Minimally invasive sensing of beta-lactam antibiotics

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SPONSOR: Imperial College London
Joint Research Compliance Office,
Room 215, Level 2, Medial School Building, Norfolk Place,
W12 1PG
T: 0207 594 1872

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

NRES REF:

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Protocol authorised by:

Name & Role	**Date**	**Signature**
(Chief Investigator)		
(Sponsor)		

Chief Investigator:

Prof Alison Holmes

Co-investigators:

Prof Tony Cass

Dr Pantelis Georgiou

Dr Danny O'Hare

Dr Timothy Rawson

Dr Pau Herrero

Dr Sanjiv Sharma

Dr Sally Gowers

Dr Michelle Rogers

Mr Mark Gilchrist

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:

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

Tel: 020 33132732

Fax: 020 8383 3394

Email: head.ops@imperial.ac.uk

Clinical Queries

Clinical queries should be directed to Dr Timothy Rawson (tmr07@imperial.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, W12 1PG

Tel: 0207 594 1872

Funder

Imperial Biomedical Research Centre, Institu Merieux Research Grants, EPSRC EMBRACE pump priming award.

This protocol describes the IC REACT 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.

CONTENTS

GLOSSARY OF ABBREVIATIONS

POC	Point of care
DSS	Decision support system
AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
PCA	Principle component analysis
PPI	Patient and public involvement
AE	Adverse event
SAE	Serious adverse event
PIL	Participant involvement leaflet

KEYWORDS

Antimicrobial resistance

Closed-loop control

Microneedle array

Pharmacometrics

STUDY SUMMARY

TITLE	Minimally Invasive Sensing of Beta-Lactam Antibiotics
DESIGN	Evaluation of a microneedle array device for the monitoring of beta-lactam antibitocs
AIMS	Evaluate the effectiveness of a minimally invasive microneedle biosensor for monitoring antibiotic concentrations in humans.
OUTCOME MEASURES	1) To investigate whether a microneedle biosensor can be used to monitor beat-lactam antibiotic concentrations in humans
POPULATION	(i) Healthy volunteers
DURATION	2 years

1. INTRODUCTION

1.1 BACKGROUND

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 [1].

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 [2]. 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 [3]. 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.

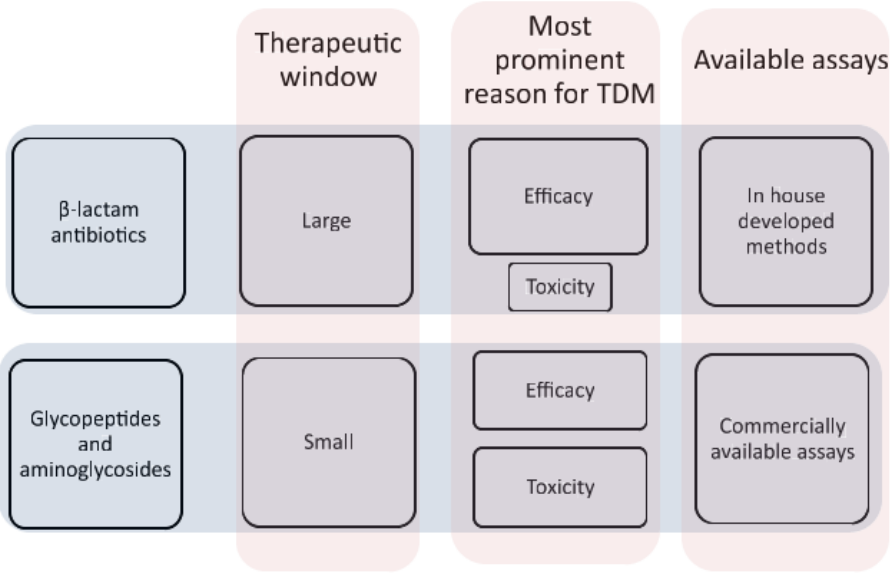


Figure. Concepts of therapeutic drug monitoring between different antimicrobial agents

From: J. A. Roberts *et al 2010*

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 [5]. 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). 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.

1.2 RATIONALE FOR CURRENT STUDY

Bacteria and other microorganisms can cause infections in people outside of hospitals and also among patients admitted to hospital. The antimicrobials (drugs that kill or stop the growth of microorganisms including bacteria, thereby treating infections) commonly used to treat infections are becoming less effective over time as bacteria develop resistance to them. Antimicrobial usageage itself can leads to development and spread of antimicrobial resistance.

