INHALE: Work Package 3

The Impact of using FilmArray Pneumonia Panel Molecular Diagnostics for Hospital-Acquired and Ventilator-Associated Pneumonia on Antimicrobial Stewardship and Patient Outcomes in UK Critical Care: A Multicentre Randomised Controlled Trial.

Version	1.2
Date	11th July 2019
Sponsor	University College London (UCL)

IRAS number:	250289
Sponsor protocol number:	18/0602
NRES number:	19/LO/0400

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1 Administrative information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol template Version 4. It describes the INHALE WP3 trial, sponsored by University College London and co-ordinated by the NCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at the NCTU.

The NCTU is committed to ensuring that its trials adhere to the SPIRIT guidelines. As such, the protocol template is structured around the Standard Protocol Items as specified in 'Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials' [1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of the NCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, the General Data Protection Regulation (GDPR) (EU) 2016/679, the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF), the Mental Capacity Act 2005 and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and the NCTU.

Participating sites will inform the NCTU as soon as they are aware of a possible serious breach of compliance, so that the NCTU can fulfil its requirement to report the possible breach to Sponsor and to ethics if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

University College London (UCL) is the trial sponsor and has delegated responsibility for the overall management of the INHALE WP3 trial to the Chief Investigator and the NCTU. Queries relating to sponsorship of this trial should be addressed to the Chief Investigator or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN:
Date of Registration in Primary Registry	Date when trial was officially registered in the primary registry. -TBC
Secondary Identifying Numbers	• Sponsor identifier: 18/062 • IRAS number: 250289 • Clinicaltrials.gov number: • UEA RIN number: R200771
Source of Monetary or Material Support	NIHR PGfAR ref: RP-PG-0514-20018
Sponsor	University College London (UCL) Joint Research Office, UCL, 1st Floor Maple House, 149 Tottenham Court Road, London W1T 7NF Postal address: Joint Research Office, UCL Gower Street, London WC1E 6BT
Contact for Public and Scientific Queries	Juliet High Senior Trials Manager Norwich Clinical Trials Unit 01603 591708 inhale.study@uea.ac.uk
Short Title or Acronym	INHALE WP3
Programme Title	INHALE: Potential of Molecular Diagnostics for Hospital Acquired and Ventilator-Associated Pneumonia in UK Critical Care.
Scientific Title	The impact of using FilmArray pneumonia panel molecular diagnostics for hospital-acquired and ventilator-associated pneumonia diagnosis on antimicrobial stewardship and patient outcomes in UK critical care: A multicentre randomised controlled trial.
Countries of Recruitment	England
Health Condition(s) or Problem(s) Studied	Hospital-Acquired and Ventilator-Associated Pneumonia in UK Critical Care

Intervention(s)	**Intervention** Treatment guided by the BioFire FilmArray molecular diagnostic machine (The "FilmArray test"), a PCR-based pathogen and bacterial resistance detection system for identifying candidate pathogens driving lower respiratory infections, together with a trial-based prescribing algorithm adapted to accommodate site-specific requirements where appropriate. Treatment will follow standard care with the aim of moving to intervention-guided prescribing as soon as results are available (machine test time is 1-2h) **Control** Standard care, which consists of empirical antibiotics, based on local policy and adapted once microbiology culture and susceptibility testing results are available (typically after 48-72 h)
Key Inclusion and Exclusion Criteria	**Inclusion criteria:** 1. About to receive an antimicrobial to treat a suspected lower respiratory infection (LRTI – including suspected HAP/VAP) for the first time, or a change in existing antimicrobial for LRTI because of deteriorating clinical condition. This relates both to spontaneously breathing patients and those who are intubated for any reason 2. In-patients in a participating ICU/CCU 3. Hospitalised for >48 hours 4. Sufficient volume of airway specimen obtained for routine testing at site plus 200μL for the FilmArray test **Exclusion criteria:** 1. Previous inclusion in WP3 2. Concurrent participation in the active phase (defined as within 30 days of primary end point) of an interventional trial not agreed as acceptable for co-enrolment by the local PIs of both trials. Participants will be permitted to co-enrol in studies that do not involve an intervention (e.g. observational studies). 3. Moribund and/or not expected to live more than 48 h 4. Presence of an existing directive to withhold life-sustaining treatment, in relation to antibiotic use 5. Prisoners or young offenders currently in custody of

