EPIC IMPOC

Enhanced, Personalized and Integrated Care for Infection Management at Point of Care

V9.0 25/10/2016

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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:

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This protocol describes the EPIC IMPOC 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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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
Decision support system
eHealth
mHealth

STUDY SUMMARY

TITLE	Enhanced, Personalized and Integrated Care for Infection Management at Point of Care (EPIC IMPOC).
DESIGN	Development, and prospective mixed methods evaluation, of a medical (software) device
AIMS	Development, validation and ascertainment of the effectiveness of a point-of-care decision support system (POC DSS; i.e. a piece of advisory software accessible by clinicians on mobile devices) for infection management (i.e. antimicrobial prescribing) for secondary care inpatients.
OUTCOME MEASURES	1) Development of the POC DSS. 2) Improved understanding of decision making in antimicrobial prescribing in secondary care. 3) Development of a pharmacokinetic/ dynamic and therapeutic drug monitoring (TDM) software module. 4) Development of a patient engagement module. 5) Evaluation of the implementation of the product and its impact on antimicrobial prescribing behaviour. 6) Evaluation of the impact of the product on antimicrobial prescribing practice and antimicrobial resistance.
POPULATION	(i) Healthcare professionals, (ii) Patient and public representatives, and (iii) Patients with infections, at Imperial College Healthcare NHS Trust
DURATION	3 years 6 months

1. INTRODUCTION

1.1 BACKGROUND

Antimicrobials (drugs that kill or stop the growth of microorganisms including bacteria, thereby treating infections) commonly used to treat patients with infections are becoming less effective over time as bacteria develop resistance to them. Antimicrobial usage itself can lead to development and spread of antimicrobial resistance. Antimicrobial resistance is now a major threat to patient safety. To conserve the effectiveness of antimicrobials we need to develop ways to use them more sensibly healthcare professionals who diagnose and treat infections must be able to access antimicrobial guidelines and test results at the patient bedside. This needs to be provided rapidly and with support to make sure that the decisions on prescribing antimicrobials are the best that can be made.

Prototype software to achieve this has been developed through collaboration between healthcare professionals and biomedical engineers. This prototype software (run on a mobile device) retrieves patient results from various laboratory and clinical databases (securely within the Trust firewall) and displays this to the clinician making the prescribing decision. Furthermore a machine learning algorithm is applied to the data, and similar anonymised historical cases (and the antimicrobials prescribed and the clinical outcomes) are also displayed to the clinician to further inform their decision making. The prototype has been designed for use in intensive care, where the risk of infection is high, but through the research project detailed here, the software will be developed and validated across other areas of hospital patient care. Furthermore there is a key need to engage patients with how decisions are made around antimicrobial prescribing. We propose to adapt the prototype to meet these needs. This system should improve patient safety and help preserve the effectiveness of existing antimicrobials.

1.2 RATIONALE FOR CURRENT STUDY

Antimicrobial resistance is a major UK public health threat and optimising antimicrobial prescribing is a high impact intervention to combat this. Policies and guidelines play a central role in such optimising of antimicrobial prescribing [Charani et al, Infect Dis Clin North Am.2014;28(2):169176]. Strategies to control antimicrobial resistance to date have focused on the interrelated elements of ‘prudent’ antimicrobial use, surveillance, and infection control. In pursuit of ‘prudent’ antimicrobial use, a balance in antimicrobial spectra advocated in policies must be achieved to ensure care for the patient, but not exert unnecessary pressure toward generation of resistance. However, an implementation gap exists between policy and practice, and the social elements inherent in antimicrobial prescribing create a need for innovative methods to influence antimicrobial prescribing at point of care. An additional factor contributing to broad spectrum antimicrobial use is uncertainty around the antimicrobial resistance of the causative organism in any given patient, particularly during the early phase of infection management. Advances in rapid diagnostics may, in the near future, decrease this window of uncertainty, but the mechanism for feeding back these results to point of care needs clarification. We have successfully developed a prototype point-of-care decision support system (POC DSS) which is about to be deployed for use at the bedside in critical care which addresses these issues. The prototype runs on a mobile tablet, drawing patient data from NHS servers and utilizes case based reasoning (CBR) artificial intelligence to aid clinician decision making when prescribing antimicrobials. This POCDSS may play a key role in integrating systems and results such that antimicrobial policies, stratified to individual patients with timely microbiology results, can realise ‘prudent’ antimicrobial use.

