**PROCalcitonin-based algorithm for antibiotic use in Acute Pancreatitis (PROCAP): A randomised controlled trial.**

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**Trial sponsor:** Manchester University NHS Foundation Trust.:

**ISRCTN registration:** ISRCTN 50584992.

**Introduction.**

***Background and relevant literature***

Overuse of antibiotics and the resultant emergence of multidrug resistant organisms is a potent threat to the welfare of humanity in the twenty-first century (1, 2). Acute pancreatitis is an inflammatory disorder of the pancreas with an incidence of 150 to 420 cases per million population (3) and an overall case-fatality rate of 4-6% (4, 5). In addition to being a significant cause of death, severe acute pancreatitis (SAP) is associated with prolonged critical care occupancy, lengthy in-patient stay and slow

rehabilitation (6). SAP is characterized by necrosis of pancreatic tissue which with bacterial colonization leads to infected necrosis (7). Antimicrobial therapy to prevent infection of necrosis in acute pancreatitis has been evaluated in a series of randomized controlled trials with findings demonstrating lack of benefit when summarized in meta-analyses and a Cochrane systematic review (8,9). The position on use of antibiotics is not clear with treatment and prophylaxis often overlapping. Further, the clinical trials from which this evidence is derived are small and carry the attendant risks of selection and reporting bias. This is likely to account for the variation in findings reported by different systematic reviews (8,10). The International Association of Pancreatology/American Pancreatic Association guidelines for the treatment of acute pancreatitis made a definitive statement on this topic and do not recommend antibiotic prophylaxis in acute pancreatitis (11).

Correct use of antibiotics is important in patients with infected necrosis but use in patients with systemic inflammation in acute pancreatitis is non-therapeutic and possibly harmful. Discriminating between pancreatic infection and inflammation is difficult with neither clinical assessment nor markers of inflammation (such as leukocyte count or C-reactive protein) being sufficiently accurate (12). As a result there is over-use of antibiotics for suspected infection in patients with acute pancreatitis with up to two-thirds of patients receiving at least one course of antibiotics during their admission (13). Patients with prolonged in-patient stays may receive multiple courses of multi-drug antibiotic regimens (13). This specific problem of antibiotic over use in acute pancreatitis is widespread not only in the United Kingdom’s National Health Service (NHS) (14) but also worldwide (15-18). Over-use of antibiotics in acute pancreatitis is associated with the emergence of resistant organisms, antibiotic-related side-effects, compromised treatment efficacy and unnecessary health care costs. Our group has reported over-use occurring in two principal areas: incorrect commencement of antibiotics (because inflammation closely mirrors infection) and failure to discontinue (13). Nationally, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) undertook the largest survey to date of the treatment of acute pancreatitis in the NHS (19). “Treat the Cause”, published in 2016, recommends the need for better support for clinicians making bedside decisions about the use of antibiotics (19). Specifically, there is a need for assistance in differentiating infection from inflammation and better evidence for initiation, continuation and discontinuation of antibiotics in acute pancreatitis. More discriminant and better targeted antibiotic use would reduce inappropriate use, limit resistance and side effects, and promote better use of health care resources.

A method of distinguishing infection from inflammation is by measurement of procalcitonin (PCT) (20). Historically, calcitonin peptides were thought to be responsible for calcium homeostasis but this is now thought to be a relatively minor physiological role and a more contemporary appraisal is that procalcitonin is a “hormokine” sharing characteristics of both hormones and cytokines and having roles in maintaining vascular endothelial tone in response to bacterial infection (20). The procalcitonin level in the bloodstream of healthy individuals is below the limit of detection (10 pg/mL) using clinical assays. Procalcitonin levels rise rapidly in response to a pro-inflammatory stimulus of bacterial origin and normally fall after successful treatment (21). PCT is more sensitive than clinical assessment, routine laboratory markers of sepsis (such as leukocyte count and C-reactive protein) or other markers of the pro-inflammatory response such as interleukin 6 in detecting pancreatic infection (22). PCT Algorithms based on measurement of procalcitonin have emerged as a means of differentiating bacterial sepsis from a systemic inflammatory response in a wide range of settings (23).

