Study protocol

Full title

BioResource in Adult Infectious Diseases (2019-2024)

Short title

BioAID (2019-2024)

Chief Investigator and affiliations

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Supported by

National Institute for Health Research

Sponsored by

University College London Hospitals NHS Foundation Trust (UCLH)

Protocol version number and date

Version 1, 14/01/2019

R&D / Sponsor Reference Number(s)

13/0470

IRAS Registration Number:

259776

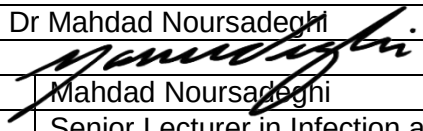
Protocol versions

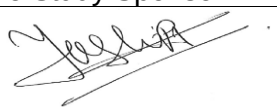
Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update

Declarations

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

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

Chief Investigator: Dr Mahdad Noursadeghi			
Signature: 		Date:	14/01/2019
Print Name(in full):	Mahdad Noursadeghi		
Position:	Senior Lecturer in Infection and Immunity Honorary Consultant in Infectious Diseases		

On behalf of the Study Sponsor:			
Signature: 		Date:	8/2/2019
Print Name(in full):	Pushpsen Joshi		
Position:	Research Governance Manager		

Summary information

IRAS Number	TBC
REC Reference No	TBC
Sponsor Reference No	TBC

Full (Scientific) title	BioResource in Adult Infectious Diseases (2019-2024)	
Health condition(s) or problem(s) studied	Adult Infectious Diseases	
Study Type	Research Tissue Bank	
Target sample size	10,000	
Study Duration/length	5 years	
Expected Start Date	1st April 2019	
End of Study definition and anticipated date	31st March 2024	
Data and sample storage	Site	Custodian
	University College London Division of Infection and Immunity, Cruciform Building, Gower Street, WC1E 6BT.	Professor Mahdad Noursadeghi
	Imperial College Health Care Trust Academic Microbiology Laboratory, Charing Cross Hospital, Fulham Palace Road, London W6 8RF	Professor Shiranee Sriskandan
	University of Oxford	Dr Alex Mentzer
	University Hospitals Birmingham NHS Foundation Trust Clinical Microbiology Queen Elizabeth Hospital Birmingham B15 2GW.	Dr Martin Gill
Funding	NIHR Biomedical Research Centres at University College London Hospitals, Imperial College Health Care and University of Oxford Hospitals. NIHR Fellowship to Dr Laura Shallcross (reference number CS-2016-16-007)	

Chief Investigator	Professor Mahdad Noursadeghi, University College London Division of Infection and Immunity, Cruciform Building, Gower Street, London WC1E 6BT. Telephone: 0203 108 2128, Email: m.noursadeghi@ucl.ac.uk.
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Key words

Infectious Diseases, Bioresource, Genomics, Transcriptomics, Proteomics.

List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
GAfREC	Governance Arrangement for NHS Research Ethics
HTA	Human Tissue Authority
IB	Investigator Brochure
ICF	Informed Consent Form
IPR	Intellectual property rights
MD	Medical Device
ISRCTN	International Standard Randomised Controlled Studies Number
PI	Principle Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Clinical Study
REC	Research Ethics committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMF	Trial Master File
UCL	University College London
UIN	Unique Identification Number

Contents

1. Introduction

The Bioresource for Adult Infectious Diseases (BioAID) is a collaborative project between multiple NHS Hospitals in partnership with closely affiliated UK Universities. BioAID aims to collect biological samples and clinical information from 10,000 episodes in which patients present to hospital with a suspected infectious disease. Participants will be asked to give consent to have their samples and clinical information collected within BioAID. The samples will be used to obtain RNA and serum from blood samples at various time points during the illness. In addition, the samples will be used to obtain the participants DNA and the microbial organism causing the illness where possible.

This will provide an invaluable bioresource to evaluate new strategies for diagnosis of infectious diseases and predicting the outcome of specific diseases in individual patients. BioAID will also help to establish the framework for research sampling and data collection to complement existing studies in infectious diseases, and inform the design of new studies as well as provision of NHS services for infectious diseases. The samples and clinical information collected within BioAID will be held within the participating sites. Access to these collections will be provided to research investigators under the terms of material and data sharing agreements. Identifiable patient information will not be disclosed.

