Centre for Trials Research
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# PEACH

Procalcitonin: Evaluation of Antibiotic use in COVID-19 Hospitalised Patients

## THE PEACH STUDY

**PROTOCOL VERSION 1.2**

**DATE 25.08.22**

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|---|---|
| **Sponsor:** | University of Leeds<br>School of Medicine<br>Worsley Building<br>University of Leeds<br>Leeds<br>LS2 9JT |
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**SIGNATURE PAGE**

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the relevant study regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

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**General Information** This protocol describes the PEACH clinical study, and provides information about the procedures for entering participants into the study. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the study. Problems relating to the study should be referred, in the first instance, to the CTR.

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The PEACH study is being coordinated by the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the PEACH Study Management Group (SMG).

For **all queries** please contact the PEACH team through the main study email address. Any clinical queries will be directed through the Study Manager to either the Co-Chief Investigators or a Co-Investigators.

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## Glossary of abbreviations

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| **CA** | Competent Authority |
| **CAP** | Community Acquired Pneumonia |
| **CF** | Consent Form |
| **CI** | Chief Investigator |
| **CRF** | Case Report Form |
| **CTA** | Clinical Trials Authorisation |
| **CTR** | Centre for Trials Research |
| **CU** | Cardiff University |
| **CURB-65** | Confusion, Urea, Respiratory Rate, Blood Pressure Age (>65) score for pneumonia severity |
| **DDD** | Defined Daily Doses |
| **GCP** | Good Clinical Practice |
| **HCP** | Health-care professional |
| **HE** | Health Economics |
| **IC** | Informed consent |
| **IEC** | Independent Ethics Committee |
| **ISF** | Investigator Site File |
| **ISRCTN** | International Standard Randomised Controlled Study Number |
| **NHS** | National Health Service |
| **NICE** | National Institute for Health and Care Excellence |
| **NEWS2** | National Early Warning Score 2 |
| **PI** | Principal Investigator |
| **PIS** | Participant Information Sheet |
| **PCT** | Procalcitonin |
| **PPI** | Patient and Public Involvement |
| **QA** | Quality Assurance |
| **qSOFA** | quick Sepsis related Organ Failure Assessment |
| **R&D** | Research and Development |
| **REC** | Research Ethics Committee |
| **SOP** | Standard Operating Procedure |
| **SSA** | Site Specific Assessment |
| **SMF** | Study Master File |
| **SMG** | Study Management Group |
| **SSC** | Study Steering Committee |

# 1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

| Amendment No. | Protocol version no. | Date issued | Summary of changes made since previous version |
|---|---|---|---|
| 1 | 1.2 | | 1. Addition of ISRCTN trial registry number.<br>2. Removal of 'acute kidney injury' from aim (section 9.2.1.1) in WP 2.1.<br>3. Removal of duration of "CAP" antibiotics, both early and late from secondary outcomes in WP 2.1.<br>4. Removal of defined daily doses of "CAP" antibiotics, both early and late from secondary outcomes in WP 2.1. (Section 2: Synopsis and Section 9.2.1.10)<br>5. Removal of AKI from secondary outcomes in WP 2.1 (Section 2: Synopsis and Section 9.2.1.10)<br>6. Removal of sterile site cultures from section 9.2.1.6 (variables and data sources).<br>7. Removal of AKI from study scheme (Figure 3.1). |

# 2 Synopsis

| | |
|---|---|
| **Short title** | Procalcitonin: Evaluation of Antibiotic use in COVID-19 Hospitalised Patients. |
| **Acronym** | PEACH |
| **Internal ref. no.** | |
| **Development phase** | N/A |
| **Funder and ref.** | NIHR COVID-19: Recovery and Learning Call XP NIHR132254 |
| **Study design** | Multi-centre retrospective, observational data study. |
| **Study participants** | Patients admitted to hospital with COVID-19 |
| **Planned sample size** | Separate sample sizes for each work-package. The main work-package (WP 2.1) includes data sourced from ~ 7000 COVID-19 patients from 11 NHS acute hospitals. |
| **Planned number of sites** | 11 sites for work-package 2.1 |
| **Inclusion criteria** | **WS1: Trust-level clinical data**: Acute NHS hospital trust caring for COVID-19 inpatients >16 years.<br><br>**WS2, WP 2.1: Patient-level clinical data**: Confirmed COVID-19 and admitted to participating trust (any reason).<br><br>**WS2, WP 2.2:** Healthcare workers caring for patients admitted to hospital with COVID-19 |
| **Exclusion criteria** | N/A |
| **Treatment duration** | N/A |
| **Follow-up duration** | N/A |
| **Planned study period** | 18 months |
| **Primary objective** | To assess whether the use of PCT testing, to guide antibiotic prescribing, safely reduced antibiotic use among patients who were hospitalised with COVID-19 during the first wave of the pandemic. |
| **Secondary objectives** | 1) Describe which hospitals have introduced PCT testing during COVID-19, date of introduction, where and how PCT testing was undertaken in the patient pathway.<br>2) Using aggregated NHS trust level data, determine whether, at an organisational level, having a pathway which incorporated PCT testing modified the impact of the first COVID-19 wave on antibiotic use.<br>3) Measure the difference in antibiotic use, length of stay, mortality (30 and 60-day), intensive care unit admission and resistant secondary bacterial infections between COVID-19 patients who did/did not have PCT testing at baseline. |

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| | 4) Explore the decision-making process around the use of antibiotics in management of patients with COVID-19 using interviews with clinicians.<br>5) Integrate and triangulate findings from qualitative and quantitative sources to explore whether PCT testing impacted on antibiotic use during the first wave of the COVID-19 pandemic.<br>6) To provide detailed understanding of health professionals' decision-making process around the use of antibiotics in the management of patients with COVID-19<br>7) To explore health professionals' attitudes and experiences of the feasibility, acceptability and implementation of PCT algorithms in the management of COVID-19.<br>8) To explore health professionals' views on whether PCT testing impacted on antibiotic use during the first wave of the COVID-19 pandemic.<br>9) Determine the cost-effectiveness of additional PCT testing, and the optimal strategy of integrating PCT testing into current practice to guide antibiotic prescribing decisions in patients with COVID-19, by assessing cost of illness per patient from COVID-19 from an NHS perspective, and assessing cost-effectiveness of different PCT testing strategies. |
| **Tertiary/Exploratory objectives** | N/A |
| **Primary outcomes** | **WS 1**<br>• WP1.2 Change in level and/or trend of antibiotic prescribing rates following the introduction of PCT testing. (Weekly trend of: number of defined daily doses (DDDs) of prespecified antibiotics commonly used for respiratory tract infection ('CAP-DDD') per number of COVID+ hospital admissions)<br><br>**WS 2**<br>• WP2.1. Length of early antibiotics therapy (within the first 7 days).<br><br>**WS 3**<br>• Identifying and reviewing published evidence of cost effectiveness.<br>• Patient level cost of illness from COVID-19 in NHS trusts versus those that do not.<br>• Cost-effectiveness of different PCT testing strategies in COVID-19. |
| **Secondary outcomes** | **WS 1**<br>• Weekly trend of: number of CAP-DDDs per total number of admissions<br>• Weekly trend of: number of DDDs of all antibiotics (excluding anti TB etc, 'tDDD') per number of COVID+ admissions<br>• Weekly trend of: number of tDDDs per total number of admissions<br>• Weekly trend of: number of CAP-DDDs per total number of patient bed days |