Antimicrobial resistance is now a major threat to patient safety - increasingly we are seeing patients infected with bacteria for which there are very few antimicrobials that remain effective. If untreated, these infections can be fatal in some patients. To conserve the effectiveness of antimicrobials we need to develop ways to use them more effectively. One way to do this is ensure that we are providing the best dose (amount of drug) of an antimicrobial to kill the organism causing infection, whilst also ensuring that we don't cause toxic side effects or promote the growth or antimicrobial resistance through giving too much or too little of a treatment.

Currently we give most antibiotics in a (almost) one-size-fits-all way. However, everyone is different. This includes how our bodies process and excrete antibiotics. This can even change for the individual depending on how unwell you they are. There is evidence that shows that our current approach to giving antibiotics means that some people are not treated effectively, potentially leading to development of antimicrobial resistance, side effects, or even failure or treatment.

We aim to investigate a small sensor that sits just beneath the skin to detect the amount of antimicrobial within a patient's body. By linking this to a computer dosing algorithm we can adjust the amount dose of antimicrobial given to a patient ensuring that we give the optimal amount to kill bacteria, whilst preventing any of the harmful consequences that may occur due to inappropriate therapy.

Microneedle technology was developed in the 1980's. Since then it has been applied to a number of different fields, including for the sensing of glucose levels in patients with diabetes as well as a mechanism for drug and vaccine delivery.

Despite this, its role for the monitoring of antibiotic concentrations in patients has never been explored. Below the initial layer of the skin is an area called the dermal interstitial compartment. This compartment does not have blood vessels or nerves, but does contain interstitial fluid. This interstitial fluid is in equilibrium with capillary blood, meaning that it contains metabolites, proteins and drugs within the patients system. This includes antibiotics. This offers an opportunity to be able to detect the concentration of antibiotic within the interstitial fluid without having to take blood samples from the patient. Evidence provided by Roberts and

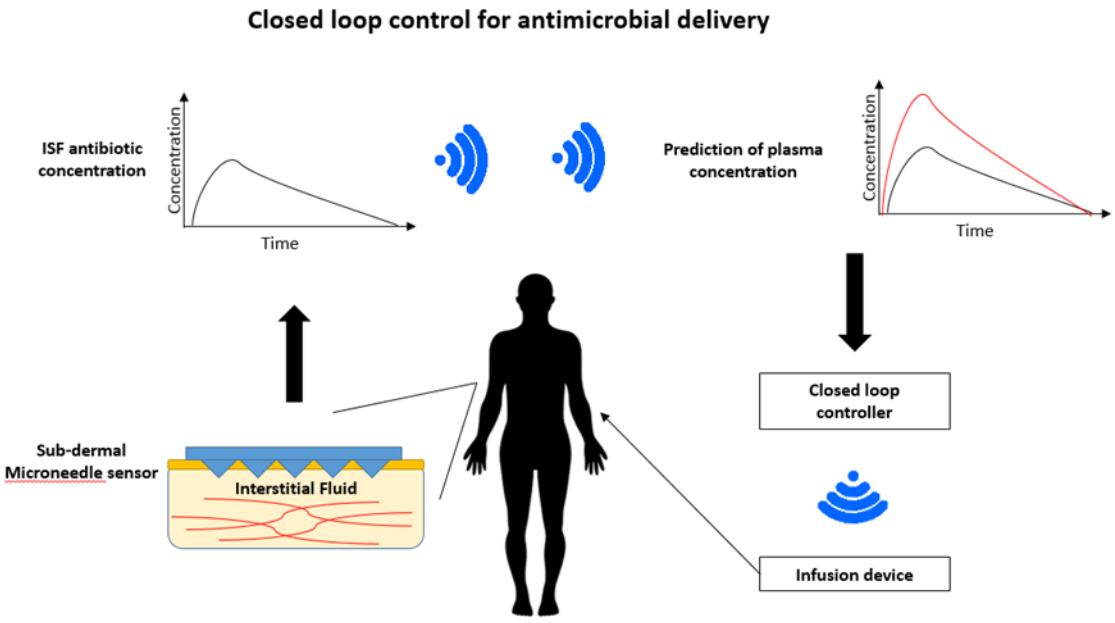
colleagues already supports the mirrored PK profiles observed between free antibiotic levels in both the plasma and extra-cellular compartment (evaluated using microdialysis).

At Imperial College, we have developed a number of microneedle biosensors based on enzyme and aptamer based technology, that are able to detect changes in antibiotic concentrations at the levels expected in the interstitial fluid. This has been validated in the laboratory and is now ready for testing in human participants. The specific microneedle structure has been tested in healthy volunteers and type 1 diabetics as part of a separate study monitoring glucose. It has been demonstrated to be safe and effective.

