvement in relation to surgical care pathways to optimise development, refinement and understanding of this intervention

3) To assess the cost-effectiveness of the quality improvement intervention compared to ongoing clinical practice without the intervention

4) To evaluate the long-term effects of the intervention on standards of care and mortality following emergency laparotomy in participating hospitals

Research Plan

Multi-centre, randomised stepped wedge cluster trial conducted in 90 hospitals over an 85 week period (18, 19). 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.

Choice of trial design: We have explored the relative merits of the stepped wedge and cluster trial designs as the two most appropriate options for this research question. These offer many of the same advantages, allowing delivery of the intervention at an organisational level with evaluation of outcome measures at a patient level. The principal advantage of the cluster design is flexibility in timing of start-up for individual sites, in turn allowing flexible deadlines for completion of R&D approvals. Sites which experience a delay in R&D approval would still be able to participate with only minor impact on the overall trial. This flexibility may also introduce bias if investigators who best engage with R&D approvals prove more effective in leading care pathway implementation. This would result in an association between the time of exposure to the intervention and susceptibility to benefit from it. The principal advantage of the stepped wedge design is the opportunity to control this form of adoption bias and adjust for time-based changes in the background level of patient care in the statistical analysis. The quality improvement component of the intervention (page 10) is too time consuming to be introduced in all sites simultaneously and some form of staggered site activation is therefore inevitable. By structuring this process through a staged activation of sites in a random order the stepped wedge design offers important methodological advantages. A parallel cluster trial of this size would involve staggered site activation but in a haphazard order without the protection against adoption-bias offered by randomisation. Furthermore, a parallel cluster design would, by its nature, withhold the intervention from half the hospitals taking part. A key strength of the stepped wedge design is that we can offer the quality improvement project to every site which takes part, creating a major incentive to participate in this large trial. Finally, the step-wedge study is more efficient in a statistical sense than a parallel study with the same number of hospitals and observations per hospital, but allowing a comparison of outcomes before and after integrated care pathway adoption in all of the 90 hospitals taking part.

Integrated studies

- An ethnographic study will identify an optimal approach to implementation of the quality improvement intervention and the care pathway before the trial intervention period and then investigate barriers to implementation allowing further optimisation during the intervention period

- A health economics analysis will allow us to calculate the cost effectiveness of implementing the care pathway compared to not doing so
- Long-term evaluation of the effects of the intervention on standards of care and mortality in participating hospitals utilising data from the National Emergency Laparotomy Audit

Patient inclusion and exclusion criteria: All 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 EPOCH trial.

Setting: Ninety acute NHS hospitals admitting patients for emergency abdominal surgery with at least three nominated local investigators (champions) and the support of the NHS Trust board.

Data collection

Patient level data will be collected and collated by the **Healthcare Quality Improvement Partnership National Emergency Laparotomy Audit (HQIP-NELA)** in all participating hospitals from the beginning of the intervention period (17). Before the randomisation period commences, investigators will be trained to use an internet based data entry system to collect baseline and 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 inclusion criteria for the EPOCH trial are identical to those of HQIP-NELA and the core EPOCH dataset only includes patient level data gathered by the audit. The EPOCH and HQIP-NELA teams will work in a co-ordinated manner to ensure investigators return complete data on all eligible patients. To facilitate the health economics analysis, research staff will collect additional data describing quality of life and patient resource use in one six hospital cluster over the duration of the intervention period.

Baseline 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), Documentation of 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.

Health economics: In one six hospital cluster, EQ-5D and healthcare resuorce use at baseline, 90 and 180 days (telephone). Staff resources associated with the quality improvement intervention.
180-day follow-up: Critical care admission, Duration of hospital stay, Hospital readmission and mortality.

Outcome measures

Primary outcome measure

- All cause mortality at 90 days following surgery

Secondary outcome measures

- All cause mortality at 180 days following surgery
- Duration of hospital stay
- Hospital re-admission within 180 days of surgery
- Health economics outcome: Quality adjusted life years over the patients' lifetime

Process measures

- Time to diagnostic imaging
- Consultant surgeon present in operating theatre
- Consultant anaesthetist present in operating theatre
- Admission to critical care within six hours of completion of surgery (level 2 or level 3 care)
- Documented evaluation of mortality risk prior to surgery