| | |
|---|---|
| | • Weekly trend of: number of CAP-DDDs per number of COVID+ patient bed days<br>• Weekly trend of: number of tDDDs per total number of patient bed days<br>• Weekly trend of: number of tDDDs per number of COVID+ patient bed days<br><br>**WS 2, WP 2.1**<br>• total length of antibiotic treatment;<br>• total defined daily doses of antibiotics;<br>• duration of late antibiotic treatment;<br>• defined daily doses of late antibiotic treatment;<br>• defined daily doses of early antibiotic treatment;<br>• appropriateness of antibiotics according to local guidelines (%compliance); if practicable;<br>• 30-day mortality;<br>• 60-day mortality;<br>• ICU admission;<br>• ICU length of stay;<br>• length of hospital stay;<br>• antimicrobial resistant secondary bacterial infection.<br>• Descriptive outcomes (e.g. types of antibiotic, route of administration and durations; frequency of PCT testing; types of secondary bacterial infection).<br><br>**WS 2, WP 2.2 and 2.3**<br>• Report on decision making process around using antibiotics for patients with COVID<br>• Report on the feasibility, acceptability and implementation of PCT testing algorithms in the management of COVID-19<br>• Report using mixed methods on how PCT testing impacted on antibiotic use during the first wave of the COVID-19 pandemic |

# 3 Study schema

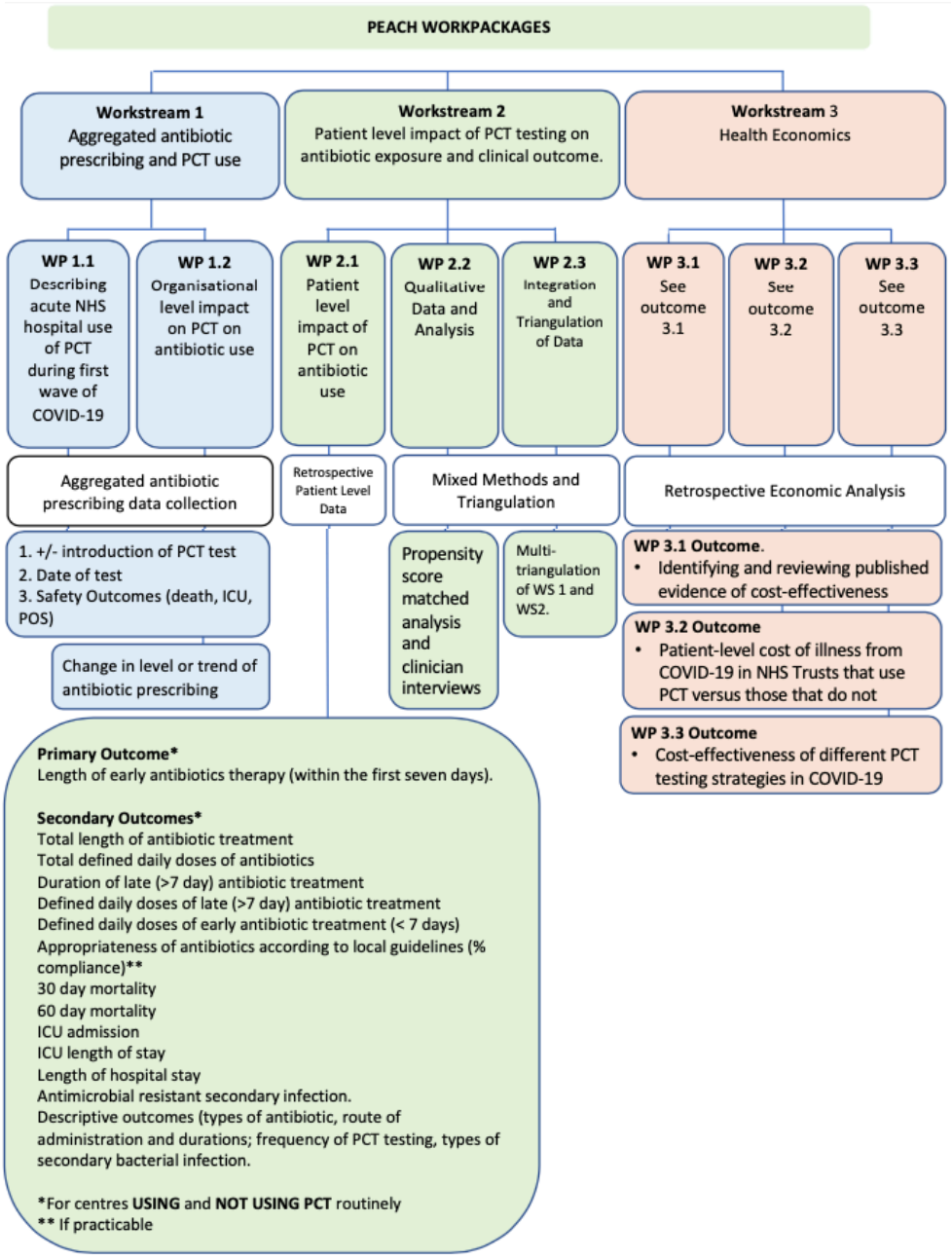


Figure 3.1 Study Schema

## 3.1 Study lay summary

Antibacterial agents (antibiotics) are usually used during treatment of patients with more severe COVID-19 even though COVID-19 is caused by a virus, and antibiotics don't work against viruses. This

is because doctors are concerned that there might be a bacterial infection on top of the viral infection, a so-called secondary infection, that is making matters worse. In fact, there is no good evidence to guide the use of antibiotics in COVID-19 and rates of secondary bacterial infection are thought to be low. The COVID-19 pandemic has therefore resulted in an unwanted increase in antibiotic use which will expose patients to more side effects, an increased risk of infection with superbugs and increase cost. This is a study about a blood test called procalcitonin which is used in many hospitals to help diagnose bacterial infections and guide antibiotic treatment. There is a lack of clear evidence to support its use in lung infections, which means in some hospitals, clinicians have used the procalcitonin test to guide antibiotic decisions in COVID-19, whilst in other hospitals, they have not. The PEACH study will analyse data from hospital trusts that did and did not use procalcitonin testing during the first wave of the COVID-19 pandemic. It will determine whether and how procalcitonin testing should be used in the NHS in future waves of COVID-19 to protect patients from antibiotic overuse.

