Study Title: The BCAE Study: Best Care for Abdominal Emergencies

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

2. SYNOPSIS

It may be useful to include a synopsis of the study for quick reference. Delete or alter as appropriate/required.

Study Title	The BCAE Study: Best Care for Abdominal Emergencies
Internal ref. no.	PHT/2019/72
Problem statement	Abdominal emergencies are common, involving perforation, obstruction or ischaemia of the bowel, often needing life-saving emergency surgery, with a large incision to access the abdominal cavity called "laparotomy". This procedure is high risk with 10% mortality rate. 30,000 emergency laparotomies are performed each year in England and Wales. Since 2013, the National Emergency Laparotomy Audit (NELA) has set standards of care and monitored outcomes for emergency laparotomy, which has reduced mortality from 11.8 to 9.5%. However, patients who do NOT have a laparotomy are not well characterised and do not receive the prioritised care patients having surgery do, even though their condition is no less severe. Initial research has shown a surprisingly large group of patients (32%) with an intestinal emergency do not have surgery and have 30-day mortality of 63%. There are two additional groups of patients admitted with abdominal emergencies: patients having keyhole surgery and patients for whom any treatment would be futile and would benefit most from an end of life care pathway. Clearly further work is needed to investigate the management of ALL patients with intestinal emergency, to optimise care for each group of patients.
Research question / hypothesis	The aim of this study is to improve care for all patients with an intestinal emergency, irrespective of whether they have surgery or not.
Study Design	This is a single-centre retrospective cohort study utilising electronic hospital records.
Study Participants	Data will be derived from electronic patient records collected as part of routine clinical patient care on all general adult wards (excluding maternity) between 2013 and 2020. *Inclusion criteria:* • Must have an acute intestinal condition, based on their ICD-10 codes and OPSC-4 codes • Must be >= 16 years of age at the time of admission • Have at least one full set of vital signs recorded on the day of admission • Have at least one full set of routine blood tests recorded on the day of admission *Exclusion criteria:* • Maternity admissions during/after pregnancy • Patients admitted or undergoing abdominal surgery for a second time or more Using OPCS-4 codes from PAS and TheatreMan™ and NELA data, we will then identify patients who had an emergency laparotomy, and those who had a laparoscopic procedure. We aim to identify a further group where treatment is futile, suggesting that an early focus on end of life care might be appropriate.
Planned Sample Size	2,500
Follow-up duration	1 year (retrospectively)

Planned Study Period	01 Dec 2020 – 31 May 2021
Primary Objective	Provide mortality rates for different treatment options, and analysis of short- and long-term outcomes.
Secondary Objectives	Define patient sub-groups with similar health characteristics based on clinical data and an established risk index. Use statistical analysis to predict the risk of death for each patient group and treatment option, which will allow us to identify the best care pathways for each cluster.
Primary Endpoint	Mortality risk for each treatment group
Secondary Endpoints	Risk of other outcomes and long-term complications and association between patient factors and these outcomes
Intervention (s)	N/A

3. ABBREVIATIONS

AUROC	Area Under the receiver operating characteristic curve
EWS	Early warning score
ICD-10	International Classification of Diseases, version 10
GDPR	General Data Protection Regulation
LDTEWS	Laboratory decision tree early warning score
NELA	National Emergency laparotomy audit
NEWS	National early warning score
NHS	National Health Service
OPCS-4	Office of Population Censuses and Surveys, Classification of Surgical Operations and Procedures (4th revision)
PAS	Patient Access system
PHUT	Portsmouth Hospitals University Trust
P-POSSUM	Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity
PRA	Patient Research Ambassador
QI	Quality improvement
UoP	University of Portsmouth
ViEWS	VitalPac Early warning score

4. BACKGROUND AND RATIONALE

4.1 What is the problem being addressed?

30,000 emergency abdominal laparotomies are performed each year in England and Wales (1). Each involves making a large incision down the middle of the abdomen to gain access to the abdominal cavity. In 2011, the Royal College of Surgeons England issued a report highlighting concerns that the mortality rate for patients having laparotomy was about twice that of open-heart surgery, with a number of shortfalls in patient care contributing to this (2, 3). Since 2013, the National Emergency Laparotomy Audit (NELA) has monitored outcomes from emergency laparotomy across the UK. The audit sets standards of care against which hospitals are benchmarked, such as early administration of antibiotics, CT-scan for diagnosis, pre-operative risk assessment, consultant surgeon/anaesthetist presence in theatre and transfer to intensive care postoperatively, leading to better outcomes (1, 4-6).

Conversely, patients with intestinal emergencies who do NOT have a laparotomy are not well characterised and do not receive the prioritised care that patients having surgery do; even though their condition is no less severe. There is a significant lack of information on the outcome and quality of life of patients who do not have a laparotomy. In the UK, only a single small study, the NoLap Study (7), has looked at this. They found a 30-day mortality of 63% in these patients compared to 13% for those who had a laparotomy. It is this surprisingly large group of patients (32%), who have such a poor outcome that deserves further investigation.