Trial intervention

The trial intervention fits neatly into the ***MRC Complex Interventions framework*** and following feedback from the previous submission, we have further structured our application to illustrate this (20). A pre-trial systematic review and Delphi consensus process will revise and refine the integrated care pathway with any outstanding evidence. The Emergency Laparotomy Quality Improvement Care Bundle programme (ElPQuIC) is a Health Foundation funded pilot study in four acute hospitals (Bath, Exeter, Guildford, Torquay). Along with an organizational audit conducted by HQIP-NELA and phase A of the ethnographic evaluation (page 14), ElPQuIC will provide a comprehensive theory of change for the intervention including the quality improvement work and the care pathway. We will then evaluate the intervention in a randomised stepped wedge trial followed by dissemination and long-term follow-up work which will together provide definitive evidence (21). The dissemination of innovations or new

practices in healthcare is not necessarily a linear processes and scientific evidence is only one element influencing the change process (22). The trial intervention itself is therefore comprised of ***two major components***: (1) an integrated care pathway defined through systematic review and designed to provide optimal care for patients undergoing emergency laparotomy and (2) a quality improvement project to promote the implementation of the care pathway and effect real changes in clinical practice. In terms of implementation science, the intervention might be seen as containing a ***'hard core'*** of irreducible elements which carry the key potential benefits for patients. This is surrounded by a ***'soft periphery'*** of various complementary elements intended to maximise the chance of delivering the benefit (22). Whilst the hard core of the intervention is unlikely to change, the soft periphery may do, since staff will find more effective and efficient ways of working, and different organisational contexts will require different adaptations to ensure fit. If the soft periphery of the intervention is poorly organised, or inflexible, or maladapted to particular contexts, it may destroy the benefit of the hard core.

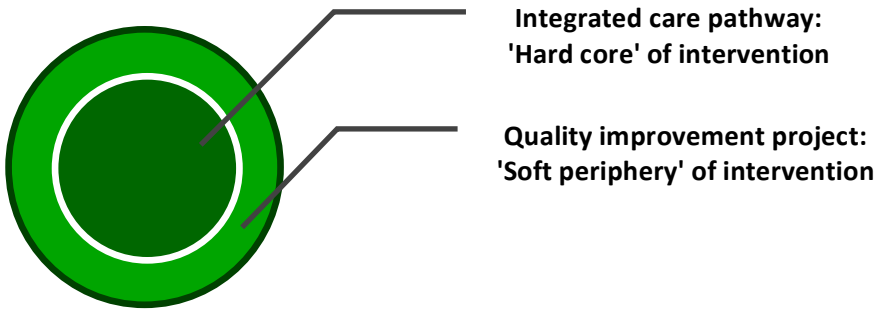

Figure 1. Structure of the EPOCH trial intervention

The integrated care pathway represents the'hard core' of the intervention defined through systematic review and consensus methods and will remain fixed through the trial. Quality improement methods represent the 'soft periphery' and will be adapted and optimised during the trial period.

In the EPOCH trial, we see the integrated care pathway as representing the hard core of the intervention and the quality improvement project the soft periphery. We will not seek to make changes to the integrated care pathway during the trial but we will actively seek ways to maximise the effectiveness of the quality improvement intervention. We recognise that participating sites may vary in the extent to which they implement the full care pathway, and how they change this in response to local circumstances. Such adaptations may or may not impact upon the effectiveness of the care pathway in improving outcomes, and so merit attention. Given this, and as we discuss in more detail below, the ethnographic sub-study will therefore serve two principal objectives: (i) to provide ***formative*** lessons

about how the quality improvement work can be optimised; and (ii) to generate ***summative*** understanding of the 'fidelity' with which the care pathway has been implemented and the impact of this, and thereby offer insight into heterogeneity in outcomes between sites, understanding of aspects of the pathway that are more challenging to implement or sustain, and recommendations to address this. Although, in treating it as the 'hard core' of the intervention, we propose to hold the care pathway constant for the duration of the trial, these recommendations may ultimately include changes to the content of the integrated care pathway (described next), especially if implementing it faithfully in its entirety proves problematic across sites.

Integrated Care Pathway

Whilst the RCS integrated care pathway was created through multi-disciplinary expert review process, the need remains to refine and better define the final care pathway for use in the EPOCH trial. RM and his group have completed a ***systematic review*** to identify candidate interventions for a revised and refined integrated care pathway (Appendix 1).

Pre-operative care

- Consultant led decision making
- Computed tomography imaging (wherever indicated) within two hours
- Goal directed therapy for patients with severe sepsis or septic shock within one hour
- Analgesia within one hour
- Antibiotic therapy (unless inappropriate) within one hour
- Correction of coagulopathy
- Maintain normothermia
- Active glucose management
- Documented mortality risk estimate
- Oral and written information about peri-operative care provided to patient and relatives

Intra-operative care

- 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
- 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

Post-operative care

- 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
- Critical Care Outreach review of patient on standard ward with use of Early Warning Scores
- Daily haematology & biochemistry until mortality risk is low (senior opinion)
- Nutrition: early dietician review with careful consideration of benefits of enteral feeding
- Chest physiotherapy review on day one after surgery