This novel product builds on: 1) our innovative work integrating antimicrobial policies into patient care pathways through mobile platforms [Charani et al, J Antimicrob Chemother. 2013;68(4):960967]; 2) our seminal work on understanding prescribing etiquette [Charani et al, Clin Infect Dis. 2013;57(2):18896]; and 3) our extensive experience in bioinspired circuits

and systems [Herrero et al, J Diabetes Sci Technol. 2012;6(3):60616; Herrero et al, J Diabetes Sci Technol. 2012;6(2):462465(A64)].

However, whilst critical care has a particularly high level of antimicrobial resistance, levels in other areas of secondary care are still significantly higher than in the community [Moore et al, J Antimicrob Chemother. 2014;69(12):340922]. There is therefore a need to develop the prototype, adapting it for use for clinicians prescribing antimicrobials for other secondary care inpatients. Furthermore there is a key need to engage patients with how decisions are made around antimicrobial prescribing. We propose to adapt the prototype to meet these needs. This system should improve patient safety and help preserve the effectiveness of existing antimicrobials.

Inherent in development of this decision support system is the need to evaluate its utility. This will require a mixed methods analysis, incorporating qualitative methods looking at implementation and impact on prescribing behaviour, and also quantitative methods looking at impact on prescribing practice, patient outcomes and antimicrobial resistance rates.

2. STUDY OBJECTIVES

1) Development of the POC DSS to support clinicians in providing personalised, optimised, antimicrobial management for secondary care patients outside of critical care.

2) Improved understanding of the decision making processes around antimicrobial prescribing in secondary care patient cohorts.

3) Personalisation of antimicrobial dosing to optimise therapy and minimise toxicity through a pharmacokinetic/dynamic and therapeutic drug monitoring (TDM) software module.

4) Engagement with patients in decision making around antimicrobial prescribing through a module for use within the POC DSS.

5) Evaluation of the implementation of the product and the impact on antimicrobial prescribing behaviour.

6) Evaluation of the impact of the product on antimicrobial prescribing practice and antimicrobial resistance.

3. STUDY DESIGN

This study relates to the development, and prospective mixed methods evaluation, of a medical device. The prototype POC-DSS has now been developed and is ready for in-house, proof of concept testing in the hospital setting.

3.1 STUDY AIMS & OBJECTIVES

The principle objective of this in-house proof-of-concept study is to develop, validate, and ascertain the effectiveness of a point-of-care decision support system (POC DSS); i.e. a piece of advisory software accessible by clinicians on mobile devices) for infection management (i.e. antimicrobial prescribing) for secondary care inpatients.

This builds on an already developed prototype targeted at infection management for patients in critical care. It targets improvement among clinicians in three areas: 1) personalisation of infection management through real-time adaptation of evidence based guidelines to cohort level antimicrobial resistance data and patient/drug/organism specific variables; 2) continuity through support for interpersonal communication; and 3) education during interactions between clinicians and infection specialists, and between doctors and patients.

The prototype has been modified so the software is usable for clinicians caring for other secondary care patient cohorts (i.e. specialties outside of intensive care) and two software modules have been added to; (i) further personalise antimicrobial dosing and,(ii) to enable clinicians to engage with patients regarding their antimicrobial therapy.

The secondary research objectives include:

1) Development of the POC DSS to support clinicians in providing personalised, optimised, antimicrobial management for secondary care patients outside of critical care.

2) Improved understanding of the decision making processes around antimicrobial prescribing in secondary care patient cohorts.

3) Personalisation of antimicrobial dosing to optimise therapy and minimise toxicity through a pharmacokinetic/dynamic and therapeutic drug monitoring (TDM) software module.