This study will benefit patients by providing information on the outcomes for ALL patients admitted with an intestinal emergency. Effective alternatives to laparotomy exist, including keyhole (laparoscopic) surgery (8-12) and interventional radiology procedures (13-16). These are less invasive and could carry lower risks than a laparotomy. By identifying groups of patients for whom these less invasive procedures may be more appropriate, the development of new alternative care pathways for them can be prioritised. There will sadly be some patients for whom active treatment is futile, such as those with loss of blood supply to the bowel or advanced cancer (17). Defining this patient group too will facilitate the development of pathways that have an earlier focus on symptomatic best end of life care. The characteristics of patients and their outcomes undergoing all the above 4 options will be investigated. Knowing these risks will help us better inform patients of the likely outcomes of their choices.

4.2 Why is this important?

Patients who do have a laparotomy are high risk, with a 10% mortality rate at 30 days measured nationally. This group is closely scrutinised by the National Emergency Laparotomy Audit (NELA) who set strict standards of care, and outcomes from surgery are well characterised (1, 2, 4-6). However, there is clear evidence that patients with intestinal emergencies who do NOT have emergency abdominal surgery (laparotomy) do very poorly, with only 30% of patients surviving to a year from admission (7). Our concern is that patients not undergoing laparotomy, but with the same life-threatening pathology, are being forgotten and do not receive the focus of care that they deserve. To improve the quality of care for these patients, better understand the risk of mortality and associated patient factors for ALL patients admitted with an intestinal emergency is needed.

This much-needed study will benefit patients by providing information on the 30-day and 1-year mortality for all patients with an intestinal emergency admitted to our hospital over a 6.5-year period. By observing relationships between mortality and patient factors like age, diagnosis, co-morbidities, vital signs, blood tests and surgery versus no-surgery, factors influencing patient outcomes will be identified and better understood. The "NoLap" study (7) suggested that a cohort of these patients who didn't have a laparotomy might in retrospect have had a better chance of survival if they had. To investigate this, patient factors will be analysed and patterns that significantly influence mortality will be determined. Results will provide insights into the different patient groups and improve our

understanding of their risk of death, with or without surgery. This will enable clinicians to more intelligently advise patients and their relatives on risks of laparotomy against alternative management.

The NoLap study does not provide information on the performance of laparoscopic (keyhole) procedures compared to laparotomies for abdominal emergencies. PHUT has championed the use of laparoscopy in emergency surgery, with progressive uptake by all consultants from 2014 onwards (11). By 2018, 60% of cases were completed laparoscopically, far higher than the national average of 8% (1). More importantly, this approach has been shown to be safe, with reduced mortality and length of stay (11). For patients unfit or unable to have any surgery, the Department of Interventional Radiology provides an on-call service to drain sepsis and embolise bleeds under local anaesthesia. In this study, information on the outcomes for patients who had an intestinal emergency managed laparoscopically or had an interventional radiology procedure will be collected. The effect of alternative treatments on patient outcomes will be assessed to determine which patient groups would most likely benefit from these interventions. This will benefit patients by providing clinicians with the scientific knowledge needed to develop better care pathways using these less invasive procedures. This will provide clinicians and their patients with the evidence they need to make a better-informed choice between laparotomy, minimally invasive procedures and symptomatic end of life care.

4.3 Why is this research needed now (existing evidence)?

Emergency laparotomy remains a common, high-risk operation (1). It is mostly performed for emergencies where there is perforation, obstruction or ischaemia of the bowel (intestine) that could lead to peritonitis. These are time critical pathologies requiring urgent treatment and careful peri-operative care, with a poor chance of survival without surgery (2-3). Since 2013, the National Emergency Laparotomy Audit (NELA) has monitored outcomes from emergency laparotomy across the UK, with a strong focus on identifying high-risk patients, ensuring consultant-led care and admission to intensive care postoperatively to improve outcomes (1, 4-6).

However, very little research has investigated the outcomes and the care received by patients with intestinal emergencies who do not have a laparotomy. The NoLap study (7) collected data on 314 patients admitted with an intestinal emergency and found a substantial patient group (32%) who do not have surgery. Of these, 74% were not felt to be fit enough for laparotomy, 6% had advanced cancer, 4% declined surgery and 16% undocumented. The 30-day mortality rate for patients with laparotomy was 13%, in-line with expected outcomes, yet the rate for patients who did not have surgery was 63%. This group were older (78 vs 63.7 years old) and frailer (30% vs 81%) and more likely to have co-morbidities. This study will build on this information to provide clear answers about which patient groups could benefit from laparotomy or alternative, less-invasive treatments. Factors significantly influencing mortality will be identified for clinicians to better inform patients/relatives of risks of their treatment. The NoLap study also compared two surgical risk models (18-19) to benchmark outcomes (7). Observed mortality (13%) in the laparotomy group closely matched the predicted mortalities (12% and 17%).

