Study protocol

Defining adult beta-lactam antimicrobial pharmacokinetics across the secondary care setting

V6 31/01/2018

SPONSOR: Imperial College London (DOCUMAS: 16HH3571)

FUNDER:

STUDY COORDINATION CENTRE: National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infection and Antimicrobial Resistance at Imperial College London.

IRAS REF: 207217

Protocol authorised by:

Name & Role	Date	Signature

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Study Management:
National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infection and Antimicrobial Resistance, Imperial College London (Hammersmith Campus), Du Cane Road. London. W12 0NN.

Study Coordination Centre
For general queries, supply of study documentation, and collection of data, please contact:

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Tel: 020 33132732
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Clinical Queries
Clinical queries should be directed to Dr Timothy M Rawson (tmr07@ic.ac.uk ; 02033132732) who will direct the query to the appropriate person

Sponsor
Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office, Imperial College London, Room 215, Level 2, Medical School Building, Norfolk Place, London, W2 1PG **Tel:** 0207 594 1872
Fax:

Funder
National Institute for Health Research Invention for Innovation Product Development Award & Imperial College EMBRACE pump priming award
This protocol describes the study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator. This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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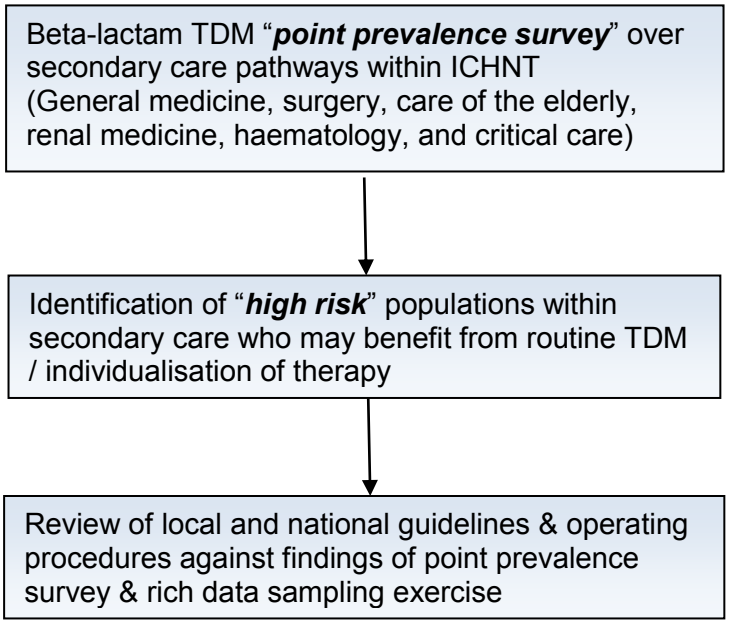
STUDY SUMMARY

TITLE	Defining adult beta-lactam antimicrobial pharmacokinetics across the secondary care setting
DESIGN	Prospective, observational study
AIMS	1. To investigate the role of therapeutic drug monitoring for optimising the use of beta-lactam agents in secondary care 2. To identify areas across secondary care where we are currently failing to optimise beta-lactam therapy 3. To explore potential pharmacodynamics indices that can be associated with treatment response across this cohort
OUTCOME MEASURES	1. Justification for the use of therapeutic drug monitoring of beta-lactams within secondary care populations 2. Identification of areas where rich data sampling and population pharmacokinetic modelling may be of benefit in future investigations 3. Identification of a potential pharmacodynamic model to guide describe response to therapy with beta-lactams
POPULATION	Hospital in-patients receiving beta-lactam antimicrobials at Imperial College NHS Healthcare Trust.
DURATION	January 2017 to August 2019