# 4 Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus currently causing a pandemic of illness called coronavirus disease 2019 (COVID-19). Although the majority of patients affected by COVID-19 experience mild illness, a large number of people have been admitted to hospital and this continues to be the case.[1] Many patients require oxygen therapy via positive pressure ventilation and some require mechanical ventilation on intensive care.[1] SARS-CoV-2 is a virus and antibacterial agents (antibiotics) therefore have no direct killing effect on it. In spite of this, many patients (45-100%) are being prescribed antibiotics.[2-8] Empirical antibiotic therapy is recommended in World Health Organisation guidelines for patients with suspected or confirmed severe COVID-19, COVID—19 related sepsis, and community and hospital acquired pneumonia.[1] The evidence base to support this practice is limited and current recommendations are based on concerns that patients may experience secondary bacterial infections that may respond to antibiotic therapy.

The COVID-19 pandemic therefore has potential to drive an unnecessary increase in antibiotic use at a time when accumulating antibiotic resistance is also a global threat to health.[9] It is possible that antibiotic prescribing in patients who do not need antibiotics may drive excess mortality, for example

through selection for resistant pathogens, *Clostridioides (Clostridium) difficile* infection and adverse drug reactions. There is indirect evidence of unnecessary antibiotic prescribing during the COVID-19 pandemic. Published data indicate that rates of secondary bacterial infection are low at 7-15%[2,6,7,10] and many confirmed secondary bacterial infections occur late in the illness; antibiotic use early in the course of COVID-19 may drive resistance in these later infections. Crucially, therefore, there is a big difference between the number of patients with secondary bacterial infection and those receiving antibiotics, particularly early in the course of infection, indicating that more studies are needed to guide appropriate antibiotic use. Procalcitonin (PCT) is an inflammatory marker that can be measured in blood samples and is widely recommended to help diagnose bacterial infections and guide antibiotic treatment.[11] However, reviews of evidence to support its use in respiratory infections before the COVID-19 pandemic have found conflicting results.[12,13] Local guidelines were developed in several NHS hospitals which advised use of PCT testing to assist in the decision to start or stop antibiotics in patients with COVID-19, but other NHS hospitals have not adopted this approach. The recommendation to use PCT is pragmatic, in the absence of high-quality evidence in this clinical context, therefore its impact requires evaluation. A key question is whether such testing impacts on antibiotic use, length of stay, intensive care unit admission, resistant infections and mortality.

NIHR HTA funded randomised controlled trials (ADAPT-Sepsis, PRONTO and BATCH) are currently underway to assess the impact of PCT testing on antibiotic use but these are neither specifically focused on COVID-19 patients nor due to report for at least two years. A rapid assessment of the utility of PCT testing in COVID-19 is needed to inform care during any subsequent waves of infection, and to make interim recommendations using the best available evidence. Only observational (retrospective) and qualitative studies are open to us during this time-critical, recovery and learning period. We have therefore devised a mixed methods approach to answer our research questions. Because of the limitations of retrospective observational data, we have planned two quantitative work packages – one using patient level data, the other aggregated hospital data.

# 5 Study objectives/endpoints and outcome measures

## 5.1 Primary objectives

To assess whether the use of PCT testing, to guide antibiotic prescribing, safely reduced antibiotic use among patients who were hospitalised with COVID-19 during the first wave of the pandemic.

We will answer this question through three different, and complimentary, work streams (WS). Each WS will contain discrete work packages (WP).

**WS 1:** Utilization of PCT testing to guide antibiotic prescribing during the first wave of COVID-19 pandemic.

**WS 2:** Patient-level impact of PCT testing on antibiotic exposure and clinical outcome. (Main Work Stream)

**WS 3:** Health economics analysis of PCT testing to guide antibiotics in COVID-19.

# 6 Study design and setting

## 6.1 Design

This study is organised as three separate work streams. Study design for each work stream is detailed in section 9.

## 6.2 Setting

UK Acute NHS hospital trusts

# 7 Site and Investigator selection

WS 2 will be carried out at 11 large acute NHS trusts within the UK (Leeds Teaching Hospitals NHS Trust, Liverpool University Hospitals Foundation Trust, Salford Royal NHS Foundation Trust, Brighton and Sussex University Hospitals NHS Trust, Royal Cornwall Hospitals NHS Trust, Aneurin Bevan University Health Board, Sheffield Teaching Hospitals NHS Trust, Newcastle Upon Tyne Hospitals NHS

Foundation Trust, North Bristol NHS Trust, North Yorkshire Hospitals NHS Trust and Nottingham University Hospital NHS Trust). These trusts were chosen specifically to reflect differences in those that did or did not use PCT testing during the first wave of the COVID-19 pandemic and that could supply the required data for this study.

Before any site can begin data collection and recruitment of HCPS for qualitative interviews, the following documents must be in place and copies sent to the PEACH Study email account (see contact details on page 4):

- The approval letter from the site's R&D Department, following submission of OID (Organisation Information Document) form and the UK local information pack.
- Favourable opinion of host care organisation/PI from Main Ethics committee
- A signed Study Site Agreement (PI, sponsor and site signatures).
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)

# 8 Selection of Patients

## 8.1 Participant identification for work package 2.1

Consecutive patients fulfilling the eligibility criteria will be included. This will be facilitated by the use of prospectively collected institutional clinical data.

## *8.2* Informed consent.

Informed consent is not required for WS 1 or WP 2.1 (WS 2). For qualitative interviews in WP 2.2, informed consent is outlined in section 9.2.3.3.

# 9 Study Plan: Work Streams

## 9.1 Work Stream 1. Utilization of PCT testing to guide antibiotic prescribing during the first wave of COVID-19 pandemic.

WS1 will have two work packages:

### 9.1.1 WP1.1 Describing how acute NHS hospitals used PCT during first wave COVID-19.

#### 9.1.1.1 Aim:

Describe how NHS hospitals used PCT testing to guide antibiotic prescribing during the first wave of the COVID-19 pandemic, including when testing was undertaken and how results were used.