However, predicted mortality for the patients who did not have surgery was much lower (30% and 40%) than the actual observed mortality (63%). This suggests that some patients who were perceived as not fit enough for surgery actually had a better chance of survival with a laparotomy. This highlights the need to better understand why patients with intestinal emergencies do/do not have a laparotomy: why are patients not receiving the best possible care and so missing potentially life-saving treatment? The discrepancy could be due to unmeasured confounding patient factors that are not included in the risk model. Our study will identify the factors that influence mortality, enabling clinicians to select the best care pathway for individual patients and benefit those who may have been advised against surgery in the past, but for whom surgery (possibly using a laparoscopic approach) may indeed be the best way forward.

NELA standards of care have reduced 30-day mortality in emergency laparotomy from 11.8% to 9.5% since 2013(1, 4-6). However, the NoLap study (7) indicated these standards of care were less

frequently achieved in patients who did not have surgery. Decisions not to operate were less often informed by a CT scan (67% vs 82%), risk assessed (24% vs 37%), or involved documented consultant decision (66% vs 83%). There are possibly other factors that have influenced the decision not to operate, such as severe health problems precluding anaesthetic. Nevertheless, this highlights concerns that patients not having laparotomy are less likely to receive the same high standards of care. This study therefore seeks to redress this by focusing on *all* patients with abdominal emergencies, not just those who have had a laparotomy, to also improve the outcome of this neglected group of patients.

4.4 Impact of research

This study will provide new information on the outcomes for ALL patients with abdominal emergencies and the treatment they receive. By identifying groups of patients for whom less invasive procedures or end of life care may be more appropriate, it will support the development of new alternative care pathways.

This study will contribute novel information on the outcomes of minimally invasive procedures in abdominal emergencies (laparoscopy and interventional radiology). This information will be highly relevant to acute hospitals providing an emergency general surgery service across the UK. Initial analysis of the national NELA database has shown that currently only 8% of surgeries for abdominal emergencies in the UK are performed laparoscopically. Early data from Portsmouth Hospitals NHS Trust suggests patients may do better with this approach. The findings from this study will provide the necessary evidence to increase the proportion of laparoscopies nationwide and, thus, potentially significantly reduce risk for patients with abdominal emergencies.

5. PRELIMINARY STUDIES AND EXPERIENCE OF INVESTIGATORS

This study is a continuation of a long-standing collaboration between the University of Portsmouth (UoP) and Portsmouth Hospitals NHS Trust (PHU). The team has 20 years of experience in extracting and linking these types of data sets for work in clinical outcome modelling and risk prediction.

Our work has previously led to the development of VitalPAC, P-POSSUM (Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) (18) and ViEWS. NEWS was a minor modification of ViEWS and its latest version (NEWS2) is now mandated for use in NHS hospitals and ambulance trusts (37,22). P-POSSUM, although initially developed as an audit tool, was recommended for use by the Royal College of Surgeons in 2011 as pre-operative risk prediction tool (2) They quote:- “P-POSSUM, freely available on the internet, is possibly the simplest and best-validated method” and: “The POSSUM score is the most validated risk prediction method for general and vascular patients that takes into account pre-operative and peri-operative factors. P-POSSUM may be used for all patients. A predicted mortality risk ≥10% indicates a need for critical care admission, except for patients on end-of-life pathways with appropriate palliative care facilities available at ward level.”

Importantly, this team has a track record and ongoing studies of the outcomes of major abdominal surgery and less-invasive approaches, as evidenced by these 2 recent publications in peer reviewed journal:

- Pucher PH, Carter NC, Knight BC, Toh S, Tucker V, Mercer SJ. Impact of laparoscopic approach in emergency major abdominal surgery: single-centre analysis of 748 consecutive cases. *Ann R Coll Surg Engl*. 2018;100(4):279-284. doi:10.1308/rcsann.2017.0229
- Darbyshire AR, Kostakis I, Pucher PH, Toh SKC, Mercer S. The impact of laparoscopy on emergency surgery for adhesional small bowel obstruction: prospective single centre cohort study. . *Ann R Coll Surg Engl*. 2020. *Accepted for publication.*

Simon Toh is a Consultant Surgeon at PHU and Hon Senior Lecturer at UoP. He has been site principal investigator in multiple clinical trials over his career, most recently for the NIHR Studies GAPS-2 (38) and FrOGS Frailty and Sarcopenia Outcomes in Emergency General Surgery (39), and currently ROSSINI-2 and MASH Studies. He is the Chief Investigator of the Dynamic RCT (40). He has been joint lead in PHU for the past 6 years to implement and achieve the NELA Best Practice Tariffs.