PROJECT FLOW CHART

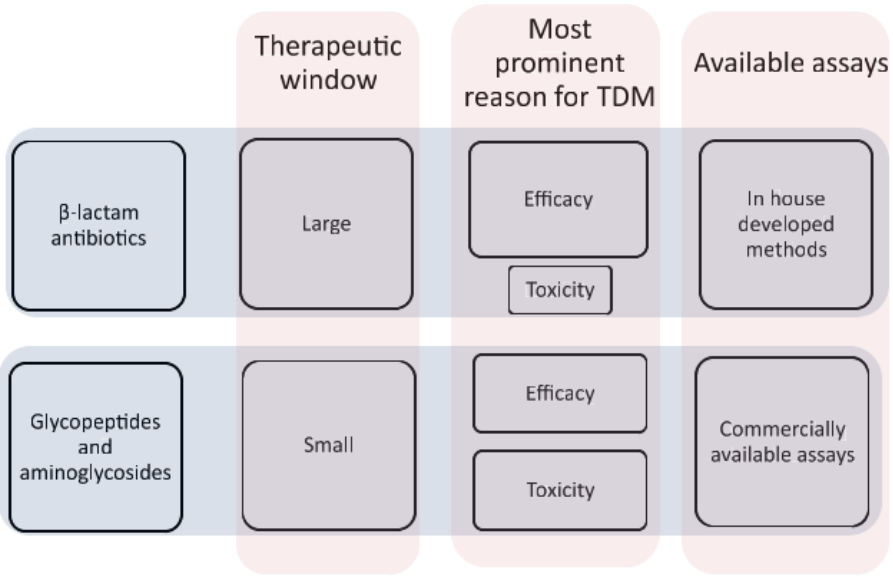


1. INTRODUCTION

Antimicrobial chemotherapeutic agents are drugs which kill or inhibit the growth of micro-organisms. Whilst essential to modern medicine, the exposure of micro-organisms to antimicrobial agents also drives generation of resistant strains, termed antimicrobial resistance (AMR). This, combined with a paucity of new antimicrobial drug development, has led to AMR becoming a global threat to modern medicine and a leading patient safety issue (Holmes et al., 2015).

To address the challenge of AMR, it is imperative that the current finite pool of antimicrobial agents is optimised, maximising therapeutic success whilst minimising emergence of resistance (Mouton et al., 2011). One avenue to optimise the use of antimicrobials is to ensure correct dosing strategies. Population pharmacokinetic (PK) modelling was developed from the simple concept of dose-response relationships in the 1960's (Csajka & Verotta, 2006). More recently the idea of individualised dosing, which accounts for intra- and inter-individual variability in PK parameters, has gained popularity and has been demonstrated to improve patient outcomes in secondary care settings (J. A. Roberts et al., 2014). In tandem to optimisation of therapy through individualising dosing, population PK modelling also allows for the consideration of individualised therapeutic drug monitoring (TDM) protocols to help provide robust and accurate data to drive individualised dosing regimens.

Currently in the UK, TDM is routinely performed for aminoglycosides and glycopeptide antimicrobial agents, given fears over the narrow therapeutic window of these agents and the serious adverse events associated with toxicity. However, in critical care the role of TDM for optimisation of therapy has been demonstrated to help optimise dosing of patients who tend to have variable pharmacokinetic parameters (J. A. Roberts *et al,*). This is of growing importance given that low concentrations of antimicrobial agents, below a micro-organisms minimum inhibitory concentration (MIC) is believed to be a major driver of AMR.



Moreover, in individuals managed with enhanced TDM protocols and individualised dosing protocols there is evidence that this enhances patient outcomes and reduces the cost of care for these patients, reducing hospital stay and lengths of therapy (van Lent-Evers, Mathôt, Geus, van Hout, & Vinks, 1999). Whilst, most evidence in this field currently focuses primarily on critical care setting, there is evidence to suggest that optimisation of therapy in secondary care can impact significantly on AMR in crititical care. However, this must go beyond simply selecting the optimal antibiotic for the organism in question. We must also ensure that the optimal dose is selected to maximise micro-organism killing, whilst minimising the risk of toxicity or development of AMR. The observation of wide variability in