Quality improvement (QI) methods

We will use an evidence based QI project design to change the practice and culture of care for this patient group, engendering the belief that survival can be improved and providing a model of optimal care (integrated care pathway) alongside the QI methods to implement it (23-29). Hospitals will be linked in clusters of six on a geographical basis. This will facilitate adoption by building on existing local and regional relationships and minimise bias caused by natural workforce movements between hospitals. Each hospital will nominate at least one local 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 policy change to implement the care pathway. Exposure will start in each participating hospital as they are randomised to the intervention. Over the period of the trial, approximately half the patients in all centres will receive care from staff 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 relevent process measures. The QI methods will be reviewed at three, six and nine months by the EPOCH QI team informed by the early ethnographic findings (page 14) allowing iterative changes to the intervention. The major features of the QI methodology are:

- *Engaging frontline staff and executive leaders* providing clear evidence that change is required and proposing the technical component of the intervention (integrated care pathway) 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 clinical champions* through meetings and web-based forums

QI Educational meeting for champions in each six hospital cluster: To develop the knowledge, skills and attitudes required to effect change, staff will attend a half day regional meeting led by the EPOCH QI team. As a minimum this will include the nominated frontline champion from each stakeholder discipline although attendence by other frontline staff and NHS trust board members will be strongly encouraged. Rigourous planning and widespread engagement of senior leaders will ensure meetings are well attended. 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 meeting which will itself have **four distinct aims**:

A) Raise awareness of poor outcomes for emergency laparotomy patients & propose technical solution

- Describe epidemiology, clinical outcomes and challenges from a clinician perspective
- Filmed patient stories to present patient perspective and gain emotional buy-in to 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 diagram to help teams understand the basis for change and where to target QI activities

B) Introduce quality improvement as a method to maximise opportunities to improve patient outcomes

Local champions will be trained in basic QI methodology supported by on-line resources and materials. We will teach basic process mapping and segmentation techniques to help teams understand how the care pathway will function in the context of their hospital. These techniques will help teams to identify areas where they can maximise impact ('easy wins') and local barriers to change that must be overcome. Any adverse effects of implementation will also be highlighted. Early after the QI educational meeting, teams will undertake formal process mapping activities in their hospital and share the results with the EPOCH QI team. Plan-Do-Study-Act (PDSA) cycles will allow observation of incremental changes in key areas identified through process mapping and segmentation activity. Time series audit data (run-charts)

will be used 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 material such as pens, badges, lanyards and posters
- Encourage and facilitate sharing of good practice through meetings and web-based forums
- Encourage local patient and public input and provide resources and tools 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 and a simple smart phone application for champions to disseminate to local staff
- Setting key milestones for local implementation with process mapping and frontline staff meetings

Maintaining momentum of the intervention: 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. This will also allow identification of strong and weakly performing hospitals so the ethnographic team in particular, may identify reasons for success and failure of pathway implementation.