Alexander Darbyshire is a registrar in general surgery undertaking a research fellowship at PHU and completing an MD Res at UoP. His MD is investigating innovative ways of using clinical and biochemical data to improve risk modelling for emergency laparotomy, supervised by Briggs and Prytherch. He is the study co-ordinator and PI for the NIHR feasibility study "PLUG" at PHU, and associate PI for ROSSINI 2 trial at PHU. He has a keen interest in patient safety and improving outcomes for patients who may need surgery. His role will include responsibility for the application for ethical review, assistance with the data analysis and in the dissemination of findings.

Jim Briggs has extensive research management experience having led or co-led over 30 externally funded projects. His expertise is in health informatics, particularly the collection, processing, and analysis of data for operational and research purposes. He is currently Chief Investigator for the multi-site Frequency of Observations (FOBS) project funded by NIHR HS&DR.

David Prytherch is also a health informatician with a long record of publication in clinical outcome modelling. He was the key contributor to the development of the widely adopted standard predictor of surgical risk, P-POSSUM. He was also instrumental in developing ViEWS (22), the basis of the National Early Warning Score (NEWS) published by the Royal College of Physicians and now mandated for use in NHS hospitals and ambulance trusts.

Paul Meredith has a doctorate in databases and more than 25 years of experience extracting, integrating and analysing healthcare data. He is also a member of the Royal Statistical Society. He is currently an investigator in two other NIHR funded projects and has contributed to more than a dozen peer-reviewed publications in the last three years. He is based in the research and innovation department of PHU and will oversee and coordinate data extraction.

Anna Glanville-Hearson is our PPI representative and is an integral part of the team. She is the sister of a patient who died after an abdominal emergency. Anna is a volunteer in the PHU Emergency Department and often sees the beginning of the patient journey for people with an abdominal emergency. She has been an active member of the PHU Patient Research Ambassador Group for several years and is also a volunteer on the PHU Research & Innovation Steering Group. Anna has contributed throughout the development of this project, the preparation of the application. She will regularly attend project progress meetings and be heavily involved in dissemination activities.

6. AIMS AND OBJECTIVES

6.1 Aim

The overall aim of this study is to improve the quality of care for patients with an abdominal emergency, irrespective of whether they have a laparotomy or not. The evidence gathered will provide new estimates of the average risk of death for different treatment options and inform the development of care pathways. In addition to guiding clinical decisions, our findings will make more robust the communication with patients and relatives around different treatment options.

6.2 Objectives

1. Identify all patients with a condition that would qualify them for emergency abdominal surgery, both laparotomy and keyhole (laparoscopic) procedures, regardless of whether they had surgery

or not. This will be done by filtering electronic hospital records for appropriate diagnosis and operation codes.
2. Provide updated estimates of the average risk of death for different treatment options, including surgical and non-surgical intervention, using statistical analysis of short-term and long-term outcomes. Describe health characteristics of the typical patient population receiving one of the treatment options, based on their clinical data and an established risk index.
3. Logistic regression will be used to predict the risk of death for each patient group and each treatment option, which will allow identification of the best care pathways given a patient's health characteristics.
4. Identify patients who would have likely benefited from a different care pathway than the one they received, using machine learning classification algorithms

Our analysis will form the foundation for the establishment of four well-defined care pathway options, each with the patient's best interest in mind: laparotomy, laparoscopy, other alternative treatment, and end of life care.

7. STUDY DESIGN

7.1 Summary of Study Design

This single-centre retrospective cohort study will use data derived from electronic patient records collected as part of routine patient care. It will be conducted at Portsmouth Hospitals University Trust NHS Trust, a large acute District General Hospital. Logistic regression and other classical statistical techniques will be used to predict the risk of death for different treatment methods and to identify clusters of patients with the same characteristics. This will allow identification of lower-risk treatment options for different patient groups.

7.2 Primary and Secondary Endpoints/Outcome Measures

The primary outcomes to be assessed will be length-of-stay, in-hospital, short-term (30-day), and long-term (1- year) mortality.
Secondary outcomes include: long-term complications, such as re-admission to hospital, additional abdominal surgery and the development of new medical conditions as well as the relationships between any of these outcomes and patient characteristics.

7.3 Study Setting

This single-centre retrospective cohort study will use data derived from electronic patient records collected as part of routine patient care. It will be conducted at Portsmouth Hospitals NHS Trust (PHUT), a large acute District General Hospital. Logistic regression and other classical statistical techniques will be used to predict the risk of death for different treatment methods and to identify clusters of patients with the same characteristics. This will allow us to identify lower-risk treatment options for different patient groups.