A recent Health Technology Assessment (HTA) report evaluated Procalcitonin testing as a guide to antibiotic therapy when treating sepsis in intensive care units and for suspected bacterial infection in emergency departments (24). The report concluded that although procalcitonin testing is widely available in the NHS, further studies are needed in specific disease settings. Current evidence for the use of PCT algorithms to guide antibiotic use in critical care, emergency departments and primary care is reviewed and summarised in detail in the HTA systematic review (24). These studies included a range of algorithms and clinical indications. Studies based their algorithms on repeated PCT measurement and provided guidance both on commencement and discontinuation of antibiotic therapy. Overall, 4467 patients were included in 14 randomized controlled trials (2227 PCT; 2240 control). The studies found consistent reductions in antibiotic use with PCT guidance without an adverse effect on mortality (24). Much of this evidence is derived from study populations with respiratory tract infections, critical care admissions or those with medical emergency conditions and cannot readily be extrapolated to the care of patients with acute pancreatitis.

PCT has also been evaluated as a biomarker in severe acute pancreatitis, mainly for early prediction of severity and for identification of patients with a high risk of infected pancreatic necrosis (25). Analysis of 329 patients from 7 studies shows that the pooled sensitivity and specificity of PCT as a predictor of developing infected pancreatic necrosis is 0.80 (95% CI [confidence interval] 0.70 – 0.87) and 0.91 (95% CI 0.87-0.94) respectively with an AUC (area under curve) of 0.91. These studies show that PCT is an accurate biomarker of infection in acute pancreatitis.

Qu and colleagues reported the results of the only randomized controlled trial of a procalcitonin algorithm in severe acute pancreatitis: a single-centre study of 71 patients from China (26). They compared a PCT-based algorithm for guidance of antibiotic use to routine care in patients with acute pancreatitis. The duration of antibiotic treatment in the PCT-guided group was significantly shorter (10.9 ± 2.8 vs 16.1 ± 2.5 days, p<0.001) without any adverse effects on outcome. Duration of intensive care treatment, overall hospital stay and cost of care were significantly reduced in the PCT-guided group. In Qu’s study all patients in the control arm were given antibiotics for up to 14 days which is not reflective of current international guideline recommendations. Thus the findings of this study need to be reproduced in a setting where antibiotic use follows contemporary practice before procalcitonin-based algorithms can be recommended for guidance of antibiotic use in acute pancreatitis.

***Hypothesis***

This study tests the hypothesis that a procalcitonin-based algorithm to guide initiation, continuation and discontinuation of antibiotics will lead to reduced antibiotic use in patients with acute pancreatitis without an adverse effect on outcome.

**Methods.**

***Design***

This is a single-centre, randomised, controlled, single-blind, two-arm phase III pragmatic clinical and cost-effectiveness trial. Patients will be allocated on a 1:1 basis to intervention and control. Clinicians will not be blind to allocated arm. Patients will be blind to their allocated arm.

***Participants***

Patients with a clinical diagnosis of acute pancreatitis admitted to the Hepato-Pancreato-Biliary (HPB) service of the Manchester Royal Infirmary (MRI). The Manchester Royal Infirmary is the regional specialist HPB service for the Greater Manchester and Cheshire region, a conurbation of 3.2 million people. Patients admitted directly to the service and those arriving as tertiary transfers from other hospitals will be included (but will be separately stratified).

***Inclusion criteria***:

Adult patients presenting with acute pancreatitis admitted or referred to the service. Inclusion criteria include:

1. Patients over the age of 18 years of age.
2. Valid informed consent.
3. The diagnosis of acute pancreatitis requires two of the following three features (7):
4. abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back).
5. serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal.
6. Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) or transabdominal ultrasonography.