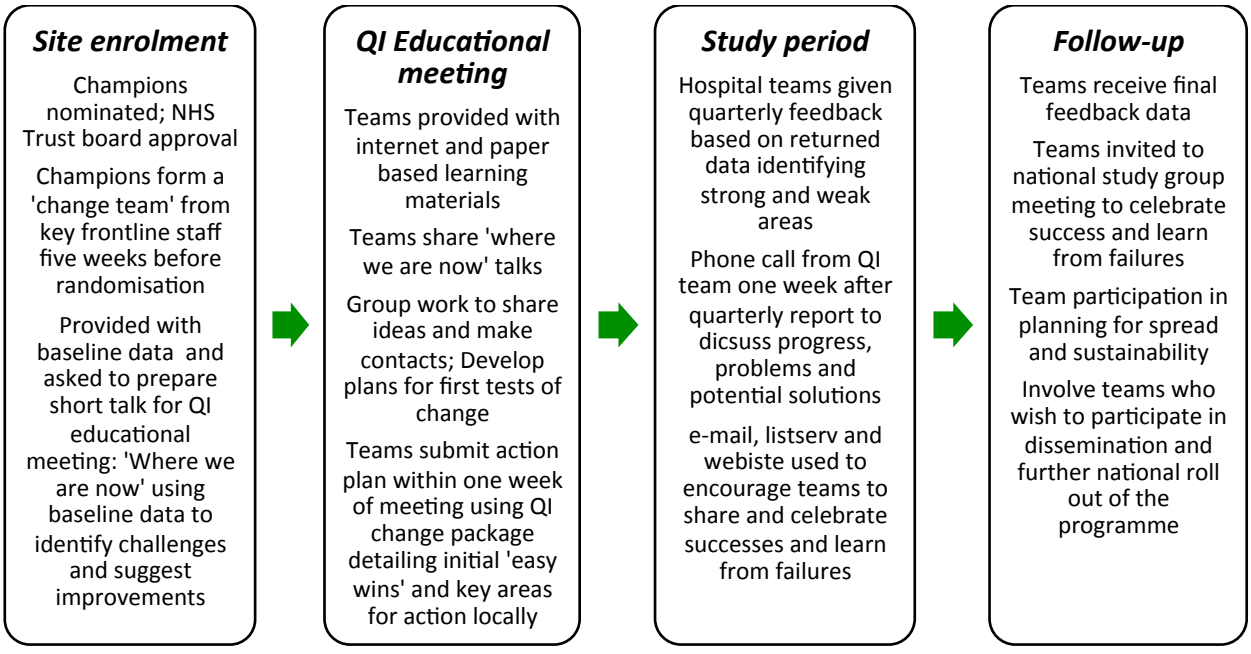

Figure 2. EPOCH quality improvement intervention from perspective of participating hospitals

Statistical methods

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% (90-day mortality data not provided) (8). Data from the Hospital Episodes Statistics (HES) for the year ending April 2011 gives the average 30-day mortality as 17% (10^{th} centile 13% – 90^{th} centile 22%) and the average 90-day mortality as 25% (10^{th} centile 20% – 90^{th} 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 (30), 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 **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 coffeicient 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 values of the coefficient of variation but sensitive to the effect size. In practice, power may be attenuated 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%.

Statistical analysis

This will be conducted on an intention-to-treat basis, i.e. 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-mobid disease and ASA score and adjustment for a fixed time effect between 5-week periods. Patients will be excluded during the earliest period following implementation of the intervention (five week period immediately after randomisation). An independent statistician will

randomise the clusters and keep randomisation records. 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 co-variates 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.

Procedures to minimise bias: Due to the nature of the intervention, it is not possible to blind hospital staff. Confirmation of the primary outcome assessment is objective and automated through use of Office for National Statistics data. Incomplete data collection may lead to selection bias. Randomisation will be performed by an independent statistician allowing data quality checks. Site visits for data monitoring undertaken by research staff blind to the intervention status of the hospital will allow data completeness to be checked against hospital records. All hospitals participating in the EPOCH Trial will return data from the beginning of the trial. Local investigators will be trained by the NELA team to enter data onto a simple internet based data entry system. To ensure data capture on 100% of eligible patients, the principal investigator or designee will screen operating theatre lists at least once each week. In cases of doubt regarding eligibility, local investigators may discuss with the trial team using anonymised data. All patients included in the EPOCH trial meet the inclusion criteria of the NELA project.

Complexity relating to partial adoption of component pathway interventions: It is recognised that some hospitals will meet some of the recommended standards of care for some patients. This partial adoption is a well recognised challenge of quality improvement and represents a significant part of the problem we seek to address with the trial intervention. We will approach this in a standard manner by monitoring process measures which reflect compliance with key components of the integrated care

pathway. An understanding of the relationship between changes in process measures over time and changes in clinical outcomes over time provide a greater understanding of the specific impact of the integrated care pathway. A common observation is for all participating hospitals to show improvement measures and a reduction in the variation between high and low performing hospitals. In statistical terms, the stepped wedge design allows us to better understand time-based changes which may affect clinical outcomes across participating hospitals because of the structured introduction of the intervention over time. Process measure data will also allow us to conduct secondary analyses to test for possible effects of partial adoption on patient outcomes.

Ethnographic evaluation

An integrated ethnographic study will inform the development, design and reconfiguration of the QI intervention (formative input) and provide generalisable learning about the QI approaches used and the reasons for the success or failure of the integrated care pathway in improving outcomes (summative output). The study will inform efforts at improvement in an area where professional scepticism, inter-professional boundaries and challenges around management and finance must be overcome. This requires effective training, local ownership and engagement of broad stakeholder groups (25), as well as sensitivity to the divergent contexts in which the pathway will be implemented. The ethnographic study will provide insights into how implementation has been achieved in sites that have already made progress in adopting the care pathway, how pathway components may improve practice, ongoing analysis of the quality improvement intervention as it takes place and formative feedback to refine it.

A) Retrospective interviews with staff in four 'early adopter' sites: A theory of change will be developed for the quality improvement process, the pathway and its implementation, drawing on interviews with staff who developed the pathway and / or successfully adopted it in four early adopting hospitals, as well as documentary analysis of the prototypical care pathway described by the ICP, the final pathway being developed by the Delphi consensus process, and interviews with study team members responsible for leading the quality improvement work. This will be used to further develop and hone the quality improvement approach to be adopted in the first step of the trial, to ensure that it is as appropriate for its task and the contexts it will face as possible.