#### 9.1.1.2 Methodology:

We will integrate data from different sources to maximise completeness and accuracy using 1) a questionnaire distributed to the antimicrobial pharmacist's network and through contacts within professional networks of infection and critical care specialists; and 2) information from providers of testing resources. A pilot of data collection has confirmed feasibility. We will prepare a descriptive report of how widely PCT was used before the first COVID-19 wave and how widely it was introduced during it. We will report how it was introduced (e.g. PCT thresholds, use to guide antibiotic starting/stopping, routine or ad hoc use, what communications/educational activity was undertaken).

### 9.1.2 WP1.2. Organisational-level impact of PCT on antibiotic use.

#### 9.1.2.1 Aim:

Determine whether, at an NHS trust level, having a suspected COVID-19 antibiotic pathway which incorporated PCT testing, modified the impact of COVID-19 on antibiotic use.

#### 9.1.2.2 Methodology:

Data will be gathered through our partners Rx Info Ltd, Public Health England and Public Health Wales. We will describe antibiotic consumption (Defined Daily Dose (DDD) by route and agent) from 1/3/20 to 30/6/20. This will be adjusted for activity (e.g. admissions and bed days). We will perform a

controlled interrupted time series analysis, with non-PCT using trusts acting as controls, to estimate the trust-level impact of introducing PCT on antibiotic consumption rates. Impact will be assessed for total antibiotics, broad spectrum and 2019 WHO AWaRe Classification (Access, Watch or Reserve) antibiotics.

**9.1.2.3 Study design**:

Controlled multi-centre, aggregated data, interrupted time series analysis. Case NHS trusts will be those who started PCT testing between March and June 2020, controls will be those that did not use PCT, as well as those already using PCT pre-COVID-19.

**9.1.2.4 Setting**:

Acute NHS hospital trusts in England and Wales.

**9.1.2.5 Participants**:

Aggregated data from acute admissions to trusts between 1/3/20 and 30/6/20 to encompass the first peak of the COVID-19 pandemic across the UK.

**9.1.2.6 Inclusion criteria**:

NHS hospital trust caring for COVID-19 inpatients >16 years.

**9.1.2.7 Exclusion criteria:**

Non-acute or teaching trusts

**9.1.2.8 Variables and data sources:**

Aggregated weekly antibiotic usage data will be collected from Rx Info Ltd/PHE/PHW and weekly patient activity data from PHE/PHW. Date of introduction of PCT testing, or not, will be collected via direct contact with hospitals in WP1.1. We may focus on acute admission wards to enrich the population with COVID-19. Total defined daily doses of antibiotics, broad spectrum and WHO 'AWaRe' categories will be calculated pre- and post-introduction of PCT testing.

**9.1.2.9 Bias**:

To reduce the risk of bias we will use data from all acute NHS hospital trusts. Routine hospital activity has markedly reduced during COVID-19 (e.g. cancellation of elective work) and this will have affected antibiotic prescribing and makes the pre-COVID-19 prescribing data invalid for comparison. In addition, PCT testing will impact on suspected COVID-19 patients who will only make up a proportion of inpatients at any one time. Hospital activity data will therefore be used to control for reduced inpatient activity.

**9.1.2.10 Outcomes:**

9.1.2.10.1 Primary outcome

- WP1.2 Change in level and/or trend of antibiotic prescribing rates following the introduction of PCT testing. (Weekly trend of: number of defined daily doses (DDDs) of prespecified antibiotics commonly used for respiratory tract infection ('CAP-DDD') per number of COVID+ admissions)

9.1.2.10.2 Secondary outcomes

- Weekly trend of: number of CAP-DDDs per total number of admissions
- Weekly trend of: number of DDDs of all antibiotics (excluding anti TB etc, 'tDDD') per number of COVID+ admissions
- Weekly trend of: number of tDDDs per total number of admissions
- Weekly trend of: number of CAP-DDDs per total number of patient bed days
- Weekly trend of: number of CAP-DDDs per number of COVID+ patient bed days
- Weekly trend of: number of tDDDs per total number of patient bed days
- Weekly trend of: number of tDDDs per number of COVID+ patient bed days

**9.1.2.11 Sample size and analysis:**

Specifying a formal sample size target is not possible as this is an opportunistic retrospective analysis. A controlled interrupted time series will be undertaken with variable date for introduction of PCT testing. We will estimate the level and trend of the rate of antibiotic usage before and after the introduction of PCT testing using a segmented linear regression model for the differential effect (PCT vs. non PCT trusts) and test the null hypotheses that 1) the level (i.e. model intercept) and 2) the trend (i.e. model slope) do not change following the introduction of PCT testing.

## 9.2 Work Stream 2. Patient-level impact of PCT testing on antibiotic exposure and clinical outcome

WS 2 will have three work packages:

### 9.2.1 WP2.1 Assessing the patient-level impact of PCT on antibiotic use

#### 9.2.1.1 Aim:

To measure the difference in antibiotic use, length of stay, mortality (30 and 60-day), intensive care unit admission, and resistant bacterial infections between COVID-19 patients who did/did not have PCT testing at baseline.

#### 9.2.1.2 Study design:

A retrospective observational analysis of patient-level clinical data using propensity score matching. This study has been designed taking STROBE criteria into consideration.[14]

#### 9.2.1.3 Setting:

Data will be collected from 11 UK NHS trusts which did/did not use PCT routinely in COVID-19 patients >16 years.

#### 9.2.1.4 Participants:

Data from all patients admitted to a participating trust with COVID-19 between 1/2/20-30/6/20 will be eligible. Participants will be identified from institutional databases. This will include approximately 7000 patients.

#### 9.2.1.5 Inclusion criteria:

Confirmed COVID-19 (positive test) and admitted to participating trust (any reason).