therapeutic levels of antimicrobials being delivered to patients across a number of settings (e.g. ICU, obese, paediatric) has promoted the idea of individualised dosing that accounts for intra- and inter-individual variability in PK parameters. This has been demonstrated to improve target attainment and outcomes in secondary care (J. A. Roberts et al., 2014). However, outside controlled trial environments implementation of individualised dosing using population PK models, plasma sampling, and pre-determined PK-PD indices has been challenging to implement for several reasons. These include difficulties in access to appropriate antimicrobial assays, poor integration of dosing software with electronic health records and decision support systems, challenges with taking and handling PK samples, and the centralised nature of population PK's with very few qualified healthcare professionals. To address the challenges of AMR and rapidly improve the use of antimicrobials in clinical practice, urgent validation of novel methods for precision prescribing and delivery of antimicrobial agents is required. However, before steps can be taken to develop methods for improving the precision prescribing and delivery of antimicrobial agents the size and breadth of the problem must be clearly described.

2. STUDY OBJECTIVES

Given the paucity of data to support the need for individualised TDM and dosing strategies outside of critical care we aim to:

1. To describe the current level of success of beta-lactam dosing across secondary care pathways in terms of attainment of target drug levels
2. To investigate the potential role of therapeutic drug monitoring for optimising the use of beta-lactam agents in secondary care
3. To use data generated through this study to develop a concept for novel methods for the therapeutic drug monitoring and precision delivery of beta-lactam agents

These aims will be achieved through addressing the following:

1. Describing the current state of PK-PD target attainment for beta-lactam agents across secondary care to highlight populations most in need of intervention
2. Evaluate the role of beta-lactam TDM in different secondary care settings including impact on the patient, prescriber, and hospital (economic evaluation).

3. STUDY DESIGN

3.1 STUDY PARTICIPANTS

(Applicable for all objectives)
Inclusion and exclusion criteria can be found below (**section 4**)

- Participants receiving oral or intravenous therapy will be included in this study.
- Drug level sampling will be undertaken once the participant is at steady state (after at least 4-5 doses have been administered to those on treatment).
- All patients will be consented using the participation information leaflet and consent form provided in **appendix 1**.

3.2 DRUG LEVEL SAMPLING

- Patients will be identified for inclusion, and researchers will discuss inclusion in the study with the patient and provide clinical information for them to consider. Individuals will be recruited from all areas of secondary care (including, general medicine, general surgery, augmented care, and out-patient parenteral antimicrobial therapy (OPAT).
- They will then be consented by researchers after being given at least 24 hours to consider this information and as long as the patient has expressed interest in participating to their treating physician.
- This will include permission for basic, anonymized demographic and clinical data to be collected related to the patients infection, for which they are receiving antimicrobial therapy (appendix 2).
- An extra 3mls of blood will be collected during the patient's routine daily phlebotomy round following their consent. They will be enrolled for up to 72 hours or two days of routine blood tests (whichever is shorter). Up to 10 samples may be taken during the 2 days the patient is enrolled, depending on the number of routine blood tests the patient receives during that day. No more than 3mls will be taken per each routine blood sample. For example, if the individuals will only have routine blood tests taken at 8am on day 1 and day 2. Then only two extra samples will be taken (3mls on D1 and 3mls on D2).
- The time they received their dose of antimicrobials, the length of infusion time (if available), and time the sample was collected will all be recorded.
- PK/PD indices for evaluation will be calculated post-hoc during pharmacokinetic-pharmacodynamic analysis. TDM sampling can occur at any time during the dosing schedule (in line with routine blood testing).
- A standard operating procedure for this study can be found in appendix 3.

3.3 SAMPLE PREPARTION AND ANLYSIS

- All blood samples will be allowed to clot and placed on ice. They will be centrifuged at 2,400rpm for 10 minutes. Sera from each sample will be separated into three vials and stored at -80^{0}C.
- Beta-lactam concentrations will be measured using validated high-performance liquid chromatography methods.
- Samples will be stored for up to three years post completion of data collection.
    - Consent will be gained for samples to be used for calibration of electrochemical sensors in ex-vivo studies. This will be performed within 90 days of the samples being collected.