4) Engagement with patients in decision making around antimicrobial prescribing through an interactive, personalised information document for use within the POC-DSS. This will aim to facilitate improvements in doctor-patient communication during infection management.

5) Evaluation of the implementation of the product and the impact on antimicrobial prescribing behaviour.

6) Evaluation of the impact of the product on antimicrobial prescribing practice and antimicrobial resistance.

3.2 STUDY DESIGN

Phase 1: Infection specialist feasibility study

This initial pilot will follow a previously validated format, used to test the prototype POC-DSS in the intensive care setting. The primary aim of this phase is to ensure that the POC-DSS provides appropriate decision support advice in line with expert practice. Furthermore, each of the three core modules within the POC-DSS will be individually tested over a three-month period beginning in January 2017. This phase will be a mixed methods assessment involving both qualitative and quantitative methods. Participants will be identified based on their roles within the infectious disease team (level and areas of the hospital covered) and will be directly approached by the study PI / lead infectious diseases clinician and provided with the participant information documents if they are happy to consider participating with this phase of the project. Physicians will then be consented to participate by a member of the research team at least 24 hours after being provided with a participant information leaflet. They will be consented to participate in using the application during infection management rounds to support their decisions for antimicrobial prescribing in a range of clinical settings. They will also be consented to participate in providing feedback on the POC-DSS to help with iterative development and identification of any technical issues that arise. They will undergo a short 10 minute training session on the background of the study and the device.

Technical evaluation & review of the Case-Based Reasoning alorithm: Written and verbal feedback will be collected through regular micro-feedback physician interviews during the intervention period as well as researcher observation of the POC-DSS being used in clinical practice. This will initially occur at approximately 1-2 x per week with diminishing frequencies over time (as issues with the system are dealt with). Furthermore, evaluation of reported use and physician engagement will be compared to automated audit logs within the application, which allow us to track time spent using different sections of the device. This will facilitate identification of issues with the POC-DSS workflow, usability, and data acquisition compared to usual practice with normal hospital systems. Concordance of the suggested antimicrobial regime suggested by the CBR algorithm against expert opinion will also be assessed during this period using a recording feature within the device, based on a 5 point Likert scale as well as comparison with microbiology data, where available fpr comparison. They will be responsible for selecting patients that they deem as appropriate for use of the POC-DSS to manage infections. This will be assessed through:

Precision dosing / TDM module: A prospective pilot interventional study to demonstrate proof-of-concept and assess the potential impact that an iterative learning control (ILC) algorithm would have on the management of patients receiving vancomycin and amikacin therapy. This will be undertaken by members of the research team.

i. 20 patients receiving vancomycin & 20 patients receiving amikacin across secondary care for documented infections captured within the POC-DSS will have their data prospectively input into the ILC algorithm. These patients will be identified by infection clinicians during their usual practice as they use the POC-DSS. Consent will not be required as all data used by researchers will be anonymised before inclusion in this aspect of the study. If additional information not collected by the POC-DSS is required for this phase, a member of the patients clinical team will be responsible for collecting and anonymising this data before passing it onto the research team.

ii. Simulation will be performed to assess the potential impact of use of the ILC algorithm in the management of these patients. Dosing recommendations from the ILC algorithm will be compared to dosing in clinical practice to assess the potential impact on optimisation of therapy for these patients. This will then be tested under strict infection specialist supervision on the 40 patients identified in point i.

iii. Quality control checks will be undertaken during this period to assess the safe limits of operation of the ILC algorithm. This will ensure that all safety limits placed on the controller appear correct and that it recommends dosing within acceptable limits.