	HM Prison Service or supervised by the probation service
Study Type	This interventional trial is an open-label, parallel, randomised controlled trial exploring the potential of FilmArray molecular diagnostics versus standard care.
Date of First Enrolment	May 2019
Target Sample Size	466 participants
Primary Outcome(s)	Two primary outcomes will be used: 1. Non inferiority in clinical cure of pneumonia at 14 days post randomisation 2. Improvement in antimicrobial stewardship at 24 hours post randomisation (measured as % of patients on active and proportionate antibiotics)
Key Secondary Outcomes	- ICU/CCU length of stay – time from randomisation to discharge from ICU/critical care - Number of ventilator-free days within 21 days after randomisation (VAP participants only surviving 21 days post randomisation) - Mortality - death from any cause within 28 days of randomisation - Incidence of septic shock – within 21 days of randomisation. - Change in SOFA (ΔSOFA) score from randomisation to 7 days post-randomisation (adults) - Change in PELOD-2 (ΔPELOD_2) score from randomisation to 7 days post randomisation (children) - Change in pSOFA (ΔpSOFA) score from randomisation to 7 days post-randomisation (children) - % of participants on antibiotics active/inactive against the pathogen(s) found at 24 and 72h from randomisation - % of participants on proportionate/disproportionate antibiotics in relation to pathogen(s) found at 24 and 72h from randomisation - % of participants on narrow-spectrum antimicrobials at 24 and 72 h from randomisation - % of participants with specific adverse events associated with antibiotics within 21 days from randomisation - % of participants that contract a secondary pneumonia within 21 days from randomisation - Total antibiotic usage in Defined Daily Dose (DDD)s at 21 days post randomisation (all conditions)

	- Inpatient stay related costs

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Prof Ann Marie Swart	NCTU	NCTU Director and Co-applicant
Juliet High	NCTU	Senior Trial Manager
Charlotte Russell	UEA	Senior Research Associate in Medical Microbiology
Dr Vicky Enne	UCL	Programme Manager
Dr Vanya Gant	UCLH	Chief Investigator
Dr Julie Barber	UCL	Lead Statistician
Prof. David Livermore	UEA	Co-Chief Investigator for INHALE Programme
David Turner	UEA	Health Economist
Dr Adam Wagner	UEA	Health Economist

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
Ramnath Elaswarapu	NIHR	Funder representative and main point of contact
Pushpsen Joshi	UCL	Sponsor representative

1.4.3 Trial Management Group

Name	Affiliation	Role and responsibilities
Dr Vanya Gant	UCLH	Chief Investigator and Co-applicant
Dr Vicky Enne	UCL	Programme Manager and Co-applicant
Prof Ann Marie Swart	NCTU	NCTU Director and Co-applicant
Juliet High	NCTU	Senior Trial Manager
Charlotte Russell	UEA	Senior Research Associate in Medical Microbiology
David Turner	UEA	Health Economics Lead and Co-applicant
Prof Rob Horne	UCL	Behavioural Science Lead and Co-applicant
Prof David Livermore	UEA	WP2 Lead and Co-applicant
Dr Justin O'Grady	UEA	WP1 Lead and Co-applicant
Dr Julie Barber	UCL	Lead Statistician and Co-applicant
Sue Stirling	NCTU	Trial Statistician
Dr David Brealey	UCLH	PI and Co-Investigator
Prof Mark Peters	GOSH	PI and Co-Investigator
Dr Jeronimo Cuesta	BUPA	PI and Co-Investigator
Dr Suveer Singh	ChelWest	PI and Co-Investigator
Rebecca Harmston	Independent	PPI representative
Elisabeth Cooper	Independent	PPI representative
TBC	UCL	Sponsor representative

1.4.4 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Dr Paul Dark	University of	Chair- Independent