Portsmouth hospital provides acute services to a population of about 860,000 people, covering a mix of rural, urban and coastal areas. Portsmouth is the most densely populated city in the UK. Interspersed with areas that attract well-educated professional families and wealthy retired residents, Portsmouth has several areas of 'multiple deprivation' and it's in the top 20% of areas in England for deprivation (deprivation index 27.1, England average 21.8) (23). It's a very diverse city with a large student and military service population as well as a high number of elderly people in their 80s and 90s. In 2015-2016, PHUT was placed 120 out of 135 acute trusts in England, according to the standardised hospital mortality index (SHMI) (24). Preliminary analysis using the Dr. Foster Healthcare Intelligence Portal showed that mortality of patients with abdominal emergencies admitted

to Portsmouth Hospital Trust in 2018 was in line with the national average. In other words, Portsmouth is a representative microcosm of the UK in terms of its demographic profile and hospital performance. PHUT is, however, exceptional as it performs an unusually large proportion of laparoscopic procedures every year making it ideally suited for this study.

7.4 Study cohort

Data will be derived from electronic patient records collected as part of routine clinical patient care on all general adult wards (excluding maternity) between 2013 (beginning of NELA and collection of data of interest) and 2020.

All patients with a condition that would qualify them for emergency abdominal surgery will be identified, using their ICD-10 diagnosis and OPSC-4 procedure codes which are part of the electronic patient record. Once patients have been identified, they will be screened against the inclusion/exclusion criteria (see below). For each patient, this will include only the first intervention within the study period in the analysis. Subsequent admissions with an abdominal condition or subsequent interventions will be classified as complication and therefore considered as an outcome.

Inclusion criteria:

- Must have an acute intestinal condition, based on their ICD-10 codes and OPSC-4 codes
- Must be >= 16 years of age at the time of admission
- Have at least one full set of vital signs recorded on the day of admission
- Have at least one full set of routine blood tests recorded on the day of admission

Exclusion criteria:

- Maternity admissions during/after pregnancy
- Patients admitted or undergoing abdominal surgery for a second time or more

8. SAMPLE SIZE

This study will identify patients diagnosed with an intestinal emergency who may require surgery and observe patient outcomes, and how they correlate with the treatment they received. Trial analysis of all admissions in 2018 identified 901 patients with an abdominal emergency, 59% (530) of which had surgical intervention, either a laparotomy or a laparoscopy. Scaling these numbers to the study period of 6.5 years, we expect to identify a total of over 5,800 patients with an intestinal emergency and over 3,400 patients undergoing surgery. All UK hospitals have to submit data on all their intra-abdominal procedures to the National Emergency Laparotomy Audit (NELA). From previous analysis of PHUT NELA data (11), at least 30% of patients having an operation will have been completed laparoscopically. This is a remarkably large proportion of laparoscopic procedures compared to the UK average (8% according to NELA database) and will provide us over 1,000 laparoscopies in our study data set.

The PHUT data set includes a sufficient number of outcomes for model development (rule of thumb: 10 outcomes per predictor variable (25)). This study will be looking at a patient population with high mortality. Initial analysis of 2018 data identified in-hospital mortality as the rarest outcome with 23 deaths (4.3%) of patients having surgery and 28 deaths (7.6%) of patients not having surgery. Other outcomes occur in greater numbers. Collective numbers for the 6.5 year study period will therefore provide us with enough outcomes for the development of logistic regression models. The data set will be tested for separation and Firth's correction applied if necessary (26). Based on these numbers, we will be able to establish statistically significant correlations from this data set from a single hospital.

9. DATA HANDLING AND RECORD KEEPING

9.1 Data collection and extraction

Data will be derived from electronic patient records collected as part of routine clinical patient care on all general adult wards (excluding maternity) between 2013 (beginning of NELA and collection of data of interest) and 2020. Electronic records will include patient demographics, diagnosis and procedure codes held on the Patient Administration System (PAS), vital sign observations from the Vitalpac™ system, routine blood tests from the pathology database, surgery-specific data from TheatreMan™ and additional data from the National Emergency Laparotomy Audit (NELA; which is only available for patients who underwent laparotomy). Linked data sets will provide information on length-of-stay in-hospital mortality, 30-day mortality, 1-year mortality, re-admission to hospital and subsequent abdominal surgery.

9.2 Data Management

All data will be pseudonymised at the point of extraction and the national opt-out will be applied. Identifying characteristics (name, address, date of birth) will be replaced by a study identification number (ID) - age will be recorded as it is required for the analysis. The mapping key will only be known to the data manager and kept in a secure location at PHUT. De-identified data will be held in secure clinical data repositories that will only be accessible by relevant members of the research team for the purpose of this study.

10. DATA ANALYSIS

10.1 Data set

Patient data will include information on age, demographics, diagnosis, co-morbidities, frailty, vital signs and blood tests as potential risk factors associated with mortality. Each patient's National Early Warning Score (NEWS) will be calculated using their vital signs (21), and their Laboratory Decision Tree Early Warning Score (LDTEWS), based on blood test results. The combined LDTEWS:NEWS risk index is a highly accurate predictor of patient deterioration (unintended admission to intensive care and death) within 24 hours (27).