2. Background

Adult infectious diseases remain a major burden for health care provision in UK hospitals, compounded by the ageing population, modern medical practice (in dwelling devices, prosthesis, complex surgery, immunosuppressive drugs), global travel (migration, employment and recreational), and pathogen evolution (leading to emerging zoonoses and antimicrobial resistance)[1].

Although molecular diagnostics and identification of drug resistance have led to significant advances in the management of infectious diseases, and high throughput sequencing is emerging as potential tool for real time assessment of outbreaks[2–4], specific laboratory diagnosis of the microbial cause of unselected febrile illnesses is still out of reach in most cases presenting to hospital. A clinical diagnosis is usually derived from the association of clinical syndromes with specific pathogens, and assessment of demographic risk. In this context, empirical antimicrobial therapies are frequently inappropriate because they may not be needed in the case of self-limiting illnesses, or fail due to drug resistance- increasing the selection pressure for drug resistance, as well as wasting resources or causing a delay in initiation of effective treatments.

At a population level, microbial and drug resistance epidemiology feeds back to inform clinical decision making, but often with a significant delay. In addition, there is striking host heterogeneity in the natural history of disease and the response to therapy. As a result there is a pressing need for a range of research initiatives focussing on tackling such issues including immediate and accurate patient risk stratification, novel host biomarkers for diagnosis and improved understanding of host-pathogen interaction to guide future therapeutic development in an area where novel drug development remains unsatisfactorily low[5].

Technological advances in genomics, transcriptomics and proteomics/metabolomics are being applied to specific questions in infectious disease. Timely validation of preliminary findings and extension of these approaches to the broad repertoire of infectious disease practice within the NHS are limited by access to adequate sample size, and linkage to good clinical phenotype data. BioAID brings together multiple UK NHS hospital trusts and University partners to overcome these challenges by harnessing activity within research ready NHS institutions supported by world class research universities in a collaborative network. The initiative will establish and maintain a registry of unselected adult infectious diseases linking clinical phenotype and microbiological data to biological samples, with the capacity to recall patients for secondary studies. This collaboration seeks to complement and build on existing initiatives in pathogen sequencing, clinical trials, service development and integrating research data across the NHS.

BioAID has been established as a research tissue bank in 2014. As a research tissue bank, BioAID is subject to renewal at five yearly intervals in order to ensure that the protocol is commensurate with contemporary standards. The present protocol has been accordingly updated.

3. Objectives

3.1. Primary Objective

- To establish a registry of unselected adult infectious diseases linking clinical phenotype and microbiological data to DNA, RNA and serum biobanking, with capacity to recall participants.

3.2. Secondary Objectives

- To provide the foundation for evaluation of the clinical utility of genomic, transcriptomic and proteomic analysis for diagnosis and stratification of risk in unselected adult infectious disease.
- To provide a research sampling and data collection framework to complement clinical service developments, clinical trials and pathogen sequencing studies.
- To attract pharmaceutical clinical trials within adult infectious diseases based on clinical activity within research active NHS settings.

4. Methodology

4.1. Study design

BioAID is a multi-centre research tissue bank (Appendix 1) to enable observational studies in adult infectious diseases.

4.2. Sample size

We aim to collect biological samples and data for 10,000 patient episodes across the participating NHS hospitals. To date, BioAID has accrued biological samples and data for 4200 patient episodes. The number of participants required to achieve adequate statistical power to observe genetic variants or confidently associate expression profiles with disease states has always been difficult to calculate and is heavily dependent on the phenotype under question. The discovery of novel variants associated with susceptibility to infectious disease have commonly required discovery sample sizes in the realm of 1000 to 5000 individuals detecting variants with risk ratio effect sizes varying from 1.2 to 2.0 although samples as low as 500 have been successfully analysed. This Bioresource would therefore be expected to contribute to such studies looking at susceptibility to infection in younger individuals, or sepsis survival for example. Robust validation of suspected associated variants can be achieved with sample sizes of approximately 1000. The number of cases required for effective interpretation of whole genome expression profiling is based upon previous published data which generally include between 30 and 100 cases and such numbers generally extend to analyses of expression quantitative trait loci, epigenetics or metabolomics. Therefore, detailed expression profiling and other such analyses could be effectively applied to particular infections even when stratified by pathogen species or subtype.

4.3. Identification of potential participants

Routine blood culture sampling in adult patients (>16 years of age) presenting to the hospital Emergency Department will be used to identify potential participants.