***Exclusion criteria:***

Exclusion criteria include (27, 28):

1. Patients under the age of 18 years of age.

2. Comorbidities requiring prolonged antibiotic therapy – such as infective endocarditis.

1. Severely immunocompromised patients – such as those with human immunodeficiency virus and with a CD4 count of less than 200 cells/mm3; neutropenic patients (<500 neutrophils/mm3).
2. Patients on immunosuppressive therapy.
3. Previous thyroid surgery.

***Intervention***

The intervention is the use of a procalcitonin-based algorithm to guide antibiotic use. The algorithm is shown in Table 1. Patients will be randomised in a 1:1 ratio to receive algorithm-guided or standard care. The randomisation will be stratified by patient admission route (direct or tertiary referral).

***i) Intervention arm protocol in detail.***

1. Identification of patients: Patients randomised to the PCT measurement arm will be identified by a trial sticker in case notes and drug kardex (and/or electronic record for patients in the Intensive Care Unit). Patients in the standard care arm will also be identified by a trial sticker.
2. Baseline PCT will be measured on admission (day 0) and the algorithm followed.
3. Patients admitted to surgical wards: PCT will be routinely re-assayed on day 4 and at day 7 after admission for those patients remaining in hospital to these time points. Venesection for PCT assay will be undertaken at the same time as venesection for routine clinical blood tests. No additional venesection is required for PCT measurement.
4. Patients admitted to the critical care unit: PCT will be measured daily during the acute phase of their illness.
5. PCT intervention arm in patients remaining in hospital beyond day 7: PCT will be measured weekly on day 14, 21 and continued weekly during the in-patient stay. Venesection will be undertaken at the same time as venesection for routine blood tests.
6. Patients who are asymptomatic in terms of infection: Follow the PCT algorithm with sampling at the time points above. It is possible that any one of the above PCT assay points may yield a result above threshold for antibiotic use in a setting when antibiotics are not thought to be clinically indicated. In this situation, clinical decision making takes priority and the algorithm can be over-ridden (see below). If however the recommendation of the PCT algorithm is followed, an appropriate antibiotic should be used in compliance with Manchester University Foundation Trust (MFT) guidance for treatment of infection in acute pancreatitis.
7. Patients who become symptomatic (at any point) for infection: Assay PCT and follow the PCT algorithm. In specific terms, this means repeating the PCT assay at the time of assessment of infection. Clinically symptomatic patients with a low PCT will not receive antibiotics. If there is persisting concern of infection in patients with a low PCT, the test should be repeated at 24h. Symptomatic patients with a raised PCT will receive antibiotics according to MFT guidance. Use the PCT algorithm to guide continuance and discontinuation of antibiotics.
8. Asymptomatic or symptomatic patients with positive microbiology results. It is appropriate to treat patients with positive microbiology results with antibiotics. PCT should be measured before commencing antibiotics. PCT measurement should be used to guide cessation of therapy, either after 48h, 72h or 96h as clinically appropriate.
9. To avoid repeated short courses of antibiotics, if antibiotic use is triggered by the algorithm, continue use for at least 48h and then re-assay PCT. If there is no clinical evidence of infection at this point with this second PCT measurement below threshold, antibiotic use will be discontinued.
10. If antibiotics have been prescribed outwith the algorithm then continued use will be discussed with the consultant HPB surgeon under whose care the patient is being treated or with the Chief Investigator. After this discussion, antibiotic therapy may be stopped.
11. The Clinician over-ride can be used to either start or stop antibiotics in situations of clinical urgency. The clinician MUST be either a consultant HPB surgeon or a consultant Intensive Care Physician. The reason for over-ride will be documented.
12. Patients in the intervention arm undergoing procedures requiring antibiotic prophylaxis: If patients undergo endoscopic, radiological or surgical procedures which would normally be undertaken under the cover of antibiotic prophylaxis it is appropriate to do this without PCT measurement. If prophylaxis is merged with therapy then the PCT measurement for discontinuance is triggered.