Patient engagement module evaluation: A pre-post interventional study aiming to assess the impact of the patient engagement module. This will use a mixed methods assessment taking place on the infectious diseases ward at Hammersmith Hospital comparing the engagement module to usual care. The aims are to assess the potential impact of the module on patient engagement with infection management, improve patient – physician communication about infections and their management.

i. Patients being managed for infections will be identified by their treating clinician and consented to be approached by a member of the research team to discuss the study in detail within 5 days of commencing antimicrobial therapy.

a. Their treating clinician will identify them as appropriate for inclusion in the study based on overall inclusion/exclusion criteria for the study and make the initial approach for potential participation in the study. If the participant is happy to by approached a member of the research team will then provide potential participants with detailed information leaflet and give them 24 hours to consider involvement in the study before consent is sought.

ii. Participants upon inclusion in the trial will be asked to complete a 15 minute pre-intervention questionnaire documenting understanding about their infection, its management and their perception of the information they have received regarding this. Questionnaires have been developed deductively based on patient and public involvement sessions, where the intervention was developed previously [Rawson et al., BMJopen, 2016].

iii. Following completion of the questionnaire, a researcher will go through the patient module with the patient as it would be used in clinical practice. The participant will be provided with the personalised health information sheet based on their clinical situation. A follow up session will be offered 24 hours after the information is provided to the patient.

iv. At the follow up session the participant will be asked to complete a post intervention questionnaire designed to quantify the immediate impact that the intervention has had.

v. Participants will also be able to opt to take part in a follow up face-to-face / telephone/ electronic / postal survey approximately 5-30 days after completing the post-intervention survey that will test their retention of knowledge surrounding the engagement module and usefulness of the intervention post discharge. The timing of this intervention will be based on iterative review of emerging themes / retention rates as well as convenience for the participant.

Data analysis and evaluation

During this phase, data analysis & evaluation will be iterative to allow constant refinement & re-testing of the POC-DSS. Furthermore, this will allow rapid identification of potential technical or safety issues allowing them to be dealt with urgently. All data will be reviewed monthly during this period at working group meetings and oversight will be provided by the group steering committee during this period.

Before progression onto phase 2 of the study clearance will need to be provided by the project steering committee, following demonstration of device safety in phase 1. If there are concerns about any modules within the POC-DSS, the steering committee may opt to remove them from further roll-out of the overall device, allowing the remaining modules to be trialled in phase 2. The Caldicott approval will also be reviewed at this stage if further portable mobile devices are required to be registered for use in the trial (as per Ref.726505)

Phase 2: Testing on selected specialty wards

This phase will pilot a quasi-experimental format on several selected specialty wards across Imperial College Healthcare NHS Trust. The intervention phase is planned to commence in April 2017 (with 3 months of data collection during usual care occurring prior to intervention). Pre-intervention data collection will be anonymously extracted in the same way that it will be collected by the POC-DSS during the intervention period. Any data beyond that which can be collected by this system will be extracted by a member of the clinical research team before being anonymised and passed on to the research team.

Participants (physicians) will be identified based on the wards that they work, as in phase I, in and will be approached by members of the research team to discuss whether they would be happy to participate in the trial. If they are interested a member of the research team will provide a participant information leaflet and organise a time to go through the details of the study in detail and obtain consent. This will be at least 24 hours after provision of the patient information leaflet.

Physicians will be consented to use the POC-DSS as part of their routine clinical practice, including the patient engagement module, to support their decision making for infection management (used at their discretion). They will also be asked whether they would consent to participating in face-to-face interviews exploring their experience of using the application as described below.

In April 2017, doctors for each of the 5 wards will be given a 10 minute introduction and instructions on the background of the study. They will also be provided with information sheets and asked whether they would be willing to participate in a stakeholder interview towards the end of their rotation.

A two-week implementation period will then follow to allow acclimatisation to using the device and any technical issues to be addressed. Three months of data collection will then ensue with the device being trailed in clinical practice.

i. Before the end of this period a number of participant semi-structured interviews will be conducted as well as a team focus group for each ward, to evaluate the POC-DSS.

ii. Quantitative data analysis will be performed as described above

iii. Patients who use the patient engagement module during routine consultations with their treating clinician may be identified by their treating physician and approached to take part in a 15-30 minute semi-structured interview to assess the impact of this module on their engagement with their infection and its management.