#### 9.2.1.6 Variables and data sources:

Data will be collected from institutional clinical databases and patient medical records. Variables will include:

- Patient demographics (age, sex, ethnicity), comorbidities (Quality Outcome Framework registered conditions, frailty scores), smoking status, penicillin allergy status. (confounding factors)
- Post code/Lower level super output area (LSOA) to allow derivation of index of multiple deprivation (IMD). (confounding factor)
- Antibiotics used during treatment of episode; agent, dose, route, start and stop dates. To derive days and DDDs of 'early', 'late' and total antibiotic treatment. (primary and secondary outcomes)
- Date of hospital admission/discharge/death; date of admission and discharge from ICU. To derive: length of hospital stay and ICU stay and mortality rates. (secondary outcomes)
- Resuscitation status and level of care preference. (confounding factor)
- Presence and location of consolidation/ ground glass changes on lung imaging; COVID-19 categorisation of imaging; time to new consolidation. (confounder and secondary outcomes)
- Physiological observations at time of diagnosis (day 1); to derive qSOFA/NEWS2/CURB-65 scores. (confounding factor)
- Laboratory tests: Positive COVID-19 test date (=day 1); refined to week of test for analysis
- Laboratory tests: PCT test date (study test, within 3 days of COVID test for inclusion in PCT group)
- Laboratory tests urea, creatinine, C-reactive protein, troponin, ferritin, D-dimer, white cell, lymphocyte and neutrophil counts, haemoglobin and platelets, around time of COVID-19 positive test. (day 1 or =/- 1 day) (confounding factors)
- Laboratory tests: Microbiology (results and date of sampling): blood culture, respiratory, results. To derive resistant bacterial infection rates and time to event (secondary outcome)
- Laboratory tests *C. difficile* testing date and result. (secondary outcome)

Some study variables may be more accurately recorded in primary care medical records (e.g, quality outcome framework registered conditions (co-morbidity), body mass index, penicillin allergy records, ethnicity). We will attempt to obtain these specific variables through linkage between secondary and primary care records coordinated at local collaborating centres. Where this is not possible, we will use co-morbidities, body mass index, penicillin allergy records, ethnicity recorded in secondary care records.

#### 9.2.1.7 Definitions:

Day 1 of COVID-19 will be considered the day of first positive sample; 'early' antibiotic use will be considered prescriptions on days 1-7, and 'late' after day 7.

#### 9.2.1.8 Bias:

To reduce the risk of bias, consecutive patients fulfilling the eligibility criteria will be included. This will be facilitated by the use of prospectively collected institutional clinical data.

#### 9.2.1.9 Outcomes:

Primary outcome will be length of early antibiotics therapy[15] (within the first 7 days).

#### 9.2.1.10 Secondary outcomes:

- total length of antibiotic treatment;
- total defined daily doses of antibiotics;
- duration of late antibiotic treatment;
- defined daily doses of late antibiotic treatment;
- defined daily doses of early antibiotic treatment;
- appropriateness of antibiotics according to local guidelines (%compliance); if practicable;
- 30-day mortality;
- 60-day mortality;
- ICU admission;
- ICU length of stay;
- length of hospital stay;
- antimicrobial resistant secondary bacterial infection.
- descriptive outcomes (e.g. types of antibiotic, route of administration and durations; frequency of PCT testing;
  types of secondary bacterial infection).

**9.2.1.11 Data Collection:**

The variables that will be used in work-package 2.1 constitute objective, routinely collected data from a patient's episode of COVID-19 and each variable in the database will be collected in a standardised format. This will mean that the data for each variable can be collated into a single dataset for analysis. E.g. each centre will collect the procalcitonin (PCT) value for each patient and this will be collected into a series of PCT values for each patient in the dataset. The trust that each patient was admitted to will be collected as a separate variable for each patient.

**9.2.1.12 Sample size and analysis:**

For the patient level analysis, data from ~7000 COVID-19 patients from 11 NHS acute hospitals will be sourced, around half of which will have had PCT testing. Based on a minimally important clinical difference in antibiotic duration of 1 day (as proposed in the ADAPT-Sepsis trial) between PCT and non-PCT-tested patients, and a conservative assumption for the standard deviation (SD) of 6 days, 1500 matched patients will provide 90% power when using a two-sided test with 5% alpha.

For patient level analysis, descriptive statistics will be used for rates of PCT testing, antibiotic prescribing and secondary bacterial infection. This will be done overall and separately for those hospitals using/not using PCT, and also separately for patients who did/did not receive a PCT test. Comparative effect sizes, such as mean differences between groups, will be presented alongside 95% confidence intervals (CIs) wherever possible. Multivariable regression models with random hospital effects will be used to examine factors affecting antibiotic prescribing including but not limited to: age, comorbidity, lung consolidation, secondary bacterial infection, CRP and PCT levels, severity of illness (we will explore use of CURB-65, qSOFA, NEWS2). Results will be presented as effect estimates with 95% CIs and p-values. To assess the effect of PCT testing on patient outcomes and antibiotic use, propensity score matching will be used. We will estimate a patient's propensity for PCT testing with a logistic regression on patient characteristics including age, sex, clinical severity of illness assessments, lung imaging, comorbidity and ethnicity. Patients who did or did not receive PCT testing can be matched with a 1:1 or 1:2 ratio according to their propensity. This will enable the comparison of several outcomes on between-patient groups which are balanced on important known confounders. Potential hospital effects will be accounted for in the model (e.g. by using random effects) or will be

absorbed into the propensity scores. Alternative matching methods such as Mahalanobis distance matching, and coarsened exact matching will also be explored.

The primary analysis model for the propensity score-matched data will depend on the type of outcome e.g. logistic regression for binary outcomes (e.g. ICU admission) and linear regression for continuous outcomes (e.g. days on antibiotics). These will be adjusted for "truncation by death" i.e. the problem that some patients die before another outcome (e.g. days on antibiotics) can be fully measured, thus leaving these outcome measures censored/undefined and with a seemingly better outcome (e.g. fewer days on antibiotics) due to the early death. To take this into account we will, in addition to a crude analysis restricted to the survivors in each group, perform a survivor average causal effect (SACE) analysis of the "always-survivors" i.e. those who would have survived in either group. Survival analysis will also be undertaken for outcomes that can be expressed as time-to-event (e.g. time until antibiotics are stopped) adjusting for confounders using a Cox regression if the proportional odds assumption holds, and after stratification otherwise. This will give greater power than the above analyses but requires further modelling assumptions. Importantly, it will allow us to perform competing risks modelling with death being a "competing risk". For all analyses, sensitivity analyses, including multiple imputation, will be undertaken to explore the impact of missing data. A detailed statistical analysis plan will be finalised prior to any analysis being performed.

### 9.2.3 WP 2.2: Qualitative data and Analysis

#### 9.2.3.1 Aim:

To explore the decision-making process around the use of antibiotics, identify the contextual factors, explore the feasibility and acceptability of PCT testing algorithms, and identify the key ingredients of successful implementation and normalisation of PCT algorithms in the management of COVID-19.