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***ii) Selection of PCT cut-off threshold***

As with other biomarkers of severity, the usefulness of PCT is influenced by the cut-off values, the timing and accuracy of the assay. Although no absolute consensus exists regarding the most appropriate cut-off value for identification of sepsis in acute pancreatitis, Mofidi reports a meta-analysis of 8 studies using PCT cut-off values >0.5ng/mL (25). Taken together with the recommendations of Schuetz and colleagues for PCT algorithms in critical care settings (23), the optimum threshold for PCT for this study is 1.0 ng/mL.

***iii) PCT assay***

The Elecys® BRAHMS fully automated PCT assay immunoassay (Roche Diagnostics Ltd, Rotkreutz, Switzerland will be used for the quantitative determination of procalcitonin in serum.

***iv) Antibiotic use for patients in the control arm.***

Standard clinical care (defined below) will be applied. PCT measurement is currently not used regularly in this or other hospitals in the NHS in patients with acute pancreatitis and thus the control arm will represent current standard care. There will be no procalcitonin measurement in patients allocated to this arm. In current clinical practice, decisions on antibiotic use are made after clinical assessment including assessments of blood test results and microbiology reports. Decision making on antibiotic use typically involves consultant hepatobiliary surgeons, intensive care physicians and interaction with microbiologists and pharmacists. All current standards of care and oversight in antibiotic use decision-making will continue to apply to patients in the control arm. The grade and specialty of clinician will be recorded for each instance of antibiotic prescribing in both arms.

***v) Standards of general care for all patients with acute pancreatitis***

Standard care will follow the current IAP/APA (International Association of Pancreatology/American Pancreatic Association) guidelines for the care of patients with acute pancreatitis (11). All aspects of care with the sole exception of antibiotic use will be the same for patients in both arms of the trial.

***Outcomes***

***i) Primary outcome measure***

The primary outcome measure will be the binary outcome: whether antibiotic use is initiated during the index stay. Trial antibiotic use will exclude mandated routine antibiotic use, specifically prophylaxis before procedures such as laparoscopic cholecystectomy or ERCP.

***ii) Secondary outcome measures:***

1. Safety non-inferiority endpoint all-cause mortality.
2. Days of antibiotic use (for antibiotics initiated during the index stay) defined as any day (24 hour period) when antibiotics were prescribed on the patient’s drug prescription chart and administered
3. Clinical infections as defined according to the Centers for Disease Control (29).
4. New isolates of multi-resistant bacteria (Clostridium difficile, vancomycin resistant enterococcus [VRE], methicillin resistant staphylococcus aureus [MRSA], carbapenemase producing enterobacteriaceae [CPE]).
5. Incidence of multi-resistant organism bacteraemia.
6. Infection of pancreatic necrosis – defined either as a result of fine needle aspiration (FNA), radiological evidence of gas in a peri-pancreatic collection or positive microbiological cultures from surgical or post-mortem specimens.
7. Use of radiological, endoscopic or surgical intervention (30).
8. Survival at 90 days; time-to-event (mortality) survival (Kaplan-Maier)
9. Length of inpatient stay (in total and by level of care: critical care levels II/III, ward-based care)
10. Re-admission to hospital within 6 weeks of onset of index episode.
11. Episode-related mortality and cause.
12. Quality of life assessed by the EQ-5D-5L questionnaire, at baseline, discharge and 90 days after enrolment, completed by the patient or by telephone if discharged (31).
13. Cost analysis (from an NHS perspective, including inpatient resource use).

***iii) Measurement of outcomes***

The primary (superiority) outcome measure will be antibiotic use (binary endpoint: yes or no), initiated during the index stay. Trial antibiotic use will exclude mandated routine antibiotic use, specifically prophylaxis before procedures such as laparoscopic cholecystectomy or ERCP.