Data will regularly be reviewed on a monthly basis by the working group committee to highlight any technical or safety issues that may arise during the study period..

Data analysis

The research team have considerable experience in large dataset analysis of antimicrobial usage and antimicrobial resistance patterns and have established recourse to continual data for these two parameters from the Academic Health Sciences Centre. Near completion projects have developed surveillance tools to analyse these microbiology and pharmacy data sets for detailed geographical and temporal trends. Use of these data, combined with the database generated from the CBR algorithm, will be used to triangulate a quantitative analysis of the impact of the POC-DSS on prescribing patterns, patient outcomes and antimicrobial resistance trends.

Note: This phase is planned to run for 7 months (3 months pre-intervention, 1 month implementation and 3 months post implementation) in total. However, this may be extended to 12 - 18 months if it is deemed that further data collection is required to complete this proof-of-concept, in house study.

PLEASE NOTE:

EMAILS MAY BE USED TO RECRUIT PARTICIPANTS FOR QUALITATIVE EVALUATION OF THE APPLICATION (IF DETAILS AND CONSENT HAVE PREVIOUSLY BEEN PROVIDED DURING FACE-TO-FACE CONSENT AT RECRUITMENT). COPIES OF THE EMAILS THAT WILL BE USED FOR BOTH PATIENTS AND PRESCRIBERS CAN BE FOUND IN STUDY PROTOCOL V8.0. ALL IDENTIFIABLE CONTACT INFORMATION WILL BE KEPT ON AN ENCRYPTED SPREADSHEET WITHIN THE TRUSTS FIREWALL.

THE DIVISIONAL MANAGERS AND HEADS OF DEPARTMENT FOR SPECIALTIES WHERE PARTICIPANTS (PRESCRIBERS OR PATIENTS) MAY BE RECRUITED FROM WILL BE CONTACTED IN ADVANCE OF THESE PHASES BEING IMPLEMENTED TO ENSURE THAT THEY ARE HAPPY FOR THE STUDY TO TAKE PLACE WITHIN THEIR DEPARTMENTS/DIVISIONS.

Study outcome measures:

Derived from a systematic review of clinical decision support literature and using Delphi method with a multi-professional panel of experts. The feasibility of the device will be tested internally within Imperial College Healthcare NHS Trust in 2 stages.

Principle objective

The principle objective development and proof-of-concept of a point-of-care decision support system (POC-DSS) for enhanced, personalised infection management across secondary care.

- **Phase 1:**

    - **Primary outcome measures:**
        - Appropriateness of antimicrobial recommendations compared to microbiology confirmation/expert opinion.
        - Safe recommendations for dose optimisation of vancomycin and amikacin by the iterative-learning control (ILC) algorithm and improvements in therapeutic drug monitoring of these agents.
        - Evidence of improved patient engagement with infection management following use of the patient engagement module.

    - **Secondary outcome measures:**
        - Predicted rate reduction in interventions by the antimicrobial stewardship team if POC-DSS recommendations were followed.
        - Rate of IV-PO switching and appropriate de-escalation of therapy.
        - Economic evaluation of the POC-DSS versus usual care
        - Level of physician engagement with the POC-DSS

- **Phase 2:**

    - **Primary outcome:**
        - Appropriateness of antimicrobial recommendations compared to microbiology confirmation/expert opinion.
        - Rates of broad spectrum antimicrobial use (e.g. $3^{rd}/4^{th}$ Gen Cephalosporins. Piperacillin/Tazobactam, meropenem)
        - Rate of interventions required by antimicrobial stewardship team during control and intervention period
        - Economic analysis of the intervention

    - **Secondary outcomes:**
        - Enhanced patient engagement with infection management
        - Assessment of trends in AMR across all care pathways (including ICU)
        - Impact on length of treatment
        - Impact on 30 day mortality
        - Prescriber and non-prescriber engagement with the application
        - Number of medication adverse events
        - Assessment for unintended consequences of application use (quantitative and qualitative)

4. PARTICIPANT ENTRY

4.1 RECRUITMENT

Phase I & II - Patient recruitment:

To meet the evaluation component of patient engagement module, patients may be asked for permission to be approached by a member of the research team who will provide them with a participant information leaflet to participate in the qualitative evaluation of the the patient module in phases 1/2. The researcher will allow 24 hours for the patient to consider the PIL before discussing consent for participation in the study. During the consent phase the researcher will also offer the participant the opportunity to provide a contact email address to be contacted 5-30 days after completing use of the patient engagement module to undertake a further evaluation of the module by either telephone, survey (paper / electric), or face-to-face.