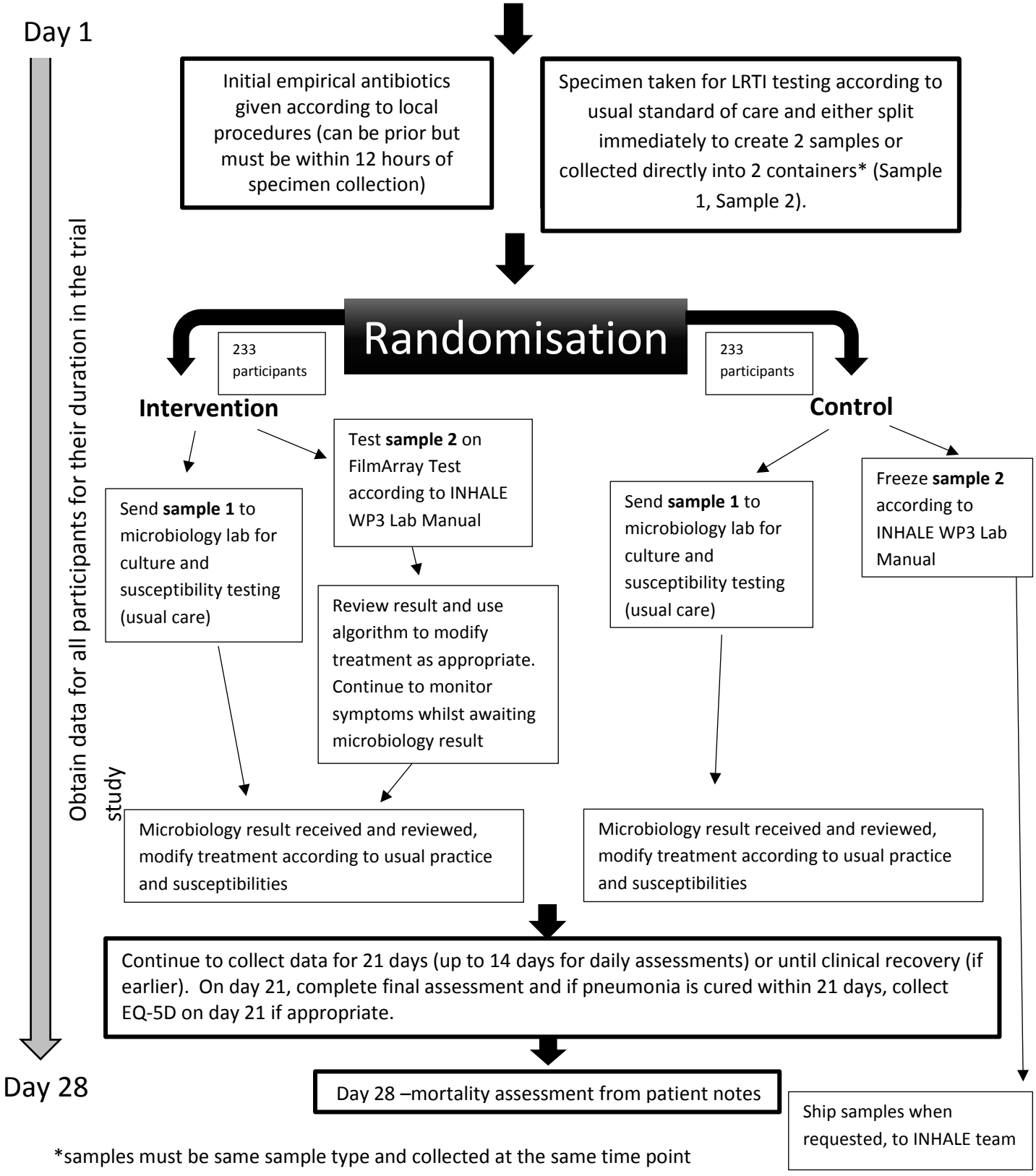
Susan Bennett	SURF	PPI representative
Andre Charlett	Public Health England	Statistician
Paul Aveyard	University of Oxford	Behavioural Science
Robert Masterton	Retired	Clinical Microbiologist
Brian Jones	NHS Greater Glasgow and Clyde	Consultant Clinical Microbiologist

1.4.5 Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Giovanni Satta	Imperial College Healthcare	Microbiologist- independent
John Simpson	University of Newcastle	Professor of Respiratory Medicine
Rosy Reynolds	University of Bristol	Independent Statistician

2 Trial Diagram

Patient about to receive a new antimicrobial to treat a suspected LRTI – including suspected HAP/VAP, for the first time, or a change in antimicrobial for LRTI because of deteriorating clinical condition.
ICU/CCU patient in approved INHALE site and meets eligibility criteria