B) Observational & interview-based study in a sample of sites randomised to the first step of the trial: Three hospitals randomised in the first step of the trial will be sampled according to criteria likely to be contextually important in the implementation process based on prior theory and issues raised in the retrospective interviews above (e.g. size, annual throughput of eligible patients, number of directorates

involved, professional leadership, baseline performance). Observation of the QI intervention (including regional meetings and local training processes) and of work done to implement the pathway in practice will be carried out (20 hours per site), along with interviews with champions and others involved in implementation (around 10 interviews per site). Data analysis will provide formative input to refine the quality improvement intervention for subsequent cohorts.

C) Ongoing observational and interview-based study in six sites: This will take place in the three sites sampled under part B, together with three further theoretically sampled sites from later cohorts (after the three-month review of the intervention), to provide a thorough understanding of the challenges of implementing the care pathway, and sustaining the changes that have been instigated. This will involve a further 20 hours' observational work in the three sites from the second phase and around 10 follow-up interviews with stakeholders, plus around 30 hours' observational work and 15-20 interviews in the three sites from the later cohorts. The primary objective of this phase of the work is to provide generalisable knowledge about using quality improvement methodologies and integrated care pathways in surgery and other complex areas. This will inform similar efforts elsewhere and provide insights into the sustainability of changes implemented (a key challenge in quality improvement) (31). Formative feedback will also continue to allow for further refinement of the quality improvement intervention at six and nine months. Findings from the qualitative work will be integrated with those from the rest of the study to provide a rich summative explanation of the degree to which the intervention has been successful in implementing the pathway, providing understanding of differential uptake between sites, and illuminating which aspects of the pathway have been successfully implemented using the intervention, and which aspects may require alternative approaches. The ethnographic work will:

- identify how to optimise the QI intervention to secure the full, faithful uptake of the pathway
- surface the challenges involved in putting the pathway into practice and the impact of these on the extent to which each part of the pathway was implemented
- explain the role played by contextual variables in determining how far the pathway is implemented;
- identify the relationship between pathway implementation and patient outcomes

Qualitative analysis: Analysis of data from part A of the ethnographic sub-study (theory of change for the pathway) will follow the framework approach to ensure that rapid, relevant insights are derived to inform the development of the quality improvement intervention (32). Analysis of data from parts B and C will use the constant-comparative method (33). Analysis will be led by researchers from the University of Leicester, but informed by regular conversations with the rest of the team. Formative feedback will

be provided through regular meetings and written reports ahead of the reviews at three, six and nine months, so that these insights inform development of the quality improvement intervention.

Cost effectiveness analysis

This 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. We will also evaluate resource use and health related quality of life using the EQ-5D questionairre in patients within one six hospital cluster randomised towards the middle of the intervention period. EQ-5D data will provide an estimate of the health related quality of life weights that could be used in the model. The primary outcome measure of this analysis will be Quality Adjusted Life Year (QALY) over the patients' lifetime estimated through the use of parametric survival modelling together with clinical and epidemiological data (34). A Markov or semi-Markov decision analytic model will be used with 90-day mortality as a key input. 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. 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 of the intervention will be defined by any differences in 90-day mortality and will be used as a parameter input into the model. Resource use associated with the quality improvement intervention and the costs of patient care will be captured as detailed on page 6. Unit costs will be estimated from published literature, NHS and government sources, including NHS Reference costs and PSSRU Unit Costs of Health and Social Care, to generate a total cost per trial participant for the relevant resource use. If appropriate, cost and QALY data will be synthesised to generate an Incremental Cost-Effectiveness Ratio (ICER) where the additional cost of the intervention is formally compared with the additional benefit. This estimate can then be compared with a threshold value of a QALY to assess whether the intervention is likley to provide value for money. 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.

Long-term follow-up

Through our relationship with NELA, we will evaluate the long-term effects of the quality improvement intervention in participating hospitals. Evaluation of changes in process measures will confirm whether compliance with the care pathway is maintained in the absence of a nationally co-ordinated project. Evaluation of clinical outcomes will demonstrate the long-term benefits of the intervention allowing comparison with hospitals which did not participate in EPOCH and therefore were not exposed to the QI intervention. This will further facilitate dissemination and implementation after the trial.

Feasibility and deliverability

The EPOCH trial proposal is highly ambitious but necessary if we are to provide the definitive evidence so urgently needed. An important change in this proposal is the introduction of a ***staged funding review*** at ten months (by which time the trial intervention period would be well under way) with the option to close the trial in the event of failure to reach agreed milestones. Ongoing feasibility work includes:

Quality improvement pilot: Led by CP and funded by a Shine grant from the Health Foundation, four acute hospitals (Bath, Exeter, Guildford, Torquay) are participating in the Emergency Laparotomy Quality Improvement Care Bundle programme (ElPQuIC). This pilot work has provided important experience and confirms the feasibility of a large scale project. The pilot has generated innovative ideas and has shown that simple changes can engender a sense of priority and urgency of care for this patient group. Early findings suggest improved process measures and a trend towards reduced hospital stay and mortality.