BioAID uses a deferred consent approach. This is necessary in order to enable a key priority of the biobank, to support research innovation that aims to improve early treatment decisions in the Emergency Department before conventional microbiological diagnoses can be made. To this end, we aim to enable discovery and evaluation of blood transcriptional (RNA) biomarkers for infectious diseases. RNA levels are labile, and may be significantly affected by time and treatment, when a patient first presents to hospital. Therefore, we require to obtain a blood RNA sample at the earliest opportunity and before the initiation of any treatment in hospital. This negates the ability to obtain meaningful informed consent in real time, when potential participants present to hospital before any treatment initiation.

A proprietary vacutainer blood sample tube (2.5 mL) for RNA collection, will be packaged with routine blood culture bottles in the ED. This represents the index research blood sample (for RNA), to be collected at the same time as routine blood culture samples used as a surrogate for suspicion of infection. The index research blood sample is transferred to the microbiology laboratories together with the blood culture specimens, and stored there for collection by the BioAID team within 72 hours.

The hospital label on the index research blood sample is then used to identify potential participants. BioAID clinical research nurses/practitioners will have access to patient identifiable data and their contact details via the hospital electronic health record system, subject to Health Research Authority Confidentiality Advisory Group (CAG) Section 251 approval.

4.4. Recruitment of potential participants

The potential participants, or consultees of potential participants will be approached by the BioAID research team (nurses, research practitioners or doctors) at each participating NHS site. Before approaching inpatients, the research team will consult clinical staff involved the care of the patients in order to assess whether the

patient is deemed to have capacity at that time. Patients who have been discharged will be contacted directly by telephone.

The next of kin of potential participants who are deceased will first be contacted by the bereavement office of the NHS participating site when the death certificate is being issued. The bereavement officer will request permission from the next-of-kin for the BioAID research team to contact them. BioAID clinical research staff or trained staff in the bereavement office will introduce BioAID and ask for their assent to include the deceased patient. If the next-of-kin are not available for a face to face meeting the BioAID clinical research staff or trained staff in the bereavement office, will ask for next-of-kin assent by telephone, using a prepared script.

For potential participants who lack capacity, the Mental Capacity Act (MCA) principles will be used to seek appropriate assent from the person accompanying the potential participant to hospital (consultee) or the next of kin. Where no consultee or next of kin is available, a nominated consultee will be identified via the Independent Mental Capacity Advocate (IMCA) Service. Their role will be to support and represent the patient; ascertain the patients past and present wishes, feelings, preferences and values; evaluate information, with the right to access a copy of the relevant records; ascertain alternative courses of action, including least restrictive options; consult with others involved in the patient's life; establish if the patient has been supported as much as possible in the decision-making process; right to seek further medical opinion; check MCA principles and best interest checklist are being followed.

Staff seeking consent will introduce the project (in person or by telephone), provide the project information sheet (in person, by email or by post as appropriate) to the potential participants, or consultees/next of kin of potential participants, and address any questions that arise. The potential participants, or consultees/next of kin of potential participants will have up seven days to decide whether they wish to give consent/assent by signing the consent/assent form.

The consent/assent forms, will detail agreement with the following statements as appropriate:

(i) they have understood the information provided and that they have had the opportunity to ask questions

(ii) they agree to participate voluntarily and can withdraw from the project at any time without giving a reason

(iii) the project can access their NHS hospital and primary care records

(iv) they can be contacted after three months to provide an additional blood sample when their present illness has resolved

(v) they can be invited to participate in future studies, and are free to decide whether or not to take part in these studies

(vi) the samples they have donated and the information gathered about them by the project can be stored for use in future research studies within the scope of the project that may include collaboration with commercial partners without disclosing their identity to any other party

(vii) they will not benefit financially if this research leads to new treatments or medical tests.

If consent/assent cannot be obtained within seven days, then all patient identifiable data recorded by the BioAID team will be destroyed.

All participants recruited to BioAID will be allocated a BioAID Unique Identification Number (UIN).

4.5. Study schedule and biological sampling

The study schedule is summarised in Appendix 2. The biological samples collected in BioAID are detailed in Appendix 3. These comprise only acellular material exempt from the Human Tissue Act.