Antibiotics prescribed before the index admission (from the referring hospital or community) will be recorded at admission but not included in the primary endpoint.

***iv) Amendment to method of measurement of outcomes***

The Data Monitoring Committee meeting on the 26th November 2019 reported that completion of EQ-5D-5L quality of life scores at recruitment was 93%, discharge 52% and 3% at 90-days. In order to improve data collection the protocol was amended to permit a trial investigator to contact a trial patient within 5 days of discharge in order to conduct a telephone conversation for completion of the discharge time point form and to contact the patient at 90 days (or within 5 days of this time point) to complete the final questionnaire. The patient information sheet, GP letter and trial consent form were modified to reflect this additional contact. If clinical concerns or issues were brought to the investigator’s attention during either of these conversations, the patient will be referred to the next available out-patient appointment of their consultant.

***Sample size***

On retrospective audit data, 60% of patients admitted with acute pancreatitis receive antibiotics (13). A 20% absolute change in antibiotic use would be a clinically important difference. This effect of intervention has been observed in other studies evaluating a procalcitonin algorithm to guide antibiotic use (23, 32). A study with 80% power and 5% significance (2-sided) requires 97 patients in each arm (194 patients in total), leading to a target recruitment of 200 patients. Assuming a 3.6% mortality rate based on unit audit data (13), this sample size provides a 6.6% non-inferiority margin for the safety measure of overall mortality, assuming no change in mortality, 80% power and 95%CI (one-sided).

The study was designed originally with 80% power on a pragmatic basis as both methodologically acceptable and achievable with the available time and resources. However 90% power is desirable (when achievable) to further reduce the risk of a type II error (missing a real treatment effect). An increased study size would also reduce the non-inferiority safety margin. Since recruitment to PROCAP has occurred steadily at a faster rate than expected and consistent with achieving 90% power in the trial time frame, the sample size has been revised prospectively during trial recruitment and following discussion with the TSC and DMC.

A study with 90% power and 5% significance (2-sided) would require 130 patients in each arm (260 patients in total). The revised trial target recruitment will be 260 patients (since loss to follow-up is 0% at the midway point the sample size has not been inflated further). Assuming a 3.6% mortality rate based on unit audit data (13), the sample size provides a 5.8% non-inferiority margin for the safety measure of overall mortality, assuming no change in mortality, 80% power and 95%CI (one-sided).

***Consent process.***

Valid consent will be obtained for all patients. Consent procedures will be governed by the Medicines for Human Use (Clinical Trials) Regulations (2004); Schedule 1, part 5 and by The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006, No. 2984 (33, 34). Where available, Trust-appointed translator services will be used for those patients who are unable to speak or comprehend English.

***Informed consent for patients with capacity***

For eligible patients who possess mental capacity, a member of the research team will make the initial approach and provide a verbal overview of the study and what participation will involve. The patient will be provided with a written information sheet and given the opportunity to ask questions. After their questions have been answered, they have had sufficient time to consider participation and if they are willing to take part in the study, they will be asked to sign the consent form.

***Consent procedures for patients who lack capacity***

As acute pancreatitis maybe severe, causing disruption of a patient’s cognitive state or requiring sedation to facilitate advanced organ support in intensive care, some potential participants will lack capacity to consent for enrolment. Such patients may still be enrolled in this study according to the following procedures. Firstly, a treating clinician who is not part of the study team will assess the competence of a potential participant to consent for research. If lack of capacity to consent is confirmed then valid consent for enrolment may be obtained from a patient’s legal representative. Ideally this legal representative will be someone who knows the patient and is able to judge whether the patient would have agreed to enrolment in this study. This ***personal legal representative*** would usually be their next of kin or someone with whom they had a significant relationship, and was willing to engage with the consent process on the patient’s behalf. If a personal legal representative is not available then the patient’s ***professional legal representative*** may provide consent instead. This person would be an independent treating clinician who is not part of the study team. Where a researcher is also the treating health professional, another member of the research team independent of any responsibility for the clinical care of that patient, will be asked to make the initial approach and/or seek consent from participants or their legal representative.