*samples must be same sample type and collected at the same time point

AR	Adverse Reaction
BAL	Broncho Alveolar Lavage
c.	Circa
CCU	Critical Care Unit
CE	Conformité Européenne
ChelWest	Chelsea and Westminster NHS Foundation Trust
CI	Chief Investigator
CMO	Chief Medical Officer
CRF	Case Report Form
DATIX	Patient safety software
DDD	Defined Daily Dose
DMC	Data Management Committee
DNA	Deoxyribonucleic acid
eCRF	Electronic Case Report Form
EQ-5D	EuroQol questionnaire, 5 levels
EU	European Union
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation
GOSH	Great Ormond Street Hospital
h	Hours
HAP	Hospital Acquired Pneumonia
HEAP	Health Economics Analysis Plan
HRA	Health Research Authority
HRGs	Healthcare Resource Group codes
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ITT	Intention to Treat
LRTI	Lower Respiratory Tract Infection
MHRA	Medicines and Healthcare products Regulatory Agency
NCTU	Norwich Clinical Trials Unit
NHS	National Health Service
NIHR	National Institute for Health Research
NNUH	Norfolk and Norwich University Hospitals NHS Foundation Trust
PELOD-2	Paediatric Logistic Organ Dysfunction Score
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PID	Participant Identification Number
PIS	Participant Information Sheet
PSA	Probabilistic Sensitivity Analysis
PSC	Programme Steering Committee
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
R&D	Research and Development
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SIV	Site Invitation Visit
SOFA	Sequential Organ Failure Assessment
SOPs	Standard Operating Procedures
SSA	Site Specific Approval
Sub-I	Sub-Investigator
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UEA	University of East Anglia
UEA RIN	University of East Anglia Research and Innovation Department
UCL	University College London
UCLH	University College London Hospital
VAP	Ventilator Acquired Pneumonia
WP	Work Package- see glossary

4 Glossary

Pneumonia: consolidative infection of the lower respiratory tract causing significant morbidity and mortality.

There are several types of pneumonia, which differ in aetiology and patient demographics. Pneumonia can be categorised as community-acquired (CAP) if acquired outside of a healthcare setting, or as hospital-acquired (HAP), when the onset of disease/clinical presentation occurs >48h after hospital admission; ventilator-associated pneumonia (VAP) occurs >48h after endotracheal intubation.

Molecular diagnostics:

Detection of pathogens by interrogating their DNA sequence (or RNA in the case of RNA viruses) rather than by seeking to culture them by conventional methods

CE Marking:

CE marking is a certification mark that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area.

Work Package (WP):

The INHALE Trial forms part of an NIHR Programme Grant, which consists of 6 work packages (WPs). The trial itself is WP3. WP1 and WP2 have previously been undertaken and the results from these work packages have informed the design of WP3. Clinicians' willingness to adopt molecular diagnostics and treat patients based on their results will also be measured (WP4), some of this data is collected during WP3 and is explained further in section 8. An economic analysis will then assess if the outcomes justify the cost (WP5).

Antibiotic stewardship:

An organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness.

5 Introduction

5.1 Background and Rationale

Severely-ill hospital patients often develop pneumonia. Hospital-acquired pneumonias (HAP) are life-threatening, particularly in mechanically-ventilated patients (Ventilator-associated pneumonia (VAP)).

HAP and VAP are important infections owing to their frequency, high mortality, and because they are frequent settings for the use of broad-spectrum antibiotics. In the US there are *c.* 250,000 hospital pneumonias annually, 36,000 of them fatal. In the UK, VAP occurs in 9-27% of ventilated patients, with an incidence of 5 cases/1000 ventilator days [3]. The cost per case is c. £19000 [4]. Most ventilated patients are in intensive care, which has heavier antibiotic use and selection pressures than elsewhere in the hospital, with correspondingly greater resistance [5]. Pulmonary infections account for c. 50% of all ICU antibiotic use [3, 6], underscoring their contribution to these antibiotic pressures.

Immediate antibiotics are crucial to outcome in HAP and VAP, with mortality increased if these are withheld or delayed [7]. Empirical treatment is therefore given, typically based on guidelines, local resistance rates and patient risk factors for resistant bacteria, (e.g. recent antibiotics and duration of hospitalisation/s). Treatment inadequacy, because the pathogen proves resistant to the empirical agent(s), is associated with increased mortality [8], and the risk of inadequacy inevitably grows as the resistance prevalence increases. This generates pressure to empirically prescribe the broadest-spectrum antibiotics, including carbapenems [9], with their growing use recorded in a recent NHS longitudinal analysis [10]. This approach, however worrisome for antibiotic stewardship, is argued to increase survival and to have health economic benefits, including in NHS settings [4]. In principle, broad-spectrum empirical therapy should be de-escalated once the pathogen is identified and its resistances determined, *c.* 48-72h after clinical diagnosis. This mode of practice has developed over 70 years, and its timescales depend upon speed of bacterial growth. It is inadequate on 3 counts:

1) Many patients with clinically diagnosed infection have no pathogen grown. This proportion is as high as 70% in pneumonia [11]. Failure to grow a pathogen may reflect suppression of growth by antibiotic(s) already given to the patient, inappropriate culture technique, or purely viral aetiology. Because their pathogen(s) remains undefined, these patients often spend prolonged periods on broad-spectrum empirical agents, with the contingent risk of side effects and selection of a resistant gut flora, which represents a reservoir of future opportunist pathogens and onward spread.
2) Empirical therapy is likely to prove inadequate in patients with unusually resistant pathogens, whose mortality risk is thereby increased in severe infection [12]. Peralta [13] found that the risk of empirical treatment proving to be inappropriate rose from 3% for patients with pathogens lacking resistance to 35% for those resistant to 3 or more antibiotic classes, with a commensurate increase in deaths. In the short term, under- treatment is most likely in major NHS centres providing tertiary care and serving mobile populations with extensive travel to countries with higher resistance rates than the UK (e.g. many central London teaching hospitals) and in those private hospitals that treat patients from regions where resistance is highly prevalent (e.g. in the Middle East). In the longer term the risk of under treatment is likely to increase and become more widespread, especially if, as seems

likely, the accumulation of resistance continues to outstrip antibiotic development, particularly against gram-negative opportunist pathogens.

3) The threat of increased mortality owing to under-treatment drives increasing broad-spectrum and "powerful" treatment, including the use of empirical carbapenems. This leads to overtreatment in the considerable proportion of patients whose infections are due to highly susceptible pathogens, exerts selective pressure for development of resistance in the gut flora, which represents reservoirs of future opportunist pathogens, and drives the risk of *Clostridium difficile* overgrowth.

Some measure of the extent of empirical under- and over- treatment in VAP is gained by reviewing pathogen prevalence rates, summarised by Masterton *et al*. in the UK British Society for Antimicrobial Chemotherapy (BSAC) Pneumonia Guidelines [14] *vs*. BSAC susceptibility data for respiratory (so far as possible) or blood isolates of these species [15]. This suggests that carbapenems and piperacillin-tazobactam (the standard empirical treatments for HAP and VAP in many centres) achieve 85-86% coverage, but that 49% of pathogens could have been covered by amoxicillin/clavulanate and 27% by ampicillin or amoxicillin. Put simply, empirical piperacillin-tazobactam or imipenem amounts to under treatment in 13-15% of cases and over-treatment in 27-49%. At present, however, the patients being empirically under- or over- treated cannot be identified until the laboratory results become available.

A further limitation of present patient management is that, de-escalation is only done in around half the HAP/VAP cases where it is supported by microbiological data [16] and is not scientifically sustainable in cases where no pathogen is grown but the patient remains unwell.

At the time INHALE was conceived, the CMO's report [17] rightly posited that faster recognition of pathogens and profiling of their resistances would address these problems and benefit individual patients, whose therapy could more rapidly be tailored to their particular pathogen(s), through reducing the need to use broad-spectrum empirical agents with their contingent selection for resistance. Since then, calls to increase the role of rapid diagnostics in fighting AMR have only increased. In his report commissioned by the UK government, Lord Jim O'Neill recommends that, by 2020, antibiotics should only be prescribed if informed by data and testing technology. The threats and enormous consequences for broader society on a global scale have also been made very clear [18].

Molecular diagnostics potentially offer improvement by identifying pathogens and resistances in hours, thereby allowing early therapeutic refinement. Automated pathogen- and resistance-detection platforms are now available for evaluation of HAP, but no data exist on whether these offer clinical and value-based advantage in the NHS. Several companies are developing molecular diagnostic platforms for bacterial pathogens, including the agents of VAP and HAP. Three such platforms were tested during Work Packages 1 and 2 of the INHALE programme. Through evaluation of the results from WP1, the BioFire Filmarray LRTI test (the "FilmArray test") was selected as the best performing test for this trial. Thus far, clinical evaluation data of the FilmArray test diagnostic performance remains extremely limited, with no study in a UK setting. Furthermore, there is no evidence base to direct how best such a platform might be deployed within clinical pathways to deliver maximum efficiency and value for money. Finally, it is not clear whether physicians would welcome them: If successful, tests such as the FilmArray test would be expected to deliver swifter

results, but to identify a more restricted range of bacterial pathogens than conventional microbiology; moreover they would detect resistance genes rather than measuring phenotypic resistance, as in conventional tests. Addressing these acceptability aspects is essential for effective implementation, if this trial finds this to be advantageous.