Participants that are alive at the time of recruitment to BioAID will provide an additional blood sample taken within seven days of the index research blood sample. In addition, they will be invited to provide a convalescent blood sample after three months. These additional samples will be scheduled at the convenience of the participant and where possible, taken at the time of blood tests that take place as a part of their routine clinical care. Participants are free to refuse any of the additional blood samples.

In addition, a 1 mL aliquot of serum taken as part of routine blood tests at the time of presentation to hospital surplus to routine clinical requirements, and all significant microbiological isolates identified from samples taken within the first 48 hours of the index research blood sample, are obtained from the routine diagnostic laboratories.

All biological samples collected in BioAID will be labelled with BioAID the UIN only. These will be stored in secure laboratory facilities within the participating NHS hospital at which the participant was recruited or an affiliated academic partner institution (Appendix 3).

BioAID also provides the opportunity to recall participants by selected phenotype or genotype for secondary studies. Any application that requires recall of participants will be subject to separate Research Ethics and Human Regulatory Authority approvals.

4.6. Data management

All personal data will be collected and used in accordance to General Data Protection Regulations (GDPR).

Data will be collected using paper case record forms (CRF) and secure electronic databases. Electronic databases will include the BioAID unique identification number, hospital number and NHS number only.

Demographic data will include the following: age; gender; ethnicity; country of birth; socioeconomic class. Clinical data will include the following: features of the presenting illness at the time of the index blood sample; past medical history; laboratory and imaging data; medical treatment; diagnoses and outcomes related to the illness at the time of the index research blood sample.

The paper CRF for each participant will include the unique identification number, full name, hospital number and NHS number with limited demographic and clinical data available at the time of consent. These will be stored in a locked cupboard within a specified area in each NHS participating site, with restricted access via electronic NHS ID cards, for the principal investigator and staff involved in recruitment of participants at each participating NHS site. The paper CRFs will not be allowed to leave the premises of the NHS institution at which each participant is recruited.

Electronic data will be collected in separate databases for the participants recruited at different sites. These databases will be hosted within an NHS hospital server or the Data Safe Haven of an affiliated university partner. Access will be restricted to institutional login details for specified BioAID research staff at each site. The database will include the BioAID unique identification number, and the Hospital and NHS identification numbers, but not the participant's name, date of birth or contact details (address or telephone numbers). The hospital number and NHS number are retained in these databases to allow data linkage for incoming data from other primary and secondary NHS electronic health records and up to date contact details. District level post code and occupation data will be used for geographical analysis, deprivation scoring, and lifestyle analysis.

Identifiable patient information will not be disclosed to any third party.

5. Research governance

5.1. Mandatory training

All BioAID clinical research staff will maintain up to date training in Good Clinical Practice and Information Governance, via access to accredited courses provided by their employer.

5.2. Management group

An executive committee (Appendix 1) comprising two named investigators from each participating NHS hospital/affiliated university partner and at least one lay member will meet at six monthly intervals, to review governance issues, progress, problems and resolutions, and to process applications for research use of the sample and data collections. The Executive Committee will be responsible for the operational and financial management of the project, and compliance with research governance regulations including annual reports to the Research Ethics Committee and to CAG. Each meeting will include review of feedback from staff and participants, review of the GCP and IG training log of BioAID research staff, review of the list of BioAID staff that have access to data and/or samples.

5.3. Research access to BioAID data and/or samples

All access to data and samples within BioAID will take place by completion of a written application form submitted to the BioAID Executive Committee.

Applicants will be required to specify their research question, the samples and data that they require, their analysis plan and their expected outputs. In addition, they will be required to confirm they will (i) undertake all of the costs of sample/data transfers and the processing specified in their application; (ii) abide by the conditions of the material and data transfer agreements, including data security arrangements restrictions on onward transfer to third parties, access to raw data derived from BioAID samples, intellectual property protection and dissemination of results. Applications to recall patients recruited to BioAID will be required to obtain separate Research Ethics and Human Regulatory Authority approval for the proposed studies.

Each application will be reviewed by the members of the BioAID Executive Committee (excluding any named applicants) and subjected to external review if the Executive Committee do not have adequate expertise to consider the application. Decisions will be made by consensus. If consensus cannot be reached then approvals will only be given on the basis of a majority in the Executive Committee. Decisions to approve or reject an application for access, on the basis of (i) accordance with participant consent and the terms of reference for scope of research (ii) evidence for the capability of the applicant to undertake the specified research and (iii) scientific critique, will be recorded in the minutes of the Executive Committee meetings and provided in writing to the applicants.