Care pathway development: The pre-trial systematic review is complete and the Delphi consensus review process involving patients and frontline clinicians is well under way to define a list of component interventions which are both ***effective and feasible*** to implement in the context of the EPOCH trial. This will then be tested by ethnographic study in the early adopting hospitals participating in the pilot study described above and again during the ethnographic review at 3, 6 and 9 months.

Recruitment and engagement with NHS hospitals: We have expressions of interest in participation from ***83 hospitals*** with which we have collaborated previously on the highly successful EuSOS study (3). Meanwhile, ***112 hospitals*** have registered for HQIP-NELA. A key strength is that the trial design will offer the QI project to every site which takes part creating a major incentive to particpate and engage with the intervention. We are therefore confident we can recruit the 90 hospitals we require.

Project management: We have assembled a very strong multi-disciplinary team in order to provide the expertise, skills and leadership required to ensure the project is successfully completed including those of a clinical trials unit which specialises in large pragmatic cluster trials. Of particular note, RP and MG have experience in leading large scale multi-centre studies (3). CP, TS and JB are highly experienced in the field of quality improvement and will ensure the QI design is effective and feasible.

Data capture: HQIP National Emergency Laparotomy Audit commenced on 1st December 2012 with year one milestones to develop, build and test the web-based secure data capture system as well as completion of a preliminary organizational audit of clinical activity in eligible hospitals. The specification of the data capture system has been written and development will begin in May by an IT supplier with a strong track record in delivering secure data collection systems for national clinical audits. This system will be beta-tested in Autumn 2013 and patient-level data collection will begin on 1st December 2013, well in advance of the start of the EPOCH intervention period in March 2014. RP leads a research team which has recruited more than 3000 consenting patients into peri-operative medicine trials who were followed for up for one year. Data capture at 90 days and one year ***included EQ-5D*** and similar data. We are ***justifiably confident*** in our ability to capture this data and do not regard this as a specific risk.

Project management

The EPOCH trial will be managed by the NIHR funded Pragmatic Clinical Trials Unit (PCTU) at Queen Mary's University of London which has a particular interest and expertise in cluster trials. On a day to day basis, the trial will be led by a trial management committee chaired by RP. The quality improvement committee, chaired by CP, will lead day to day organisation of the QI intervention and associated educational strategy. RP and CP will be members of both committees ensuring effective communication. RP will take overall responsibility for all aspects of trial management but will be supported by a full time trial manager. We have increased the overall senior trial manager's time to 50% FTE to ensure clear leadership and effective co-ordination in particular during site enrolment and R&D approval.

Steering and Data monitoring committees: The trial steering committee will be appointed in accordance with NIHR guidance with an independent chairperson, lay representation and two independent members. As there is no role for interim analysis or safety monitoring in the EPOCH trial, an independent Data Monitoring Committee will not be appointed (subject to NIHR confirmation).

EPOCH Advisory group: To ensure strong and effective links with stakeholder organsiastions, an advisory group has been formed with representation from Royal colleges, specialist societies, UKCRN,

NCEPOD and NHS trusts. The advisory group will be charied by Mr Iain Anderson, who was lead author of the Royal College of Surgeons integrated care pathway report (appendix 2).

Data management: Data will be collated by HQIP-NELA. Patient level data will be anonymised prior to transfer to the PCTU for statistical analysis. Through co-operation with NELA, site monitoring visits will be performed by blinded PCTU staff for source data verification. Data will be stored securely against unauthorised manipulation and accidental loss. Trial documents will be archived for twenty years.

Regulatory approval: Approval of a research ethics committee will be in place before the trial commences. The trial intervention is at an institutional level and the principal exposure is to staff rather than patients. The main ethical issue is the use of anonymised patient level data provided by NELA without patient consent. Both NELA and the EPOCH trial will require section 251 approvals from the National Information Governance Board.

Adverse events and study safety: The trial involves minimal additional risks to patients or investigators. Adverse events will be monitored in accordance with the PCTU standard operating procedures and reported in compliance with the Research Governance Framework, 2005 and sponsor requirements.

Dissemination and projected outputs

Health care policy makers: We will provide specific reports on the findings of the EPOCH trial for healthcare policy makers. Through the support of the advisory group we will ensure the findings are disseminated apropriately to the Department of Health, Royal Colleges, NHS trusts and other stakeholder groups. We will advise on the implications of our findings and optimal implementation.