<u>Outcomes</u>
The primary outcomes to be assessed will be length-of-stay, in-hospital, short-term (30-day), and long-term (1- year) mortality. This study will also assess long-term complications, such as re-admission to hospital, additional abdominal surgery and the development of new medical conditions. Additionally, it will observe any relationships between these outcomes and patient characteristics.

10.2 Data analysis

Extracted data will be cleaned and quality controlled prior to analysis to ensure all relevant patients have been extracted. Given that our analysis will use only routinely collected, clinical data, missing values are unlikely to pose an issue. Initial analysis of 2018 data confirmed that clinical data within 24h of admission was almost fully complete for a remarkable >97% of admissions, meaning there is likely no need to impute data. We will test whether excluding admissions with missing data will introduce bias.
Our analysis can be broken down into the following steps:

- Comparison of the four treatment groups based on demographics, outcomes and medical pathway. This will include calculating mortality and long-term complication rates (Objective 2).
- Construct and compare risk models for each treatment group to predict short-term and long-term risk and to investigate the effect of both patient and hospital-level factors on outcome (Objective 3).

- Identify patients in each group who are abnormal for the group and might have fared better with a different treatment, using clustering algorithms (Objective 4).

After splitting the data set into subsets for each of the four patient groups using diagnosis and procedure codes (see above), mortality and long-term complication rates will be calculated for each group. Longer-term follow-up will include rates of re-admission to hospital, additional theatre visits and development of new medical conditions, within one year of initial admission with an abdominal emergency. Results will provide updated estimates of the average risks of different surgical procedures as well as the risk of not having surgery. Results will be compared with P-POSSUM mortality. Patient groups will further be characterised the using patient factors. Parameters of interest will include but are not limited to age, sex, mortality, long-term complication rates, admission early warning scores (NEWS, LDTEWS and LDTEWS:NEWS), frailty, medical history (previous ICD-10 codes).

Patient group characteristics will be summarised with proportions for nominal and ordinal variables, means and standard deviations for continuous variables having symmetric unimodal distributions, and medians and interquartile ranges for other continuous variables. Clinical outcomes will be reported as proportions with 95% confidence intervals. Statistical tests of differences in proportions (Chi_2 - nominal variables) and means/medians (ANOVA/Kruskal-Wallis) will be performed. Post-hoc pairwise comparisons will be carried out using Scheffe's method for ANOVA and Dunn's test for Kruskal-Wallis results and Bonferroni corrections for Chi_2 results with significance at $p<0.05$.

In the next step, we will identify which patient characteristics affect the outcome for a specific care pathway. Candidate predictor variables of 30-day mortality will be assessed with simple univariable linear regression and check for non-linearity. For each treatment group, we will construct a logistic regression model with the candidate predictor variables and non-linear terms as needed. Logistic regression performance will be tested using "goodness of fit" and discrimination. Goodness of fit, the ability to correctly predict risk, will be evaluated using the Hosmer-Lemeshow statistic (28) and by 10-fold cross-validation. Discrimination, the ability to rank cases in terms of risk, will be assessed using the Area Under the Receiver Operating Characteristic Curve (AUROC) (29). The relative importance of individual parameters will be assessed by the parameters Wald and t-statistics.

The last objective is to determine outlier clusters of patients who might have fared better on a different care pathway. For each treatment group, machine learning classification algorithms will be used to identify homogenous clusters of admissions in terms of their attributes. Each clustering will be reported by its method, number of clusters and intracluster correlation coefficients (ICCs) with 95% confidence intervals and used to extend the logistic regression risk model for the treatment group to see if the model is improved as measured by a likelihood ratio test. Where this is the case the patient subgroups corresponding to the clusters will be analysed in terms of their clinical characteristics.

11. ETHICS

The research is not an interventional study and therefore poses negligible risk to patients or other participants. It nevertheless requires ethical review as it uses confidential patient data.

11.1 Declaration of Helsinki

The Investigators will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

11.2 ICH Guidelines for Good Clinical Practice

The Investigators will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

11.3 Other Ethical Considerations

Patient identity will be protected by the process of pseudonymisation at data extraction. The national opt-out will be applied to the data set and inform patients about their rights on a public project webpage.

Ethics Committee (REC) and other Regulatory review & reports
Before the start of the study, a favourable opinion will be sought from a REC for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.

All correspondence with the REC will be retained. It is the Chief Investigator's responsibility to produce the annual reports as required. The Chief Investigator will notify the REC of the end of the study.
If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. The Chief Investigator shall submit on request, a progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

Regulatory Review & Compliance
Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place.
For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment.

Peer review
The research has been peer reviewed as part of the NIHR funding process.