The transfer of samples and/or data will be subject to material and data transfer agreements between the recipient and each of the institutions participating in BioAID. Data sharing will be linked by BioAID unique identification number only and restricted to specific data fields required to undertake each approved pre-specified analysis. Data will be transferred by the provider to the recipient in an encrypted electronic format. The recipient will be mandated to have undertaken up to date information governance training and to use the data in accordance with GDPR principles. The recipient will ensure that the data are stored in a password protected encrypted format; are protected by up to date anti-virus and anti-malware software; are used solely to undertake the pre-specified analysis and will not be forwarded to a third party.

The BioAID Executive committee will be responsible for monitoring and enforcing the data confidentiality policies. The BioAID Executive committee will retain records of (i) information governance training for all staff with access to BioAID data, and (ii) data transfer agreements and a log of data transfer events. Any reported breach of the confidentiality policy will be investigated by the BioAID Executive committee, and included in annual reports to the Research Ethics Committee and to the CAG.

The use of all samples and data will be limited to the approved application for access and stipulated in the material and data transfer agreements between participating sites and investigators requesting access. Return of residual samples will be a condition of the material transfer agreements.

All studies using BioAID will be required to submit annual reports to the Executive Committee and all the raw data obtained from access to BioAID samples must be deposited within the BioAID database linked to the NHS site at which the participant was recruited.

5.4. Document archiving

In line with obligations to archive study-related documents at the end of the study. BioAID will archive the study master file at each participating site for 25 years and in line with all relevant legal and statutory requirements.

6. Clinical governance and indemnity

Participation in the study will not affect routine patient care in any way and all participants are free to withdraw consent at any time without affecting their clinical care in any way. GP's will not be informed of patient participation in BioAID.

None of the research undertaken with BioAID samples and data will inform routine clinical care and will not be disclosed to participants at the individual level. This approach is justified by the fact that (i) the analysis of individual level data and samples will not be conducted in real time; (ii) the analyses will be restricted to discovery and early validation research that is unlikely to provide definitive evidence for clinical significance; (iii) the processing of samples in research laboratories will not be subject to verifiable to quality control and therefore not appropriate to share with individual participants.

All adverse events will be recorded as described in Appendix 4. All complaints and adverse events will be reported immediately to the sponsor by email (xxxxx) and within the relevant NHS hospital site via the hospital Datix system.

The sponsor holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that the sponsor has been negligent. Each participating hospital site continues to have a duty of care to the participant. The sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

7. Intellectual property

All background intellectual property rights (including licences) and know-how used in connection with BioAID shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

All intellectual property rights and know-how arising directly from access to BioAID data and samples will be subject to the specific material and data transfer agreements with each participating NHS hospital and affiliated university partner.

8. Funding

Funding for BioAID is provided by NIHR Biomedical Research Centre funding to UCLH, Imperial College Health Care Trust and University of Oxford Hospitals, and by an NIHR Fellowship to Dr Laura Shallcross (reference number CS-2016-16-007)

NHS costs will be supported via the NIHR Clinical Research Network (reference number: CRN019884)

9. Peer and regulatory review

The study has been peer reviewed in accordance with the requirements outlined by the sponsor.

10. Publication and dissemination policy

Information about BioAID will be freely available on a dedicated project website. Periodic updates will also be provided on the research news web pages at each participating hospital/university partner and at public engagement events at each participating site. In addition, BioAID will be advertised through publications in peer-reviewed literature, presentations at research meetings.

The BioAID executive committee will ensure that all publication conform to ICJME policy on authorship and non-author contributors for publications (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). All data derived from this project will be freely available at the time of publication, through an open access publication policy.

Valuable research findings that may be of interest to the wider public, including patient communities, commercial clinical services or government policy makers, we will liaise with media offices at each participating hospital at the time of publication to maximize opportunities for media coverage and ensure timely press releases.