Patients who recover sufficiently to understand the explanation of the study will be asked to consent to continue in the study procedures as soon as possible or be offered the chance to withdraw. If the patient chooses to withdraw from the study procedures, they will be asked for permission to use their study-related data and for permission to collect and use outcome data.

For all participants written consent forms will be signed; name filled in and personally dated by the patient or by their legal representative and by the Investigator who conducted the consent discussion. A copy of the signed and dated Consent Form will be provided to the patient and/or their legal representative and another copy filed in the patient’s medical record.

***Withdrawal of consent***

Patients can withdraw consent for participation at any time after enrolment. They do not need to give a reason and their clinical care will be unaffected. Patients allocated to the procalcitonin arm will not continue to undergo PCT monitoring of antibiotic use after withdrawal. Data provided up until the time of withdrawal will be retained for use in analyses.

***Ethics review.***

Formal ethical review will be sought through the integrated research application system (IRAS).

***Randomization***

Web-based randomisation will be provided by the Clinical Trials Unit of the University of Edinburgh (<https://www.ed.ac.uk/usher/edinburgh-clinical-trials>). Allocation will be in a ratio of 1:1 to routine or algorithm-guided care. Randomization will be stratified by severity (mild or moderately severe/severe) and admission pathway (whether or not the patient has their index (first) admission with acute pancreatitis to the Manchester Royal Infirmary [direct] or is transferred from another hospital [tertiary transfer]). A random block size of 4, 6 or 8 will be applied to each stratum. Patients allocated to either arm will be separately identified by a label placed inside and on the front of the case notes with copy labels used for ward folders.

***Data collection***

Data collection will use a case report form (CRF) and include source verifiable data from patient records, including procalcitonin test findings and the list of primary and secondary endpoints. CRFs will be anonymised and contain no individual patient identifiable information. Patient-level data will be stored by screening and trial log numbers. Patients who are discharged and re-admitted within six weeks will be regarded as a re-admission for the same episode of care and treatment will be summated. Patients who are re-admitted will be in the same arm as their original allocation. Re-admission elsewhere will be a specific question sought at follow-up (typically at 6 weeks and 90 days). Patients discharged but subsequently admitted elsewhere within 6 weeks will have their pharmacy charts reviewed wherever possible and antibiotic use summated. The trial process and data collection is designed to be minimally burdensome to patients. Clinically, the 90-day follow-up period will complete the involvement of the patient in the trial.

***Data storage and transfer***

Paper copies of the Case Report Forms will be stored in a locked cabinet in the Chief Investigator’s office within Manchester University Foundation Trust. These copies will be stored for five years after completion of the trial and then destroyed.

Data will be contemporaneously stored in a password-protected database, allowing ongoing monitoring of data quality and completeness. These data will be stored on a desktop computer maintained in the office of the Principal Investigator.

Anonymised data transfer for analysis will be sent electronically only to National Health Service and University email addresses as anonymised password-protected data.

***Analysis plan***

Analysis will follow intention to treat principles. Endpoints will be assessed using appropriate general linear model adjusted for stratification factors; for the primary endpoint a general linear regression with logit link will be employed. Missing values with be addressed by multiple imputation, having appropriately explored the missingness mechanism, and in accordance with good practice (35). Chance baseline imbalances and protocol adherence will be explored within sensitivity analyses.

The trial will determine if the use of a procalcitonin algorithm reduces antibiotic use during acute pancreatitis. Currently, there is clinical uncertainty about guidelines for reducing antibiotic use in this patient group, since this draws on indirect evidence. Hence a superiority design has been selected, with a null hypothesis that antibiotic use is unchanged by use of the algorithm.