3.4 PHARMCOKINETIC-PHARMACODYNAMIC MODELLING

- Data will be anonymized and analyzed using Pmetrics in R.
- Different pharmacokinetic models will be explored using in built statistical analysis options and visual predictive checks.
- Pharmacodynamic models will then be incorporated into the model using evidence identified in the literature for selection of parameters.
- Monte Carlo simulation will then be used to for simulation of target attainments and analysis of pharmacodynamic outcomes

4. PARTICIPANT ENTRY

4.1 INCLUSION CRITERIA

- Adult subjects over 18 years old
- Capacity to consent to participation
- Receiving target antimicrobial for at least 5 doses prior to sampling.
    - Amoxicillin (oral / IV)
    - Co-amoxiclav (oral / IV)
    - Tazocin (IV)
    - Flucloxacillin (oral / IV)
    - Cefuroxime (oral / IV)
    - Ceftriaxone (oral / IV)
    - Meropenem (oral / IV)
- Appropriate venous access (or for venous access to be gained)

4.2 EXCLUSION CRITERIA

- Children under 18 years old
- Lacking capacity or prisoner
- Anaemia or bleeding disorder, deemed significant by the patients physician
- Patients physicians deems that they are not suitable for inclusion in the study
- Patient unlikely to be receiving agent for study period

4.3 WITHDRAWAL CRITERIA

Subjects will be able to withdraw at any time point during the study with immediate effect.

Researchers will be able to withdraw participants for any reason that may make the results of the study void or put the participant at risk of unacceptable harm or discomfort (including failure of cannula / poor venous access, alteration of the individuals antimicrobial treatment by the treating physician).

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.2.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.2.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to non-infective consitions and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Bromley - REC where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Fax: 0208383394,
Urgent attention Prof A Holmes
Tel: 02033132732 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

- All subjects will be consented and assessed by a GCP certified researcher before inclusion in the study (**appendix 2**).

7. STATISTICS AND DATA ANALYSIS

- On enrolment to the study participants will be given a study number, under which all data will be collected. Any identifiable data (such as enrolment list) will be kept within Imperial College Healthcare NHS Trust firewall on secure account. All anonymised data will be analysed and stored on a computer within Imperial College computer network.
- Signed consent forms will be stored in a locked filing cabinet in a security card accessible room on either the North Admin Block, 2nd Floor, Room N205, MIC Research Nurse Offic3 or the 7th floor of the commonwealth building, Hammersmith Hospital campus. Only researchers will have access to this.
- Plasma samples will be stored in a minus 80 freezer on the 8th floor of the Commonwealth Building, Hammersmith hospital, before being transported for analysis at the School of Medicine, St Mary's hospital or Bristol Antimicrobial Assay laboratory. All samples will only contain patients study number (i.e. no identifiable information).
- Statistical analysis will be performed using SPSS statistical software and Pmetrics in R, where appropriate.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator is obtaining approval from the Research Ethics Committee and the HRA. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

This study protocol and SOP has been reviewed by the MHRA and deemed to not require registration as a Clinical Trial of an Investigational Medicinal Product (CTIMP) – **Appendix 4**.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and at least 24 hours has been allowed to decide upon participation. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. If participants were to lose capacity at any point during the study they would be withdrawn. However, they will be consented for samples and data collected up to this time point to remain a part of the study.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Participants data will be anonymised and given a study number on enrolment. Participants will have the option to provide a contact address / email address to be contacted with updates of research outputs. This will be stored on an encrypted database on the lead researchers Trust account within the Imperial Healthcare NHS Trust firewall.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

National Institute for Health Research Invention for Innovation Product Development Award
Imperial College EMBRACE pump priming award
Imperial Biomedical Research Centre, Infection Theme
Merieux Research Grants

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

Project oversight meetings will be held once a quarter. This will consist of the principal investigators, the patient representatives, the project personnel as costed on the grant, the named individuals not costed but participating in the project.

10. PUBLICATION POLICY

The methods and results from this study will be presented at national and international conferences to both infection and patient safety specialists who are researchers and decision makers. Targeting of these specific groups in disseminating the research findings will allow not only engaged and productive feedback, but is also likely to generate further questions and raise awareness of the product as a resource for wider adoption.