11. References

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3. Didelot, X., Bowden, R., Wilson, D. J., Peto, T. E. A. & Crook, D. W. Transforming clinical microbiology with bacterial genome sequencing. *Nat. Rev. Genet.* **13**, 601–612 (2012).
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Appendix 1: Participating NHS sites & BioAID Executive committee

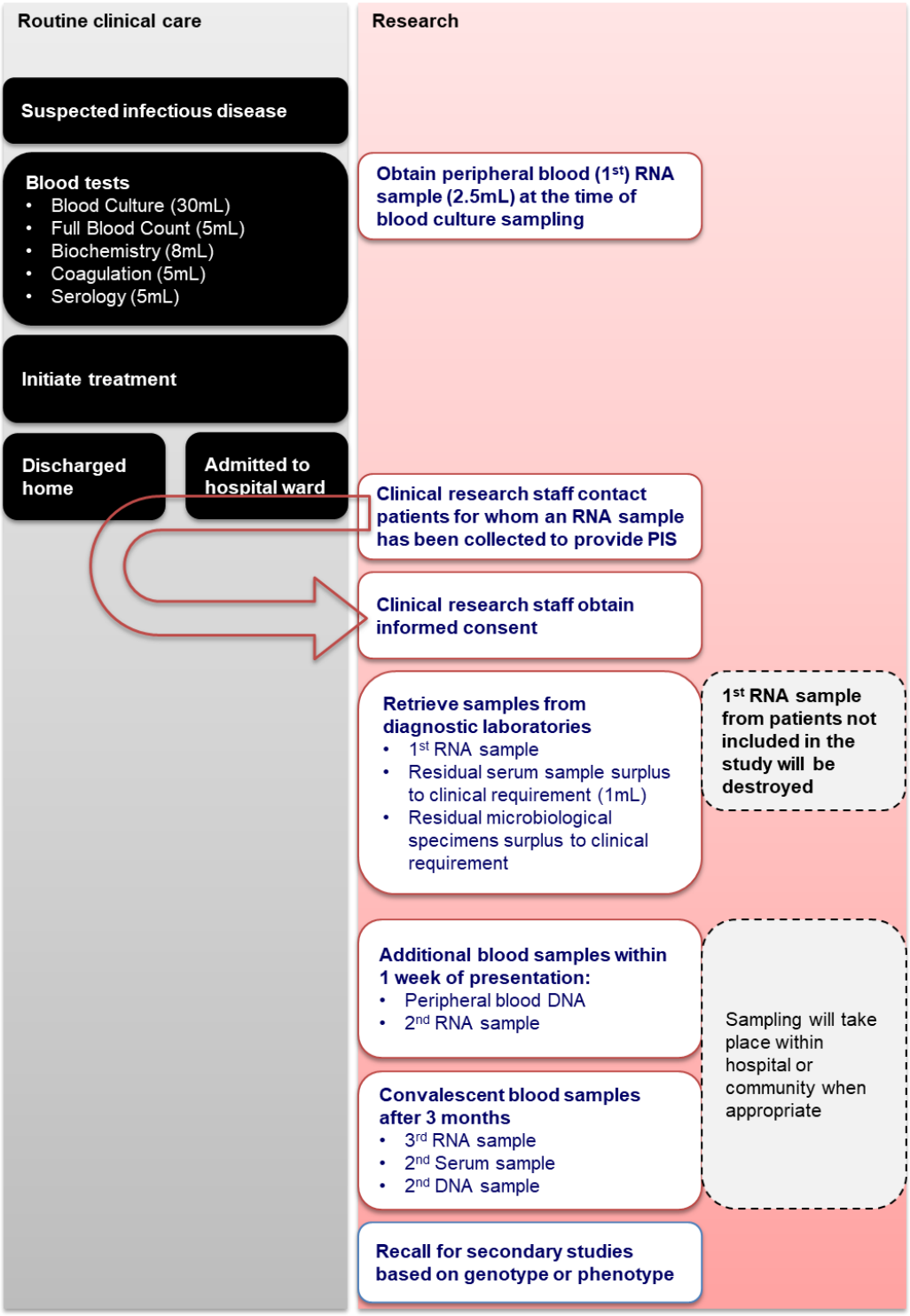
Table 1. Participating NHS sites and affiliated university partners

NHS Trust	Affiliated University	Local PI	Contact details
University College London Hospitals NHS Trust	University College London	Prof Mahdad Noursadeghi	m.noursadeghi@ucl.ac.uk
Imperial College Healthcare Trust	Imperial College London	Prof Shiranee Sriskandan	s.sriskandan@imperial.ac.uk
University of Oxford Hospitals NHS Trust	University of Oxford	Dr Alexander Mentzer	alexander.mentzer@ndm.ox.ac.uk
University Hospitals Birmingham NHS Trust	N/A	Dr Martin Gill	Martin.Gill@uhb.nhs.uk