Patient & Public Involvement
Patient identity will be protected by the process of pseudonymisation at data extraction. This has already been presented to the PHUT Patient Research Ambassador (PRA) group (a mixed group of 27 people, mostly lay members with some ex-NHS staff). The group met twice with members of the study team to review and refine an appropriate design and to consider aspects of sample size, GDPR, patient journey etc. The PRA Group routinely edits participant-facing documents such as Patient Information Sheets and questionnaires. The group was satisfied that pseudonymisation and data handling procedures sufficiently protected patients' privacy.

Protocol compliance
All members of the project team will be given copies of this protocol and briefed on its contents.
Where a deviation from the protocol occurs, this must be documented and reported to the Chief Investigator as soon as practicable. Serious deviations, or those that have put at risk confidentiality or safety shall also be reported to the Sponsor.

Data protection and patient confidentiality
The study will comply with the Data Protection Act, which requires personal/identifiable data to be anonymised as soon as it is practical to do so. All documents will be stored securely and only accessible by study staff and authorised personnel. Data stored will be subject to all standard NHS security and confidentiality policies.

The Management Group will have access to all data in order to be able to verify the conclusions of the study. Members of the team will have access to data relevant to the publications they are working on. The Chief Investigator can approve exceptional access by other members of the project team to facilitate analysis or to cover for absences.

12. PATIENT PUBLIC INVOLVEMENT (PPI)

During the project, PPI members will attend project progress meetings and provide continual feedback. In the dissemination phase, they will help develop and publicise the patient information leaflets and care pathways in collaboration with our QI Team.

12.1 Study design

We discussed this project with members of a local patient representative group consisting of patients and carers who have years of experience in advising researchers. As a result, one PPI representative, Anna Glanville-Hearson has become an integral team member, contributing the development and delivery of the project, offering editing/reviewing skills, personal experience of the ED environment and of an abdominal emergency in her family.

Key issues raised by our PPI group were:

- Lack of awareness by patients and relatives of the real risks of emergency abdominal surgery
- Limited information on the risks of surgery and potential alternative care pathways available to patients and relatives
- Lack of understanding by patients and their relatives of risk levels and how risk can be communicated effectively, especially in high-stress emergency situations

Three experienced PPI representatives where consulted who have been involved in previous similar projects. They were asked to provide insight into the patient's perspective. They recognised the need for more evidence accessible to patients with abdominal emergencies. They also highlighted the ‘considerable potential to improve patient outcomes’ and ‘that any move to assist patients/relatives to make informed decisions taken in stressful situations on their care, together with a proper awareness of the risks will be beneficial’.

The project was specifically shaped around these key PPI concerns, as evidenced by our intended outputs of clearer patient information and better care pathways above.

12.2 Study implementation

At project start-up, a group of at least one representative (patient/relative) for each of the four proposed care pathways for abdominal emergencies will be consulted. This patient-focused group will provide patient insights and will identify what information would have improved their experience.

12.3 Dissemination

Towards the end of the project, the same group will be consulted to present and discuss our results and seek feedback on our patient information leaflet.

While PPI team members will not be involved in data analysis but they will have an important role in:

- Working with QI representatives to develop new documented care pathways for patients with abdominal emergencies.
- Developing patient-facing documents that help patients and relatives to quickly understand the personalised risk of surgical and non-surgical options even under stress. The PHUT PPI team will ensure that the information leaflet is accessible to many patients, including non-English speakers, people without any medical knowledge, learning difficulties or other incapacities.

13. FINANCING AND INSURANCE

13.1 Staff costs

The project requires a team with diverse skills and knowledge to manage the project, set up the project database, collect data on observation workload and to analyse the complex data set. The costs requested fairly reflect this complex multi-disciplinary project involving surgical, informatics and analytical expertise.

The project costs requested cover significant and sustained input from the CI (ST @7.5%) who will provide clinical expertise, overview and supervision of the data extraction and accuracy, and then lead stakeholder engagement and dissemination, including the application for funds for a Wessex QI Project to develop the pathways and patient information outputs from this project. He will also manage the project day-to-day. He will be supported by co-CI, JB (@5%) who will assist in meeting regulatory requirements (research ethics, data protection etc.) and an administrator (@6%). Based on previous experience with similar studies, this combined CI commitment of 12.5% of our time will deliver this study on time and to budget.

The largest portion of the budget will cover the salary of the data analysis team, which involves a research fellow (IK @50%) who will lead the data analysis with the assistance of an experienced health informatician (DP @10%, not requested). Data analysis will also involve a more junior research associate (@20%) who will provide technical skills and support. Data extraction and integration will be led by PM (@15%) at PHT who will also contribute advice on the data sources. PM will also provide additional statistical expertise to the data analysis. A clinical research fellow will assist with data extraction and provide supplementary clinical input (AD @20%).
PPI support will be provided by SC, the facilitator of the PHT Patient Research Ambassador group (@3%).

13.2 Travel, subsistence and conference fees

The budget includes cost for travel and catering for the stakeholder meeting planned for the 2nd year of the project (£500). In addition, costs for travel, subsistence and registration fees for several members of the team (£1.5k) to present the research at national conferences throughout the project have included.