Proportion of all-cause mortality in 90 days, re-admission within 6 weeks, AE’s, SAE’s along with their 95% confidence interval will be reported and compared between the two groups. Length of stay in hospital will be reported and compared using suitable method (according to its distribution). Other secondary outcomes will be reported using appropriate summary statistics.

Data cleaning and analysis will be provided by the study statistician. Analysis will follow intention to treat principles with patients analysed according to randomisation and irrespective of actual use or compliance with the algorithm. Every effort will be made to retain and include all patients who are part of the trial. Data will be analysed using STATA (StataCorp) SE 15.

Economic analysis will be conducted from an NHS perspective, following similar principles and practices to the analysis of clinical outcomes. Analysis of costs will be limited to hospital activity since

these will effectively determine patient costs during severe disease. A within-trial economic analysis will use bootstrapped, adjusted, bivariate regression modelling of costs and QALYs (Quality Adjusted Life Years), adjusted for baseline scores and stratifying variables (36). Analyses will be presented as an incremental cost-effectiveness plane, cost-effectiveness acceptability curve and by net monetary benefit. An expected value of perfect information (EVPI) analysis will also be provided. Given the timeframe of 6 weeks, discounting of future costs and benefits will not be applied.

***Data Monitoring Committee (DMC)***

There will be an independent Data Monitoring Committee (DMC), working to a DAMOCLES charter, agreed before trial commencement (37). It is anticipated that the committee will be constituted with an independent chair, a statistician and a patient advocate. The DMC will consider protocol adherence, trial withdrawal, safety monitoring and make recommendations around the continuance of the trial.

The DMC will convene prior to commencement of the trial and at 6 monthly intervals. Recommendations for study continuation, modification or termination will be provided in a confidential report to the Trial Steering Committee.

***Trial Steering Committee***

The Trial Steering Committee will have an independent chairperson and an independent member together with the principal investigator, trial co-ordinator and statistician. The TSC will meet 6 monthly.

***Governance arrangements***

The sponsor will put in place monitoring and oversight arrangements appropriate to the needs of the trial.

***Adverse event reporting***

An adverse event is defined as “any untoward medical occurrence that may present during the conduct of the trial, not necessarily have a causal relationship with the intervention being investigated” (38, 39). An adverse event can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the trial.

All adverse events will be assessed for

1. Seriousness
2. Causality
3. Expectedness

The research fellow will notify the principle investigator of the adverse event. The principle investigator will determine whether it is an Adverse event (AE), Serious Adverse Event (SAE) or Serious adverse reaction (SAR). He will also keep the sponsor (MFT) informed of the event.

All adverse events will be recorded in line with European Directive 2001/20/EC and recorded in the case report form (40).An annual safety report to the data monitoring committee will be submitted.

Serious adverse events (SAEs) will be reported by email to the Trust ([adverse.events@mft.nhs.uk](mailto:adverse.events@mft.nhs.uk)).

SAEs will be reported quarterly.

***Stopping rules***

The trial may be stopped temporarily or permanently (following discussion with the DMC and sponsor) at any point if (41):

1. There is evidence of trial misconduct noted by the DMC or by the MFT Research and Innovation Department.
2. If there is evidence of futility or if there is evidence that the safety non-inferiority endpoint is not met.
3. If external scientific evidence emerges to render the findings of this trial obsolete or irrelevant.

***Patient and Public Involvement during protocol development***

The idea for this study was generated by a patient. Mr PD developed severe acute pancreatitis with multi-system organ failure requiring ventilatory support. He had a prolonged inpatient stay and required surgical debridement of pancreatic necrosis (necrosectomy). During his prolonged recovery he complained that having been on intravenous broad-spectrum antibiotics almost daily for a period of nearly two months he found that his appetite was poor, he could not taste his food and he had a sore mouth and discomfort from swallowing (this was related to secondary infection with candida – a consequence of critical illness and also of antibiotic therapy). In addition, his arms were sore from the repeated siting of infusion cannulae and he complained of chronic diarrhoea and peri-anal discomfort. He requested that antibiotics be discontinued and stated “by two months, the infection should have been treated”. Following cessation of antibiotic therapy, his condition improved.