Table 2. BioAID Executive Committee

Name	Affiliation
Professor Mahdad Noursadeghi	University College London
Dr Laura Shallcross	University College London
Prof Shiranee Sriskandan	Imperial College
Prof Graham Cooke	Imperial College
Dr Alex Mentzer	University of Oxford
TBC	University of Oxford
Dr Martin Gill	University Hospitals Birmingham
TBC	University of Birmingham
TBC	Lay panel member

Appendix 2: Summary of study schedule



Appendix 3: Biological samples

Table 3. Summary of biological samples collected in BioAID

Sample	Derived from	Time of collection
RNA 1	2.5 mL index research blood sample	Collected at time of presentation to ED
Serum (1 mL)	Routine blood sample, surplus to clinical requirements.	
Bacterial isolate	Routine microbiological investigations.	Performed within 48 h of presentation to ED
RNA 2	2.5 mL research blood sample	1-7 days of presentation to ED
DNA	2.5 mL research blood sample	
RNA 3	2.5 mL research blood sample	> 3 months after presentation to ED
Serum 2 (2.5 mL)	5 mL research blood sample	

RNA and DNA samples will be collected in dedicated vacutainer tubes. Proprietary nucleic acid extraction kits will be used to extract RNA and DNA for aliquoting and storage. Acute serum will be obtained from residual specimens within biochemistry laboratories.

Table 4. Biological sample storage sites

Participating recruitment site	**Research tissue bank sample storage site**
University College London Hospital Trust	University College London, Division of Infection and Immunity, Cruciform Building, Gower Street, WC1E 6BT.
Imperial College Healthcare Trust	Academic Microbiology Laboratory, Laboratory Block, Charing Cross Hospital, Fulham Palace Road, London W6 8RF
University of Oxford Hospitals	Department of Microbiology, John Radcliffe Hospital, University of Oxford Hospitals, Oxford OX3 9DU. Wellcome Centre for Human Genetics, University of Oxford, Oxford OX3 7BN.
University Birmingham Hospitals	University Hospitals Birmingham NHS Foundation Trust, Clinical Microbiology, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, B15 2GW.

Appendix 4: Adverse events

Definitions

Term	Definition
"Adverse Event (AE)"	Means any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
"Adverse Reaction (AR)"	Means any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.
"Serious Adverse Event (SAE), "Serious Adverse Reaction, or Unexpected Serious Adverse Reaction"	means an adverse event, adverse reaction or unexpected adverse reaction respectively that − results in death − is life threatening − requires hospitalisation or prolongation of existing hospitalisation − results in persistent or significant disability or incapacity or − consists of a congenital anomaly or birth defect
"Suspected Serious Adverse Reaction (SSAR)"	means an adverse reaction that is classed in nature as serious and which <u>is consistent</u> with the information about the medicinal product in question set out
	in the case of a licensed product, in the summary of product characteristics (SmPC) for that product
	(b) in the case of any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question
"Suspected Unexpected Serious Adverse Reaction (SUSAR)"	means an adverse reaction that is classed in nature as serious and which <u>is not consistent</u> with the information about the medicinal product in question set out
	in the case of a licensed product, in the summary of product characteristics (SmPC) for that product
	in the case of any other investigational medicinal product, in the IB relating to the trial in question

Adverse event reporting form

Study sponsor ID number	
Subject initials	
Subject (study) UIN	

Description of Adverse Event			
Date of onset			
Outcome	Resolved without residual effect	☐	
	Resolved with residual effect	☐	
	Continuing	☐	
	Death	☐	
Date of Resolution			
Severity Grade	Mild	☐	
	Moderate	☐	
	Severe	☐	
Casualty Assessment	Not related	☐	
	Possibly related	☐	**These qualify an Adverse event (AE) as an Adverse Reaction (AR)**
	Probably related	☐	
	Definitely related	☐	
Is it Serious	Results in death	☐	**Please complete SAE reporting form and email to UCL Biomedicine R&D Unit within 24hrs:** randd@uclh.nhs.uk
	Is life threatening	☐	
	Requires hospitalisation or prolongation of existing hospitalisation	☐	
	Results in persistent or significant disability or incapacity	☐	
	Consists of congenital anomaly or birth defect	☐	
	No	☐	