#### 9.2.3.2 Interviews with Clinicians:

This will be a semi-structured interview with clinicians at study sites, conducted virtually in line with current good practice to reduce rCOVID-19 transmission. A topic guide will be developed using a scoping literature review and input from the interdisciplinary research team, PPI advisory panel and clinicians. For centres routinely using PCT, the interview will seek to understand whether and how the use of PCT supports clinical decisions to commence/stop antibiotics in COVID-19, and where testing

algorithms are in place, reasons for adhering to algorithm or not, and what features of the algorithm they might wish to change. For centres not using PCT, the interview will seek to understand how clinicians make decisions to start, stop, or continue antibiotics in COVID-19 patients, and if there was an algorithm whether they would use it, or what they would like it to do. We will ask clinicians to reflect on the impact of the NICE COVID-19 rapid guideline[14] on their trust's decisions regarding PCT use. We will ask clinicians to reflect back on their practice during the first wave of COVID-19. We will explore how equipoise to PCT testing has been challenged as a result of COVID-19. We will also ask them to reflect on what will improve their practice and whether there are lessons we should be learning for antimicrobial stewardship in subsequent COVID-19 surges. We will then present clinicians with hypothetical scenarios, constructed by the clinical research team with input from the PPI advisory panel, and using some of their patient stories, and ask them to talk through the factors influencing their decision making. Using a scenario within the qualitative interview will allow comparison across interviewees' responses, but the interviewer/s can probe for detail and clarification on aspects which influence management decisions and the way PCT and algorithms might be used. The researcher will encourage the clinician to think about the scenarios along a timeline – allowing participants to organize their thoughts and envisage the factors influencing decision making over time. The interviewer will encourage the clinician to reflect on both clinical influences, but also all aspects of non-clinical influences at micro and macro levels e.g. personal attitude to risk (which may be influenced by a mentor when training), previous good/bad experiences, pressure from relatives, age, ethnicity or socioeconomic status of the patient, political climate, media influences, resource capacity pressures of the first wave of COVID-19, timing

The topic guide will include overarching topics we would like to cover, but will be flexible and allow the interview to be guided by the interviewee in terms of order and wording, and allow the interviewee to initiate and develop topics that have not been pre-empted by researchers and PPI advisory panel.

#### 9.2.3.3 Informed Consent for Qualitative Interviews:

For qualitative data and analysis, the clinician's (consultant, specialty trainee, nurse specialist, nurse practitioner etc) verbal informed consent must be obtained by the research team at Cardiff Centre for Trials Research prior to undertaking any qualitative interviews using the study consent form script. Potential interviewees will be given the Participant Information Sheet for HCPs by the Principal

Investigator at each site and sufficient time given after the initial invitation to participate before being asked to complete a consent to contact form which provides a name and phone number/email for the qualitative researcher at CTR to contact them on and arrange an interview.

Only when verbal informed consent has been obtained from the participant can they be considered a study participant. This verbal consent will be audio recorded, to reduce the risk of transmission of COVID-19 that could potentially occur during face to face written consent.

The right of the participant to refuse to participate in the study without giving reasons will be respected.

**9.2.3.4 Qualitative interview sampling methods:**

We will be pragmatic in sample size. The number of interviews will be based on preliminary analysis/interviewer field notes indicating whether the data collected sufficiently answer the research questions. Our proposed sample size for interviews with health professionals is 6 sites, (two who routinely used PCT pre-COVID, two who did not routinely use PCT pre-COVID and two that introduced a PCT algorithm during COVID). We will conduct up to five interviews per selected site, thus giving greater breadth of practice variation. This is based on our previous qualitative research on clinicians' and patients' perspective on antibiotic resistance and infection management (POETIC, GRACE-02, GRACE-INTRO, CHAMP-02) in which we found 15-30 to be sufficient. We will monitor the breadth and depth of data, whether interview participants are representative of the study population, and practical aspects of recruitment (attempts to invite participants, numbers declined, and withdrawn). We will continually review our sampling decisions and keep detailed notes on our sampling strategy to maintain transparency.[16] Data collection will be iterative, allowing preliminary analysis to guide the subsequent sampling decision and selection of further interviewees. We will purposefully sample interviewees with maximum variation across a) role (e.g. consultant/specialty trainee/nurse specialist etc) to gain a wide perspective on how antibiotic decisions are made; b) hospital site (comparing sites that routinely use PCT versus those that do not). We will seek a range of views i.e. PCT enthusiasts versus PCT sceptics.

**9.2.3.5 Qualitative Data Management:**

All information, including any personal information (e.g. clinician's name), will be kept confidential. Recordings will not be labelled with clinician's name. Any written research reports or publications will not include the interviewee's name. Written quotes from clinician interviews may be used word for word, but will be anonymised. All study related records will be stored for >15 years. Results will be published in medical journals over the next few years. Patients will not be personally identified in any report or publication. Full details will be specified in the Data Management Plan.

**9.2.3.6 Qualitative Analysis:**

Interview transcripts and field notes will be analysed using a five-stage framework approach[17] to take into account the different interviewee characteristics e.g. PCT vs non PCT sites, grade of clinician, etc. After familiarisation of data, we will develop a thematic framework based on the research objectives and emerging themes. After applying the thematic framework ('indexing'), the fourth stage, 'charting', will involve retrieving the coded data and producing summaries of interviewees' talk produced on each theme, for each individual participant, and visually arranging it in a table to build an overall picture of the whole data set. This will allow easier comparison across clinicians and hospital sites to identify variation and similarities in the final stage of interpretation of data. The fifth stage, 'mapping', will involve the research team using the charts to map and interpret the data set as a whole and connect with the original research objectives. The qualitative software package, NVivo (2015) will be used to manage the data. A proportion of transcripts will be double-coded until consensus is reached (likely to be 10%). Normalisation process theory (NPT) will provide an additional theoretical lens to consider whether and how PCT and algorithms were used in each site. This will allow us to consider contextual features of local site, modifications that may have been made, and the function of the PCT/algorithm. NPT is concerned with how and why things become routine and normal components of everyday work, or not.[18] It uses four mechanisms to explore this - coherence (extent to which an intervention is understood as meaningful, achievable and desirable), cognitive participation (enrolment of actors necessary to deliver the social practice), collective action (the work that brings the intervention into use), and reflexive monitoring (the ongoing process of adjusting to keep the social practice in place).[19]

We will use the qualitative data in this WP and work with WP 1.1 (WP to collect clinical guidelines and PCT testing algorithms from participating hospitals to see where and how in the patient pathway PCT testing is undertaken) to develop analysis of the PCT algorithms/guidelines in each site (including people, processes, structures, technologies and artefacts).