This study aims to test the ability of a sensor that can monitor beta-lactam antibiotic concentrations in participants who will be given a beta-lactam antbiotic as a proof-of-concept and to allow further refinement of the sensor before progressing to test it on patients. commercial antimicrobial assays; and limited clinical data to support dose changes based on certain targets for therapy (such as trough levels or pharmacokinetic - pharmacodynamic indices).

To address these problems a potential solution is to explore the use of minimally invasive biosensors linked to closed loop control systems, which will be addressed during this research study. This follows evidence supporting the equilibrium on free antimicrobial drug PK between the plasma and interstitial fluid, which may allow for tracking plasma PK.

This study aims to translate an antibiotic biosensor, mounted on a microneedle device that has been demonstrated as safe and effective in previous human studies in diabetes. Demonstration of efficacy will allow this to be linked to a closed loop control system in the future. This has already been demonstrated to be effective in delivery of insulin for the management of diabetes and for delivery of intravenous and inhaled anaesthetic agents.



2. STUDY OBJECTIVES

The principle objectives of this study are:

1) To investigate whether a microneedle biosensor can be used to monitor beat-lactam antibiotic concentrations in humans

The secondary objectives are:

(i) To determine the accuracy of an antibiotic microneedle biosensor compared to gold standard plasma drug concentration sampling.

3. STUDY DESIGN

This study is an in-house feasibility study of a microneedle biosensor and closed loop control algorithm developed within Imperial College London.

OUTLINE OF THE STUDY:

This study will comprise the recruitment of 10-15 healthy volunteers. They will be recruited to test the microneedle biosensors and undergo rich plasma sampling with or without tissue microdialysis to calibrate the microneedle biosensor and evaluate its accuracy against current gold standards (i.e. plasma drug concentration and tissue microdialysis).

This study will take place at Imperial College Clinical Research Facility

PATIENT IDENTIFICATION:

Healthy volunteers will be recruited from a healthy volunteer database held within Imperial College London and via identification of participants within the College. An initial advertisement email will be sent and individuals responding will then followed up by telephone and invited to attend a screening visit at the Imperial CRF. They will be sent the participant information leaflet in advance of this meeting to give them time to consider the information. At this visit a member of the research team will go through the study procedure and answer any questions that the participant has.

CONSENT PROCEDURE:

For healthy volunteers who wish to participate in the study after considering the participant information leaflet, a trained researcher will complete the eligibility screening and gain consent for the participant to be enrolled in phase I of the clinical study.

STUDY METHODOLOGY:

10-15 healthy volunteers will be invited to participate in an exploratory study of the sensor device. On their screening visit the patients full blood count, renal function, liver function, and C-reactive protein will be performed to ensure that the participant is not anaemic and has no evidence of current infection. Before the study day the participant will be required to take 5 doses of oral penicillin to ensure that they are at steady state and to allow for stabilization of tissue distribution.

On arrival at the study centre the participant will have a microneedle biosensor sited for upto 12 hours.

The sensor will be sited peripherally (on an arm or leg). In a small number of cases the sensor may be sited centrally on the torso. These sensors are connected to potentiostat devices that record data, which can then be downloaded onto a computer for analysis.

Following arrival on the study day and placing of the sensor devices, a cannula will be sited for phlebotomy and a baseline beta-lactam antibiotic concentration will be taken.

A microdialysis fibre will also be inserted peripherally into tissue close to the microneedle device.

Once baseline samples have been collected the participant will receive a final dose of penicillin.

The participant will then undergo rich plasma drug concentration sampling with up to 15 further blood tests taken over a 6-12 hour period. Each blood test will involve the collection of 3ml extra blood (1 teaspoons) via a cannula which will be cited on commencement of the study. Microdialysis may be performed in a number of cases as a gold standard for determining tissue drug concentrations. Participants will also be required to complete a visual analogue scale every hour testing their level of discomfort due to the microneedle sensor device.

Time points for the blood sampling are planned to initially be taken at (0, 15, 45, 30, 60, 90, 120, 150, 180, 210, 240, 360, 480, 600, 720 minutes). However, following initial PK analysis a D-optimal design will be employed using pmetrics and bestdose pharmacokinetic software to determine the optimal time points for blood PK analysis.

Clinically relevant data including demographic, co-morbidity, and medication data will be collected by members of the research team from the participant.