Whilst it is not possible to attribute clinical improvement to cessation of antibiotic therapy with certainty, the patient’s question about prolonged antibiotic therapy in the absence of infection is at the heart of this study.

Subsequent patient experience has been assessed at the HPB service “patient-listening events”. These are open sessions to which patients who have been under the care of the HPB service are invited to attend, together with family. After an informal introduction, break-out sessions listen to aspects of care. Three of these events have been held in 2013 and 2014 for a total of approximately 70 HPB patients. Notes are taken on issues and an action plan formulated. Progress on action plan is feedback at subsequent event. These events have been attended by HPB patients with cancer and with pancreatitis. The specific question of algorithm-driven pancreatitis care was discussed at a break-out table and comments from patients were:

* The protocol should avoid unnecessary antibiotic use.
* Will my family doctor have to comply with the protocol if I am ill at home? (Answer: no).
* Why can’t more treatments be tested with such algorithms?

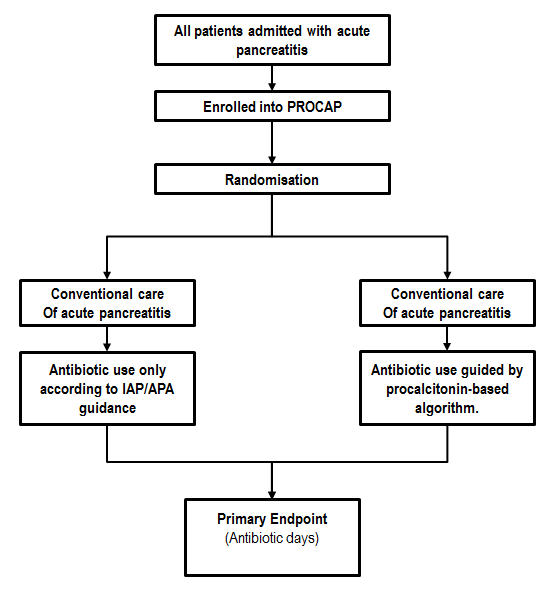
***Dissemination of results***

Results will be reported at appropriate national and international meetings and published in a peer-reviewed journal. The authors undertake to report the results of the completed trial.

***Role of the sponsor and funding***

There is no external funding for this study. Costs incurred for registration of the study with ISRCTN, web-based randomisation and the expenses of the Data Monitoring Committee were met from a Pancreatic Research Endowment fund (9033). The sponsor had no role in the design of the study.

**Figure 1: PROCAP flowchart.**

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| Table 1: Procalcitonin-based algorithm to guide antimicrobial use in acute pancreatitis. | | |
| Evaluation only after enrolment at time of admission to hospital | | |
| Procalcitonin result | **< 1.0 µg/L** | **≥1.0 µg/L** |
|  |  |  |
| Recommendation on antibiotic use | **Do not start antibiotics.**  **Stop antibiotics in patients already on antimicrobial therapy** | **.**  **Antibiotic intervention.**  **(Follow Trust guidelines for prophylaxis or treatment)** |
|  |  |  |
| Follow-up | **If there is clinical concern about infection re-check PCT after 24h** | **Reassess clinical condition and re-check PCT after 48h** |
| Procalcitonin result | **< 1.0 µg/L** | **≥ 1.0 μg/L** |
| Recommendation on antibiotic use | **No antibiotics**  **(or stop antibiotics).** | **Continue antibiotics**  **(or start if not already on antibiotics).**  **(consider change in antibiotics if clinically indicated).** |
| Over-ruling the algorithm | **Empiric antibiotic therapy is permitted in patients not allocated by PCT algorithm to receive antibiotic BUT decision to be made ONLY by ITU consultant or HPB consultant surgeon and documented in case notes.** | |

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