We will use the qualitative data in this WP to explore from the perspective of clinicians, the coherence of the PCT algorithms at their site. Depending on whether the algorithms were already in place before COVID-19, or introduced during this period, we will explore the clinician's experiences of enrolling actors (human and non-human) necessary for using the algorithm and the work needed to bring the algorithm into use and the reflexive monitoring necessary to keep using the algorithm. We will use the data to identify barriers and facilitators (clinical, management, organisational) to implementing PCT/PCT algorithms in other sites which do not routinely use them.

### 9.2.4 WP 2.3: Integration and triangulation of data

#### 9.2.4.1 Aim:

To integrate and triangulate findings from qualitative and quantitative sources to explore whether PCT testing impacted on antibiotic use during the first wave of the COVID-19 pandemic.

#### 9.2.4.2 Multi-triangulation:

WP1 and WP2 use a range of qualitative and quantitative research methods to collect data and access different types of information. We will also obtain information across a range of sources and settings e.g. hospital sites. In WP2.3 we will then carry out multi-triangulation to integrate the different components of this study, to gain a more complete picture and enhance the validity of our findings.[20] We will be able to triangulate the sources at the site level (rather than individual clinician level), so we will be able to explore clinicians' experiences and views at a hospital site, review the guidelines/algorithms available at that hospital site, and describe frequencies of testing and infection rates at that site.

#### 9.2.4.3 Triangulation Protocol:

We will use a triangulation protocol technique[20,21] to integrate our data and explore whether PCT testing made a difference in antibiotic use during the first wave of the COVID- 19 pandemic. We will use investigator triangulation to include a range of investigator perspectives including qualitative, quantitative, clinical and PPI in analysis. Two different analysts (qualitative, quantitative) will independently compare the key findings across the data sets using a convergence coding matrix and consider where findings from each method agree (convergence), offer complementary information on the same issue (complementarity), appear to contradict each other (discrepancy), or whether there is silence (where a theme or finding arises from one data set and not another)[22]. The two individual analyses, from the qualitative and quantitative researchers, will then be compared and discussed within an interactive workshop consisting of members of the SMG to include PPI representative and health professionals to obtain a consensus about the relationship between findings.

## 9.3 Work Stream 3. Health economics analysis of PCT testing to guide antibiotics in COVID-19

### 9.3.1 Aims:

To determine the cost-effectiveness of additional PCT testing to guide antibiotic prescribing decisions, and determine the optimal strategy of integrating PCT testing into current practice to guide antibiotic prescribing decisions in patients with COVID-19.

### 9.3.2. WP 3.1 Identifying and reviewing published evidence of cost-effectiveness:

We will search the published literature for economic evaluations, utility and cost studies relating to use of PCT to guide antibiotic decisions. Searches will be developed by an experienced information specialist. These studies are likely to focus on populations with acute respiratory tract infections, sepsis and suspected bacterial infection. The purpose is not a systematic review, but to identify existing high-quality studies to inform the structure of the current economic model.

### 9.3.3 WP 3.2 Patient-level cost of illness from COVID-19 in NHS trusts that use PCT versus those that did not:

Using the respective observational data collected for WP2.1, the patient-level cost of illness will be calculated from a secondary care NHS perspective. Specifically, the cost of antibiotic therapy will be costed for each individual, broken down by whether the cost is associated with early (day 1-7) or late (day >8) antibiotic use. The cost of different antibiotics for varying durations/dosage will be extracted from the British National Formulary (BNF).[22] The average cost associated with the number of bed days (including ICU) will also be calculated for each individual. In the absence of cost data pertinent to patients with a COVID-19 diagnosis, the cost of a bed day will be obtained from the latest NHS Improvement National Schedules of NHS Costs.[23] The average and distribution of patient-level costs will be aggregated based on those who did/did not have PCT testing at baseline, using the propensity score matching developed for WP2.1.

### 9.3.4 WP 3.3 Cost-effectiveness of different PCT testing strategies in COVID-19:

A de novo decision analytic model will be developed to determine the cost-effectiveness of adding PCT testing to current clinical practice to guide antibiotic prescribing decisions. A decision tree will be constructed of the comparative testing pathways and the immediate impact on short-term antibiotic prescribing decisions. The final structure of the model will be informed by the literature review, results from WP3.1, clinical and patient input. Results of WP1.1 and WP2.1 will determine whether PCT testing impacts: 1) the proportion of individuals receiving antibiotic therapy, 2) the duration of antibiotic therapy, the length of hospital and/or ICU stay, and 3) 30-/60-day mortality. These data, in combination with the cost data calculated in WP3.2, will be used to parameterise the decision model. The findings of WP1.1 will also provide the details of different PCT testing strategies. These different PCT testing strategies (e.g. repeat testing, different antibiotic treatment thresholds, and consideration of other clinical factors) may also impact on costs and outcomes. A short-term cost-effectiveness analysis will explore the possible impact of different strategies on antibiotic prescribing. Results will be presented as incremental cost effectiveness ratios (ICERs) and net health benefit. Based on the distributions fitted to each model parameter, probabilistic sensitivity analyses will be conducted to explore the impact of uncertainties in the model parameters on the cost-effectiveness results.

Decision uncertainty will be illustrated using cost-effectiveness planes and cost-effectiveness acceptability curves.

# 10 Data Management

The source data for PEACH will be collected from participants' medical notes, NHS databases, data informatics company (RxInfo), Public Health England and Public Health Wales. Informatics data will be collated and sent securely to CTR for secure storage. Data will be de-identified at source and transferred by secure file transfer protocols. All patient data will be assigned a unique identifier, the "master list" with identifiable data will be kept separately at individual centres, and used only to identify information from NHS databases (e.g. radiology, clinical chemistry and microbiology results). Only de-identified data will be collected and uploaded onto a central secure database and analysed. Training for completion of the eCRF will be provided to the appropriate study staff prior to study commencement. If missing/questionable data are identified, a data query will be raised on a data clarification form; this will be sent to the relevant site and asked to respond to the data query. The CRF pages will not be altered. All answered data queries/ corrections will be signed off and dated by a delegated member of staff at the relevant site. The completed data clarification form will be returned to the CTR and an electronic copy retained at site.

## 10.1 Data Collection

All data collection at site will be completed using a password-protected excel spreadsheet. The password will be supplied to investigators upon completion of all processes required prior to opening, and complies with the Data Protection Act 2018. The data will be sent to Cardiff Centre for Trials Research (CTR) by a secure file transfer system and inputted into a secure web-based system database once it is accessible. A full Data Management Plan will accompany this protocol and will be stored in the SMF.

# 11 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the study protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it. The

CTR will assess the nature and severity of any issues of non-compliance in accordance with their Standard Operating Procedures (SOPs).