For patients for whom their clinician chooses to use the decision support system when making antimicrobial prescribing decisions, no consent is needed, in the same way as consent is not needed for when a clinician chooses to use any other resource when making a decision (reading journal articles, text books etc).Therefore patients who are deemed suitable will be selected by their treating physician.

For prescriber recruitment to use the application the following methods of identifying participants will be undertaken:

Phase 1: Participants will be identified based on their roles within the infectious disease team (level and areas of the hospital covered) and will be directly approached by the study PI / clinical infection lead to request their support with this phase of the project. They will be provided with a PIL and then approached after 24 hours by a member of the research team for consent in using the POC-DSS

Phase 2: Participants (physicians) will be identified based on the wards that they work in. The PI/Clinical lead will make an initial approach to provide participants with the PIL. A member of the research team will approach the potential participants after leaving 24 hours for consideration to discuss whether they would be happy to participate in participating in the trial. If they are interested the researcher will go through the details of the study in detail and obtain consent. Before this approach is made the project will be fully discussed and cleared with the heads of department and senior team members responsible for the wards in question. They will responsible for suggesting suitable prescribers from the ward selected for inclusion.

4.2 INCLUSION CRITERIA

(i) healthcare professionals for evaluation phases:
- Have read the PIL and consent to participate in the study

(ii) patients for whom the clinician chooses to use the POC DSS as a resource when prescribing antimicrobials:
- Adult patients > 18 years old
- Being managed for infection outside of the critical care setting in Imperial College Healthcare NHS Trust
- Deemed appropriate for management with POC DSS by attending physician
- Prescribed antimicrobial agents outside of the critical care setting in last 5 days

(iii) Prescriber / healthcare professional for using POC DSS:
- Trained Healthcare Professional
- Working within wards under assessment
- Deemed suitable for recruitment by senior member of their team

4.3 EXCLUSION CRITERIA

(i) healthcare professionals:

Do not wish to participate in the study
Working across wards which is acting as a control ward
Deemed no suitable for recruitment by a senior member of their team
Non-permanent member of the Trust
Information governance training not up-to-date

(ii) patients recruits

Critical care patients
Paediatric patients < 18 years old
Deemed not suitable for management using POC DSS by attending physician
On palliative care, end of life pathway
Prisoners / young offenders in custody of HM Prison Service
Involved in current research or have recently been involved in any research prior to recruitment (last 3 months)

4.4 WITHDRAWAL CRITERIA

If evidence of the unintended consequences noted below becomes apparent during the course of the study, particularly when interval analysis is reviewed at the oversight committee meetings, then consideration will be given by the oversight committee as whether the research must be suspended, modified or stopped prematurely. Furthermore the application may be withdrawn upon Identification of recurring technical faults, which have the potential to affect patient outcomes.

Scoping exercises conducted for the prototype theorise a range of unintended consequences including

(i) the potential for reduced diversity of antimicrobial prescribing,
(ii) the potential for data input error
(iii) the potential for erroneous artificial intelligence learning.

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.

If any cause for concern over an individual's clinical practice are identified during the course of data collection / analysis, the involved parties will be informed of this and information will be escalated to their line managers for further review of the incidents. This is outlined in the PIL document during the consent to participate procedure.

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 <name of 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

As described, quantitative and qualitative assessment of the device will be undertaken, which will incorporate prescribing data, antimicrobial resistance data, and patient outcome data. Patients will not be followed up beyond the last use of the POC DSS by the clinician using the device as a resource for prescribing. The exception to this will be when participants consent to undergo a follow-up interview between 5 and 30 days after being engaged with the patient engagement module of the device.