Patients and frontline NHS staff: In partnership with local champions, our findings will be widely disseminated to the NHS community at regional, national and international meetings in a timely manner. A writing committee will draft manuscripts for open access publication in peer reviewed journals. Lay members of the EPOCH study group will facilitate dissemination to patient groups (e.g. bowel cancer, inflammatory bowel disease).

Continued knowledge dissemination: At the end of the intervention period, electonic and paper based educational materials will be adapted, rebadged and made freely available to allow ongoing use for quality improvement purposes by NHS trusts, NELA and EPOCH study group members.

Patient and Public Involvement (PPI)

The findings of the EPOCH trial will have a significant impact on the experience of this patient group. The project comprises significant and wide ranging patient involvement at every stage from trial design and

grant preparation through to dissemination of findings. On behalf of the Health Services Research at the Royal College of Anaesthetists (RCoA), RP is leading the development of a robust PPI process to provide a critical mass of experienced lay members who can participate in clinical research. The EPOCH Trial will be the first project to make use of this new resource and we will work with members of the Patient Liaison Group (PLG) of the RCoA with the support of Involve (www.invo.org.uk) and Bec Hanley, a professional PPI trainer from TwoCan Associates (www.twocanassociates.co.uk). This will ensure the availability of experienced and trained patient representatives for the various activities which will be carefully planned to minimise inconvenience. Lay members will be re-imbursed for their time and travel expenses.

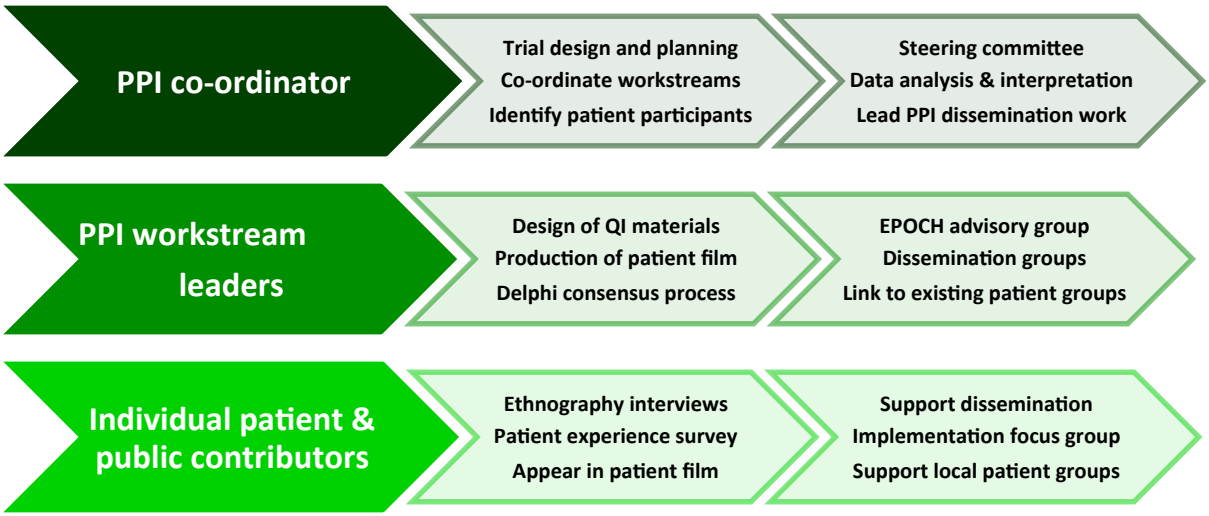

Figure 4. Tiered approach to Patient & Public Involvement in the EPOCH Trial

We plan three levels of involvement allowing us to draw on contributions from a range of patients and public whilst ensuring a realistic level of commitment in particular for patients many of whom may be frail or elderly.

PPI co-ordination: KR is a co-applicant and highly experienced lay representative in healthcare organisations and has been closely involved in the development of the trial proposal from the outset. With the support of the EPOCH trial manager, Kate will oversee and co-ordinate PPI activities across the project, delegating leadership for specific workstreams, acting as lay representative on the trial steering committee and contributing to the conduct of the trial, analysis and reporting of the findings. KR is a co-applicant on the trial and will be involved in all strategic decision making along with the other applicants; this contact will vary from a weekly to a monthly basis at different stages of the project. KR is joined by DW, also an experienced patient representative for the Intensive Care Society who has himself undergone an emergency laparotomy. DW has particuar experience working with patient groups and his

professional life involves work in radio and screen media. The trial steering committee will meet twice each year and will include two patient representatives (KR and DW). The trial advisory group consistes primarily of representatives of key stakeholder groups but includes a patient representative and will meet at least once each year. We will organise separate meetings to discuss and co-ordinate the overall PPI strategy and we envisage these taking place twice each year with regular contact between meetings.