## 12 End of Study definition

The end of the study is defined as the date of final data capture to meet the study endpoints. Sponsor must notify the main REC of the end of a clinical study within 90 days of its completion or within 15 days if the study is terminated early.

## 13 Archiving

The Study Master File (SMF) and Investigator Site File (ISF) containing essential documents will be reviewed by the study manager and archived by the Centre for Trials Research unit on behalf of the sponsor for a minimum of 15 years. All electronic study data will be electronically archived in an appropriate format.at the end of the archiving period, study data will be destroyed, as authorised by the sponsor.

## 14 Regulatory Considerations

### 14.1 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval. A favourable ethical opinion will be obtained from the REC before commencement of any study procedures.

The study will be submitted to Health Research Authority and for NHS ethical committee approval for the patient level data collection and qualitative interviews. Good clinical practice regulations will be adhered to during conduct of the study. The study management group (SMG) will meet monthly by teleconference and will include the co-chief investigators (co-CI), and all other co-applicants. Data scientists at participating NHS trusts will be supervised by the site principal investigator (PI). The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

The outcome of the study (e.g. completed) will be reported to the REC responsible for the study within 90 calendar days of study closure. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 calendar days.
A summary of the results will be submitted to the REC responsible for the study within one year of completion of study closure.

### 14.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016. The data custodian for this study is the Chief Investigator at the University of Leeds (sponsor). Patient identifiers will only be used by local research teams to identify patients and patient data from primary and secondary care records. Only pseudonymised data will be stored locally and only de-identified data will be shared with Cardiff Centre for Trials Research for analysis.

Participants will only be identifiable to the Cardiff Centre for Trails Research using their unique study identification number.

### 14.3 Indemnity

PEACH is sponsored by The University of Leeds and will be co-ordinated by the CTR at Cardiff University. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability: NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven. The Sponsor does not accept liability for any breach in any other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not.

**Clinical negligence is defined as:**

"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

The Sponsor has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical trial, including but not limited to the authorship of the Clinical Trial Protocol. The University of Leeds has appropriate insurance in place to cover this liability.

### 14.4 Study sponsorship

University of Leeds will act as Sponsor for the study. Delegated responsibilities will be assigned to the sites taking part in this study.

The Sponsor shall be responsible for ensuring that the study is performed in accordance with the following:

- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- UK Policy framework for Health and Social care Research 2017.
- The GDPR (UK GDPR is the retained EU law version of the General Data Protection Regulation ((EU) 2016/679).
- Other regulatory requirements as appropriate.

The Sponsor has/will be delegating certain responsibilities to Cardiff University (CTR), the Chief Investigators, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and study type.

### 14.5 Funding

This project was funded by the National Institute for Health Research COVID-19 Recovery & Learning Programme (XP NIHR132254) and will be published in full in Recovery & Learning. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the L & R programme, NIHR, NHS or the Department of Health. The study will be adopted on the NIHR portfolio.

## 15 Study management

### 15.1 Project Team

The Project Team (PT) will meet weekly and will include the Co-Chief Investigators, Study Manager, Data Manager, Statistician, Administrator and other research staff directly employed to the study. The project team will discuss all day-to-day management issues and will refer any key management decisions to the Study Management Group (SMG).

### 15.2 SMG (Study Management Group)

The Study Management Group (SMG) will meet monthly online. It will include the co-Chief Investigators (co-CIs), all other co-applicants, and the central project team. The SMG will provide specialist advice, develop study procedures/documents and advise on the conduct of the study. The study manager will be responsible for study conduct and will be accountable to the co-CIs. Regional research staff supervised by the site Principal Investigator (PI) will be responsible for recruitment of HCPs for qualitative interviews and data collection. Data will be securely stored locally and entered on a secure electronic recording system compliant with data management procedures. SMG members will be required to sign up to the remit and conditions as set out in the SMG Charter.

### 15.3 SSC (Study Steering Committee)

An independent Study Steering Committee (SSC) will be established with an independent chair and at least two other independent members and also including members of the PPI advisory panel in rotation. The role of the SSC will be to provide advice, support and report to the NIHR on study progress. SSC members will be required to sign up to the remit and conditions as set out in the SSC Charter.

# 16 Public and Patient Involvement (PPI)

Our PPI advisory panel, led by co-applicant Ogden, will lead on engagement with patient groups and the wider public through their involvement as members of the ICUsteps, Antibiotic Action (a public awareness group of the British Society for Antimicrobial Chemotherapy), and Antibiotic Research UK, and publicise the study through these channels. We will use press releases and social media outlets (Facebook and Twitter) to publicise the study and disseminate findings. The NIHR Leeds IVDC MIC (via co-app Shinkins) will support the project by disseminating project announcements, updates and final results via their website, social media, and their extensive network of industry partners, policy makers, clinicians and academics.

# 17 Quality Control and Assurance

## 17.1 Monitoring

The clinical study risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the PEACH study. Low+ monitoring levels will be employed and are fully documented in the study monitoring plan.

Investigators should agree to allow study related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

## 17.2 Audits & inspections

The study may be audited by NHS Digital Audit Team. The study is participant to inspection by the COVID-19 Learning & Recovery Programme as the regulatory body. The study may also be participant to inspection and audit by University of Leeds under their remit as Sponsor.

## 18 Publication policy

This study will provide seminal evidence in an area where there is a paucity of robust data to inform initiation and cessation of antibiotics for hospitalised patients with COVID-19. It should fill a significant evidence gap highlighted by the recent NICE rapid guideline[14] and facilitate adoption if the results feed into future revised NICE guidelines on PCT use in COVID-19 pneumonia.

Research findings will be disseminated through publications and reports submitted via a variety of audiences, such as NICE (via co-app Howard, member of NICE common infections guideline group); Public Health England (via co-app Hopkins); Public Health Wales (Dr Wendy Harrison, Senior Scientist, Public Health Wales); NHS-Improvement National Antimicrobial Resistance Project Lead and Royal Pharmaceutical Society Expert Advisory Group on Antimicrobial Resistance (Howard); British Society of Antimicrobial Chemotherapy (global antibiotic charity) (via Howard (as president) and Sandoe) and the British Infection Association (via co-app Llewelyn as president).

All publications and presentations relating to the study will be authorised by the Study Management Group.

## 19 Milestones

**Month 1-3**: Study and site set-up (at least 6 sites to be open for month 1 of data collection)
**Month 2-4**: WS 1 data collection commenced.
**Month 4-12** WS 2 and 3 data collection and qualitative data collection commenced.
**Month 12-16**: Data cleaning and analysis of all work streams.
**Month 16-18**: Prepare results and report to funder (NIHR R & L)

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