13.3 Dissemination costs

Funding for dissemination comprises article processing charges for 2 open access publications (£4k).

13.4 Equipment and consumables

High-performance computer workstations are already available for all members of the research team and no additional equipment or consumables are required.

13.5 Patient and public involvement

Budget also includes costs for PPI (at rates recommended by Involve, total £1.2k). This will:

- reimburse members of the PPI team for their time and travel expenses (£210)
- reimburse Anna Glanville-Hearson for her time, attending bi-monthly progress meetings throughout the project (£524)
- cover the costs for the 4 PPI representatives attending the 2 consultation meetings (£466).

13.6 Any other direct costs

Maintenance for the database infrastructure at PHT (£5.6k).

14. TIMETABLE AND ORGANISATIONAL CHART

14.1 Key milestones (by month).

M01 - Project initiation. Initial stakeholder consultation.
M04 - Ethical review obtained. Data extraction complete.
M12 - Progress report to RfPB. Advisory Group meeting.
M13 - Data analysis complete. First paper completed.
M16 - Second paper completed.
M18 - Final report submitted. Engagement with stakeholders completed.

14.2 Project management

The project will be overseen and managed by Mr. Toh with support from Prof Briggs. There will be monthly project meetings involving the leads and other team members to review and coordinate progress towards milestones. The project plan allows significant periods of time for ethics approval, data extraction, and quality control, as well as for modelling and analysis. This is based on our past experience of the complexities of these tasks, which in turn is based on the complexities of the data under consideration. If progress goes faster than expected, then more time will be devoted to the dissemination of the patient information and care pathways.
For strategic oversight and advice, a Project Advisory Group will be established, including senior clinicians and data scientists, key stakeholders and patient and public representatives, some of whom have already advised us on this project. This group will meet at the halfway mark to review progress and provide in-depth feedback and guidance on dissemination and project outputs.

Activity	Duration	Pre-project start	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12	M 13	M 14	M 15	M 16	M 17	M 18
Project management and administration																				
Ethics application	4m	x																		
Management group meetings		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Progress report to NIHR														x						
Data extraction and analysis																				
Prepare for data extraction	2m		x	x																
Data extraction and cleaning	3m			x	x	x														
Descriptive analysis (Objective 2)	5m					x	x	x	x	x										
Outcome modelling (Objective 3)	4m								x	x	x	x								
Cluster analysis (Objective 4)	4m											x	x	x	x					
Dissemination																				
Stakeholder engagement and presentation of results	5m	x	x															x	x	x
Advisory group meeting	1m													x						
Draft paper 1	3m												x	x	x					
Draft paper 2	3m															x	x	x		
Prepare final report	3m																	x	x	x

15. DISSEMINATION AND OUTCOME

15.1 Outputs

Results will be published in leading peer-reviewed surgical journals on:

1. Comparisons of acute abdominal patients' characteristics and outcomes between those who have an emergency laparotomy and those who do not.
2. Towards Best Care Pathways and better patient information for different groups of patients admitted with abdominal emergencies.

Our findings will inform the development of new care pathways and patient information using *Quality Improvement (QI) methodology* with the help of our PPI team members and the PHT *QI Team*. Additional funds for implementation will be sought from an *HEE Wessex School of QI Support Fund* (30). Mr.Toh and his Creative Media team in the UoP will use our expertise in producing award-winning patient informatics to design and test patient leaflets/video animations (31). These will be made available online for all NHS Trusts to access, for example, on the *HealthPathways* site being rolled out in the NHS (32).

15.2 Dissemination

Regionally, findings will be presented to the Wessex Emergency Laparotomy Programme partners, reaching every Wessex hospital. Specifically, patient information leaflets and best care pathways will be shared freely, via partners from the Emergency Laparotomy Collaborative (33), with all acute surgical teams in the UK and to the wider public through the Academic Health Science Network Patient Safety Collaborative (34) and a website. We will engage with our key stakeholders (Prof. Peter McCulloch (IDEAL Collaborative) and the Royal College of Surgeons of England) to implement these findings by including them in future publications of RCSE guidelines. Results will be presented at key conferences including the Association of Surgeons of Great Britain and Ireland, the United European Gastroenterology Week, and Health Service Journal Conference targeting NHS leaders.

15.3 Next steps

This study is a necessary first step to provide evidence for the design of future research, such as a larger multicentre study by giving us data on overall risks and likely patient and admission factors that could affect them. The planned, larger study will analyse and model these factors statistically to develop a replacement for P-POSSUM (18), which is the outdated risk-prediction tool currently commonly used (6,11). This novel tool will be able to predict the risk of any intervention (or no intervention) in patients with an acute abdomen more accurately than before. This will in turn help surgeons provide truly individualised informed consent to patients on their choices and predicted risks (35). This fulfils the goal for a more personalised medical care within the NHS

(36).

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