SAMPLE ANALYSIS:

All blood samples will be put straight on ice following draw and aimed to be spun down and frozen within 2-3 hours of collection. Samples should be allowed to clot for 15-20 minutes and then centrifuged at 2,400rpm for 10 minutes. Serum from each sample will be separated into two to three vials and stored at -80^{0}C. These will be stored on the 8th floor of the Commonwealth Building at Hammersmith Hospital Campus.

Beta-lactam concentrations will be measured using validated high-performance liquid chromatography methods.

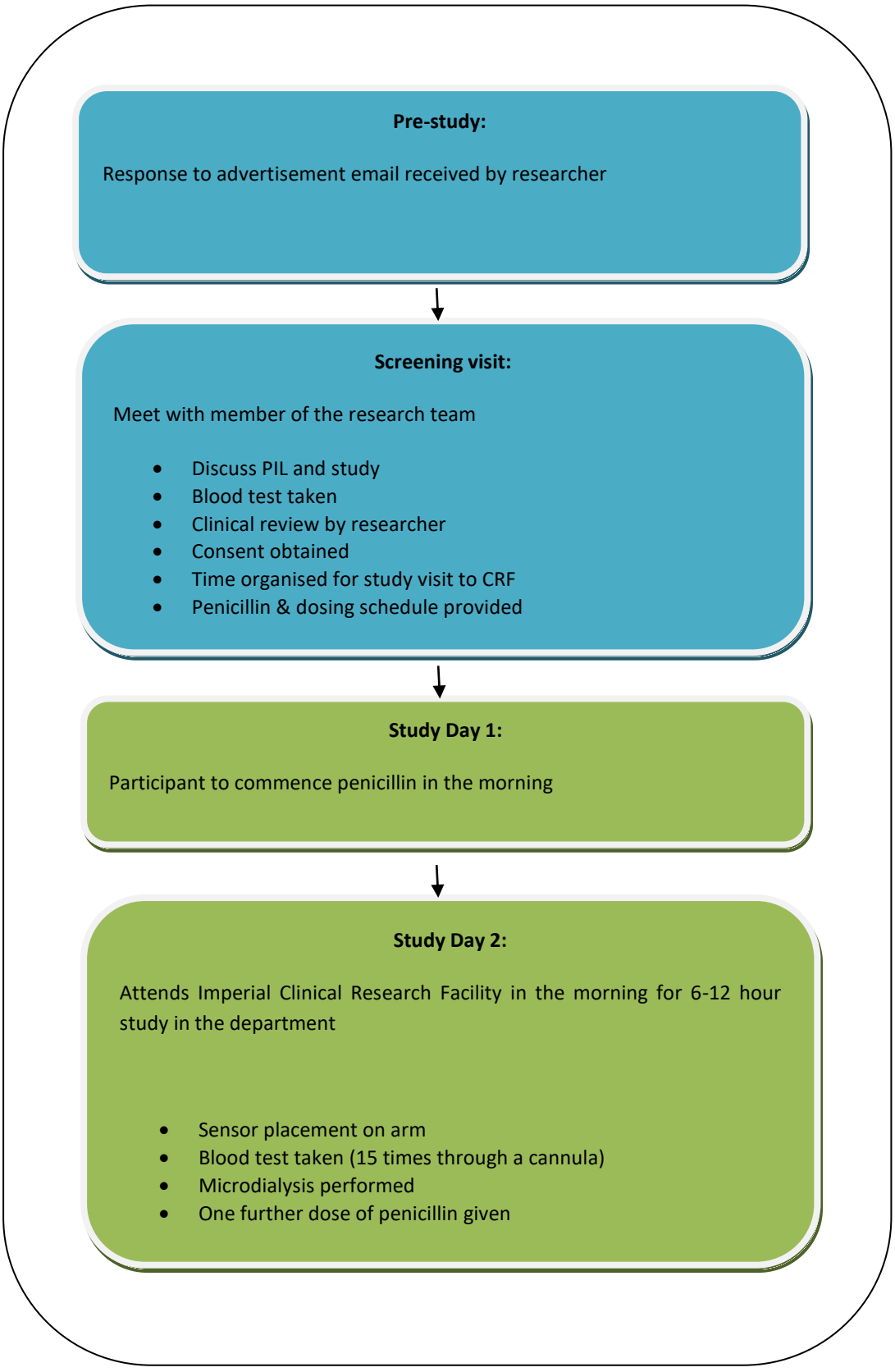
Consent will be gained for samples to be used for calibration of electrochemical sensors in ex-vivo studies. Ideally primary analysis for the study should be completed within 90 days of collection.