Serious Adverse Event Reporting Form

Definition of SAE:
An SAE can be defined as: an untoward medical occurrence in a subject during clinical research involving a pharmaceutical product, medical device, or clinical intervention that: is fatal; is life threatening; results in persistent or significant disability / incapacity; requires inpatient hospitalisation or prolongs a current hospitalisation; results in a congenital anomaly in offspring; or an event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above.
Initial Reporting:
For all initial reporting of any Serious Adverse Events / Incidents this form must be completed **fully** and sent to the UCL Joint Research Office (randd@uclh.nhs.uk) within 24 hours of the incident occurring or being known.
Follow-up Information:
For subsequent follow-up reporting of an SAE, a new SAE reporting form should be completed with just administration details and sections A, D, E and G **only** and forwarded to the UCL Biomedicine R&D Unit as soon as possible. All SAEs must be followed up until closure.
SUSARs/Expedited Reporting:
For any Suspected Unexpected Serious Adverse Reactions (SUSARs) which are life threatening/fatal, initial reports must be sent to the Competent Authority and the Main Ethics Committee by the sponsor within 7 days of being aware of the event. Follow-up information must be sent to the Competent Authority and Main Ethics Committee within 8 days after initial reporting. All other SUSARs must be reported within 15 days and any follow up information sent to the Competent Authority and Main Ethics Committee as soon as possible. A copy of these reports must be sent to the UCL Biomedicine R&D Unit if this duty has been delegated by the sponsor to the CI.

Initial report	☐	Follow up report	☐	Reporting date	
Study Title					
Ethics Ref No					
R&D Ref No					

Section A – Details of subject affected by Serious Adverse Event					
Has the chief Investigator been informed of this event prior to completion of this form?					
Subject initials		Subject DOB		Subject UIN	
Gender		Height		Weight	

Section B – Details of the Serious Adverse Event			
Date of event onset		Time of event onset	
Site		Exact location	
Study intervention			
Time of intervention			
Type of serious adverse event			
Subject died	☐		
Life threatening	☐		
In-patient hospitalisation or prolongation	☐		
Persistent or significant disability/incapacity	☐		
Congenital anomaly/ birth defect	☐		
Medically important event	☐		
Other	☐		

Describe Event: Give a summary of signs and symptoms including vital signs, diagnosis, treatment of event, concurrent treatment and other relevant medical history. Please include the point in the study at which the event occurred.

Section C – Relationship To Study Involvement				
Was the incident related to the subject's involvement in the study?	Yes	☐	No	☐
Is the event related to the study intervention?	Yes	☐	No	☐
Was this expected by the Chief Investigator?	Yes	☐	No	☐
Was this expected by the Sponsor?	Yes	☐	No	☐
Is the event related to the study intervention?	Yes	☐	No	☐
Give details if sponsor's and CI/PI evaluation of expectedness differ				

Severity grading	Mild	☐	Moderate	☐	Severe	☐
Action taken regarding subject's participation in the study						
Temporarily discontinued	☐	Permanently discontinued	☐	Subject continued	☐	
Date		Decision taken by				
Explain the reasons for the decision						

Section D – Outcome of Serious Adverse Event	
Recovered	☐
Not yet recovered	☐
Alive with sequelae	☐
Subject died	☐
Give details	

Section E – Details of Reporter and Site Chief Investigator	
Name of person completing this report	
Role	
Affiliation	
Contact details (email)	
Reporter signature	Date
Chief investigator signature	Date

Section F – Circulation				
Date form completed				
Date CI informed				
Date Ethics Committee informed				
Did this event require an expedited report?	Yes	☐	No	☐
If yes please provide date reported to the Competent Authority (ies)/Main Ethics Committee				

Please list name(s) of the Competent Authority(ies)/Main Ethics Committee reports sent to

Section G – Follow-up Information	
Date completed	
Additional information to describe progress of event	

Please forward a copy of this form to the UCL Joint Research Office (randd@uclh.nhs.uk). The original form should be kept in the Study/Trial Master File.

UCL Joint Research Office use only			
R&D Reference No			
Date received		Date reviewed	
Did this event require further action		Yes	No
If yes, provide details of action taken:			
Reviewed by			
Signed		Date	