7. STATISTICS AND DATA ANALYSIS

For qualitative evaluation: Face-to-face interviews and surveys of clinical users of the POC-DSS will provide qualitative evaluation of the impact of CBR on antimicrobial choice. Data will be interrogated using thematic analysis and a conceptual framework developed to inform evolution of this POC-DSS, and to contribute to the wider debate on healthcare software development and integration into clinical practice. The multi-professional background and qualitative analytic skill set within the research group will facilitate a robust evaluation of impact. Furthermore, the research group has the considerable experience in technology roll-out to healthcare settings [Kyratsis et al, Implementation Science.2012;7:22, Charani et al, J Antimicrob Chemother.2013;68(4):960-7] and analysis of the implementation mechanism will benefit future translation of the product to the wider NHS.

For quantitative evaluation:
A phased implementation of the POC-DSS will be implemented to ensure that decision support provided is deemed safe and appropriate (outlines below in 7.1).
Phase 1: An initial pilot implementation of the POC-DSS will be performed via the Infection teams within the Trust. These teams are made up of infection specialists, who review between 30-50 patients a day across the hospital for infection related matters. This will allow use of the POC-DSS under supervision of expert prescribers to allow for expert feedback on the devices performance. This follows a model successfully trialled during the pilot of the POC-DSS in the intensive care setting. This phase is expected to run over approximately 3 months
Phase 2: The POC-DSS will be tested within specific subgroups of core specialties within the hospital Trust (e.g. general medicine, haematology, renal medicine, general surgery and care of the elderly) on selected wards. This will utilise a quasi-experimental interrupted time series design to evaluate the impact of the product on antimicrobial prescribing, patient outcomes and antimicrobial resistance trends over a 3 month period.
The research team have considerable experience in large dataset analysis of antimicrobial usage and antimicrobial resistance patterns and have established recourse to continual data for these two parameters from the Academic Health Sciences Centre. Near completion projects have developed surveillance tools to analyse these microbiology and pharmacy data sets for detailed geographical and temporal trends. Use of these data, combined with the database generated from the CBR algorithm, will be used to triangulate a quantitative analysis of the impact of the POC-DSS on prescribing patterns, patient outcomes and antimicrobial resistance trends.

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. Participant audio recordings (anonymous) will also be stored in this manner until transcribed when they will then be erased.
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 using the SHA256(SHA2 family) one way hash algorithm. Interviews will be transcribed either by researchers in the department or by a clinical transcription company (the transcription agency). During audio recordings participants are asked to not use any identifiable information or names with all recordings checked and any identifiable information removed before being sent out for transcription. At the transcription agency confidentiality is also maintained through: All employees are subject to Baseline Security checks and have provided documentation to confirm their identity, nationality and immigration status where applicable. All staff have signed non disclosure/confidentiality agreements and are willing to do so for individual clients if required. Confidentiality clauses are written into all contracts. The Transcription Agency has an Information Security Policy and it covers the requirements for information security, the scope of the Information Security Management System, including business functions, areas and sites covered and the general philosophy towards information security. All electronic media is deleted after completion of each project and receipt of transcripts has been confirmed. Anonymised data will be analysed within Imperial College using the college network. This will be undertaken by lead researchers for the project, with support from Imperial College Statistical Advisory Services.

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

The National Institute for Health Research is funding this study through an Invention for Innovation Product Development Award of £687,000 over 3 years.

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 principal 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 engineers and the multi-professional healthcare team from the two collaborating Centres. The research team engaged in developing the prototype POC-DSS will continue to be involved in meeting the post-prototype broader objectives described.

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.

The organogram for the oversight committee and the operational management can be found in the appendix.

10. PUBLICATION POLICY

The methods and results from development of the POC-DSS 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. The mixed methods evaluations proposed for the product, utilising both qualitative and quantitative analyses, will enable a truly robust evaluation of the product. 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.

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