PENICILLIN PRESCRIBING

Upon prescription of penicillin for the study, this will be provided by the pharmacy department at Imperial College Healthcare NHS Trust. In advance of the study, the finalized ethics and study protocol will be provided to the pharmacy department for approval.

Upon enrollment of participants into the study a prescription will be written for penicillin by a physician within the research team, who has assessed the patient for inclusion in the study and obtained consent. This will then be dispensed by the pharmacy department.

Summary of study participation



4. PARTICIPANT ENTRY

4.1 RECRUITMENT

Healthy volunteer identification:

An email will be sent advertising the project to a healthy volunteer database kept within Imperial College. Furthermore, this email will be circulated internally within the college. If volunteers express an interest they will then be contacted by a member of the research team by phone to arrange a screening meeting. At the same time a copy of the patient information leaflet will be emailed to the volunteer to allow them time to consider the information prior to the screening visit.

4.2 INCLUSION CRITERIA

HEALTHY VOLUNTEER INCLUSION CRITERIA

- Adult >18 years old
- Healthy adults, with no evidence of active infection
- Previously received penicillin with no adverse effects

4.3 EXCLUSION CRITERIA

HEALTHY VOLUNTEER EXCLUSION CRITERIA

- High risk of skin soft tissue infection or local skin and soft tissue infection near sensor site
- Previous history of allergies to adhesive strips or active dermatitis
- Penicillin allergy or previous adverse event whilst receiving penicillin
- Anaemia defined as <13 g/dL in males and <12 g/dL in females

4.4 WITHDRAWAL CRITERIA

Patients can withdraw at any point during the study without being required to provide reason for this.

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 pre-existing conditions and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the London-Harrow Regional Ethics Committee 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 within 24 hours of becoming aware of these.

Contact details for reporting SAEs

Fax: 0208383394,

Urgent attention Prof A Holmes

Tel: 02033132732 (Mon to Fri 09.00 – 17.00)

Sponsor office: attn Gary Roper

Email: JRCO @imperial.ac.uk

6. ASSESSMENT AND FOLLOW-UP

Patients will not be followed up beyond the five day study period described.

7. STATISTICS AND DATA ANALYSIS

For quantitative evaluation: The sensor calibration will be undertaken by members of Imperial Biomedical Engineering department who have extensive experience of biosensor development and calibration. Pharmacokinetic analysis will be undertaken by Dr Rawson using pmetrics, within R.

Storage: Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period. Participant consent forms will be kept in a locked cabinet within a locked room on the 7th floor of the commonwealth building. Only researchers and those with clearance to perform regulatory audits of research procedures will have access to this

Anonymised data will be stored on an Imperial College networked computer within the firewall. This will be accessible to researchers only.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator is obtaining approval from the Research Ethics Committee and 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.

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.

8.3 CONFIDENTIALITY

Patient Identifiable Data from clinical and laboratory databases will only be accessed within the host NHS Trust firewall after the clinical team user has passed their Lightweight Directory Access Protocol (LDAP) authentication. Anonymised data will be analysed on an Imperial College London networked computer. Any data used for analysis outside of the firewall will be fully anonymised by recording it against the participants unique participation number.

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

Imperial College Biomedical Research Centre (BRC) (£260,000) and Institu Merieux Research Grants (Euro 100,000) have funded this research project.

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

The Chief Investigator will be responsible for overall study oversight. They will chair a formal project oversight meeting once a quarter. The meeting will act to iteratively monitor project progress against the key deliverables and outcome measures, plan all future steps and identify any potential issues including the creation of intellectual property and the best methods for dissemination and communication of research and product outcomes.

On a day to day basis the project will benefit from management by the Head of Operations within HPRU who is experienced in integrating the workflows of the multi-professional teams from the collaborating Centres.

The study PI (AH) has an established collaboration with parallel managed teams in the fields of healthcare and bio-technology. The project will be subject to the usual management practices within the groups, meaning that updates of progress will be required at work-stream meetings within HPRU and wider work-inprogress meetings at Imperial College London.

10. PUBLICATION POLICY

The methods and results from the evaluation of the closed loop system 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. A key emphasis will be placed on highlighting both the barriers and the facilitators towards project completion, and on the impact of the product on antimicrobial prescribing, patient outcomes and antimicrobial resistance. The impact on patient outcomes will focus on both individual level outcomes, but also look at the wider perspective of the impact of the product on the patient pathway.

High impact peer reviewed publications will arise from this research evaluation, enabling wider engagement of researchers and decision makers. 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.

11. REFERENCES

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