PPI workstream leaders: PPI activity will be divided into workstreams to allow a managable time contribution for named PPI workstream leaders some of whom have already agreed to contribute. The key workstreams will include contributions to the ***Delphi consensus*** process, design of ***QI educational materials (KR)***, supporting production of the ***patient film*** for the frontline NHS staff audience (DW), PPI represenation on the EPOCH ***steering committee*** and ***advisory group***, linkage with existing national and local ***patient groups*** (eg bowel cancer, inflammatory bowel disease) and support for the ***dissemination*** of findings to healthcare policy makers, NHS managers, frontline NHS staff and relevant patient groups.

Individual patient contributions: We will seek the involvement and contributions of patients who have undergone an emergency laparotomy to ensure a detailed understanding and knowledge of this specific experience. We will carefully manage the level of commitment needed for these contributions because we anticipate that many such patients may be frail or remain unwell. Particular activities will include participation in ***ethnography interviews*** to understand the patient perspective of the current system, participation in the ***patient film***, completion of a ***patient questionairre*** to provide structured information on the patient experience, involvement in ***focus groups*** and other ***local patient groups***. At the dissemination stage we may seek ***patient involvement in media interveiws*** to explain the patient perspective following completion of the trial.

Expertise and justification of support required

The proposed investigation is a large multi-centre trial which will allow implementation of the highest level of evidence throughout the NHS. The proposal represents excellent value for money given the large number of patients and hospitals involved and the potential to improve survival for a large patient population. The National Emergency Laparotomy Audit will provide a robust system for data capture at minimal cost. The ethnographic evaluation is highly integrated into the project being used to identify barriers to quality improvement before and during the project allowing us to maximise the effectiveness of the QI intervention. The ethnographic and health economics analyses will ensure we maximise the evidence created during the project. All costs are realistic and necessary and have been calculated by

finance staff using standard methods. By design, the trial is of a fixed duration making cost over-runs very unlikely. The trial team is highly experienced with internationally recognised expertise in every aspect of the methods we will use. In addition, we have convened an advisory group to draw on advice and comments from stakeholder organisations (including two Royal colleges) at minimal cost. The PCTU will provide support with regards to statistics, data management, trial management and quality assurance. The PCTU statistician will develop the statistical analysis plan, perform data manipulation and analysis and provide a final statistical report. The data manager will develop appropriate data management strategies and advise on their use, creating databases with integrated data validation checks and secure patient data management. The trial manager will maintain general oversight of the trial at participating sites, obtain all relevant approvals and project manage over the full duration of the trial. The quality assurance manager will advise on regulatory requirements and will regularly audit the trial and train trial staff in appropriate standard operating procedures. The number of co-applicants reflects the diversity of skills required to ensure successful completion of a complex project. Some applicants will devote a substantial amount of time to the project whilst others will play a responsive role, advising on trial design, management and analysis throughout. Funds are requested to support the national co-ordination of the quality improvement project including staff and development of educational materials (electronic, web-based & paper based). Research nurse funding is requested to support the cost of collecting quality of life data in one six hospital cluster. The remaining research nurse support falls into the category of NHS support costs and will be provided by clinical research networks.

RP will be chief investigator and hold overall responsibility for all aspects of the trial. RP will ensure robust and effective communication between the EPOCH teams to ensure a successful outcome.

CP will be Quality Improvement lead working closely with TS and RP to finalise the QI intervention, develop educational materials, plan QI educational visits and ensure regular QI feedback to sites.

JB will advise on methodological aspects of quality improvement and healthcare education. He will also contribute clinical expertise and facilitate communication with stakeholder organisations.

OF & **PH** will contribute clinical expertise in surgery and academic expertise in patient safety, quality improvement and the use of large scale databases to evaluate patient care.

AG will contribute statistical expertise in trial design, sample size calculation and statistical analysis.

MG is director of the Health Services Research Centre (RCoA) and chair of HQIP-NELA and with **DC** will ensure strong links with NELA, so that the two projects work effectively in unison.

SK will be the trial statistician and will contribute to trial design and oversee the data analysis.

RL will advise on the complex aspects of design, conduct and analysis of stepped wedge cluster trials.

GM & **CT** will lead and conduct the ethnographic analyses. They are experienced social scientists and qualitative researchers, having led many mixed-methods studies of healthcare quality improvement.

RM leads the systematic review and consensus based review and refinement of the care pathway. He will also contribute clinical expertise and facilitate communication with stakeholder organisations.

GR & **MA** will perform the health economics analysis and advise on dissemination to policy makers.

KR is PPI lead and lay representative on the steering committee. KR has been closely involved throughout development of the trial proposal.

TS will work full-time on the project and along with CP, will play a major role in development of educational materials and delivery of the quality improvement intervention.

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