High impact peer reviewed publications will arise from this research evaluation, enabling wider engagement of researchers in this subject. Open-access fees have been included in the research costs requested, against four high impact journals to enable the widest possible dissemination of the findings.

12. APPENDICES

APPENDIX 2

MRN Number:
Date:

Issues:

Enrolled Yes /No:

ADMINISTRATION:

Photocopy consent form: ☐
File original consent form: ☐

Review performed by:

PRINT NAME:.....

SIGNATURE:.....

DATE:.....

FOR COMPLETION ONCE RESULTS ARE AVAILABLE:

This subject meets all inclusion and exclusion criteria: ☐Yes ☐No

Eligibility confirmed by:

PRINT NAME:.....

SIGNATURE:.....

DATE:.....

Occupation:

E-mail address (optional):

GP Name/Address/Telephone No (optional):

Ethnicity:

WHITE	
British	☐
Irish	☐
Any other White background	☐
BLACK OR BLACK BRITISH	
[illegible]	☐
[illegible]	☐
Any other Black	☐
ASIAN OR ASIAN BRITISH	
Indian	☐
Pakistani	☐
Bangladeshi	☐
Any other Asian background	☐
OTHER ETHNIC GROUPS	
Chinese	☐
Any other ethnic group	☐
Please [illegible] _____	
I do not wish to disclose my ethnic	☐
MIXED	
White & Black Caribbean	☐
White & Black African	☐
White & Asian	☐
Any other mixed background	☐

Previous research participation including dates?

Donated blood during the preceding 3 months or intention to do so before the end of the study?

Current medical conditions:

Past medical history:

Drugs (inc. Prescription, OTC, vitamins,OCP):

Allergies:

Available microbiology / clinical information:

Height: ..... metres **Pulse:** ..... bpm

Weight: ..... kg **BP:** ..... mmHg

BMI: ..... kg/m^2 **Temp:** ..... °C

Central venous access available:

☐Yes ☐No

Appropriate for use in study: ☐Yes ☐No

Discussed with patient: ☐Yes ☐No

Discussed with physician: ☐Yes ☐No

VEINS (a pink cannula is required for this study)

Antecubital fossae?

Right: Left:

Dorsum of Hand?

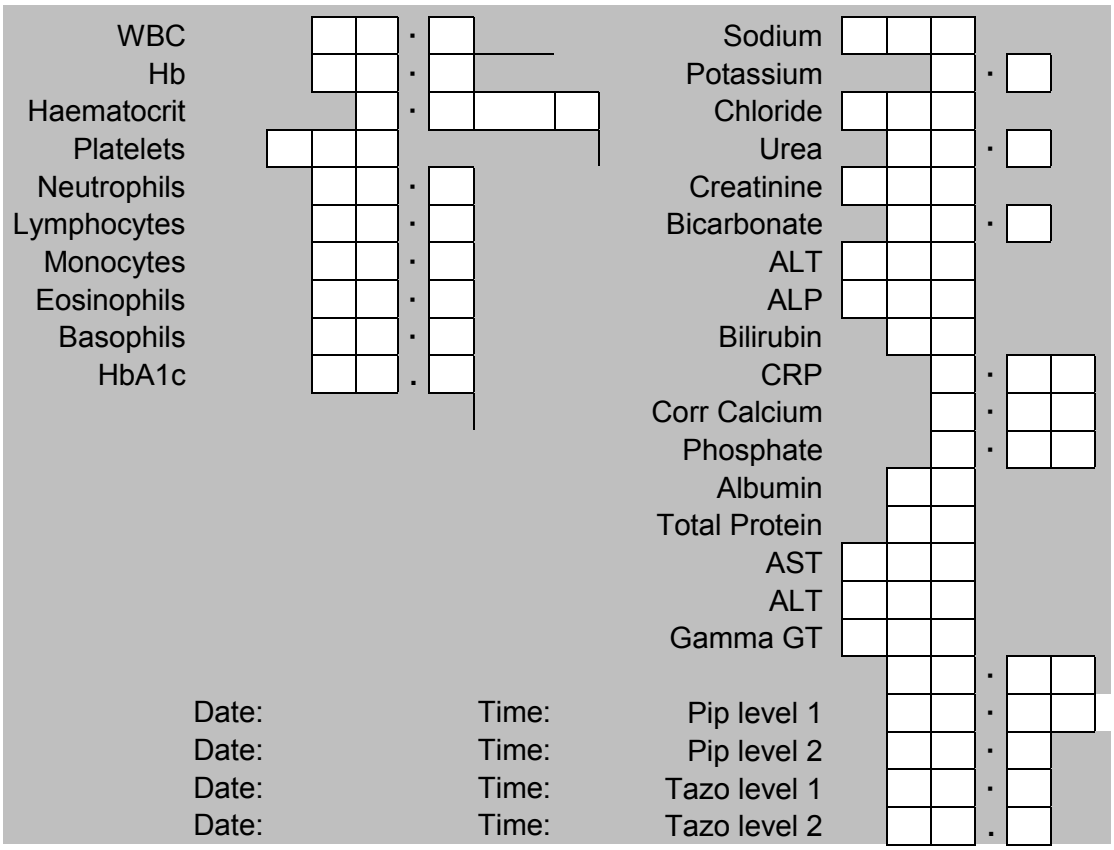
Right Left:

Access will be (please delete): EASY / POSSIBLE / DIFFICULT

URINE TESTS:

Spec. gravity		.			
pH		.			
Glucose					
Protein					
Blood					
CrCL					

CLINICAL LABORATORY TESTS:



Swab taken:
Time: _____ For repeat: Time/date:
Site: _____ Person ☐ Post ☐

Swab taken:
Time: _____ For repeat: Time/date:
Site: _____

Swab taken:
Time: _____ For repeat: Time/date:
Site: _____

Swab taken:
Time: _____ For repeat: Time/date:
Site: _____

APPENDIX 3

Point Prevalence of Beta-lactam - SOP

1. Give Participant Information Sheet allow up to 24 hours to read
2. Discuss information sheet with patient, allow to ask questions, and if happy perform consent
3. Complete page 2, 3 & 4 of study proforma
4. Identify time for plasma sampling with medical team
    a. Liaise with medical team re. next scheduled time for routine plasma sampling
    b. Select co-ordinate with routine phlebotomy in conjunction with medical team

Upon day of sampling

5. Check weight, height and recorded observations on routine clinical observations chart.
6. Briefly explain study, allow to ask questions
7. If happy to proceed – proceed
8. Go through page 3, 4 & 5 of medical screening proforma.
9. Bloods collected during routine phlebotomy (see below):

Tube required	**Test**
PRN	Routine tests as required by clinical team
Gold top	Drug level sample

All routine bottles should be sent by pod to the lab as per routine blood tests normally are.

10. Gold top TDM sample should be left to clot and placed on ice until frozen

Once gold top TDMsample has clotted

11. Samples spun down at 2400 RPM for 10 minutes in the centrifuge
12. Aliquot plasma into three separate vials
13. Freeze at minus 80^0C until shipment to laboratory for analysis

Repeat on following day / dosing schedule that co-insides with routine sampling

APPENDIX 4

Mon 08/08/2016 09:51

Clinical Trial Helpline <ctdhelpline@mhra.gsi.gov.uk>

RE: SCOPE: Protocol Review - beta-lactam drug levels across secondary care

To Rawson, Timothy Miles

Follow Up. Start by 15 August 2016. Due by 19 August 2016.

Notification that a Clinical Trial Authorisation (CTA) is not required

Dear Mr Rawson

Thank you for your email dated 19 July 2016 and apologies for the delay in responding to you until now.

I can confirm that your proposal is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC and no submission to the Clinical Trials Unit at the MHRA is required.

Kind regards

Clinical Trial Helpline

MHRA

Medicines & Healthcare products
Regulatory Agency