To assess its performance we will undertake a two-armed RCT: in one arm, therapy for HAP/VAP will be guided by the FilmArray test and by conventional culture-based tests in the second arm. The trial will be run across multiple hospitals with different resistance prevalence rates, environments and case mix: (London Teaching, Regional Teaching, District, Specialist Children's and Private with an international patient mix). Economic analysis will review the cost-effectiveness implications and behavioural analysis will review the barriers to introducing molecular diagnostics and how these can be overcome.

The work is vital because heavy use of broad-spectrum antibiotics is the major driver for bacterial resistance. Selected in the gut flora of treated patients, these constitute a reservoir of future opportunist pathogens. Improved infection control has reduced the NHS's burden of methicillin resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* but resistance rates among Gram-negative bacteria are rising and, on an international basis, are doing so alarmingly, e.g. with an explosive increase of *K. pneumoniae* with KPC carbapenemases in Italy and Greece, and Enterobacteriaceae with NDM carbapenemases in the Indian subcontinent [19]. Most carbapenemase producers are susceptible only to a few poorly-effective antibiotics e.g. colistin and tigecycline. Such organisms are repeatedly imported into the UK, with local dissemination and present a growing challenge to the NHS.

The conventional way of overcoming resistance has been development of new antibiotics, but the flow of these has slowed, reflecting the difficulty of discovering, developing and licensing them, and the low return on investment. Although several new antibiotics are beginning to reach the market none wholly overcomes existing resistance and all are vulnerable to new resistance. Restrictive stewardship conserves existing antibiotics, but at a risk of denying effective treatment to seriously-ill patients. As recognised in the CMO's Report, it is vital to find alternative, evidence-based models for antibiotic use. Molecular diagnostics, such as the FilmArray test, offer the potential to achieve this goal by rapidly and simultaneously identifying organisms and their resistance genes in the clinical specimen, without the need for culture.

5.1.1 Explanation for choice of comparators

The comparator is treatment as usual (standard care). Currently there is no other routine, safe option for rapid diagnosis of HAP or VAP infections: the FilmArray test was judged to be the best of three developmental rapid systems for the microbiological investigation of HAP/VAP in WP1 of INHALE.

5.2 Objectives

The overall trial aim is to show non- inferiority of the FilmArray test molecular diagnostic for clinical and safety outcomes compared to standard care, with altered antimicrobial prescribing leading to improved antimicrobial stewardship.

5.2.1 Primary Objectives

The primary objectives are:

1. To determine whether there is non-inferiority in clinical cure of pneumonia at 14 days post - randomisation between patients treated according to the FilmArray test's molecular results plus trial- based prescribing algorithm versus those treated with standard care
2. To determine whether there is improvement in antimicrobial stewardship at 24 h post randomisation for participants treated according to the FilmArray test versus those treated with standard care. In this context antimicrobial stewardship is defined as active and proportionate treatment

These are co-primary objectives, such that the study will be declared as a success only if the FilmArray test is found to be both non- inferior to standard care in terms of clinical cure and also provides improvements in antimicrobial stewardship.

5.2.2 Secondary Objectives

FilmArray and standard care will be compared to:

1 Determine whether there is a difference in the number of participants receiving the most appropriate antibiotic at 24 and 72h

2 Determine if there is a difference between the two groups in total antibiotic use over the 21 day study period

3 Determine if the FilmArray test with algorithm intervention is more cost effective than standard care at 21 days post randomisation

4 Determine whether there are any differences in antibiotic associated adverse events (e.g. Clostridium difficile infection) between the two groups within 21 days of randomisation

5 To determine whether organ dysfunction scores of the intervention group are improved at day 7 post randomisation

6 Determine if ICU/CCU length of stay, septic shock rates or mortality rates are decreased by the intervention

7 Determine if there is an increase in ventilator free days for any participants who were ventilated in the intervention group

8 Determine whether there are any differences between the groups in the number of participants contracting secondary infections

5.3 Trial Design

This is a multicentre, parallel group, randomised controlled trial to investigate clinical, safety and cost effectiveness of FilmArray test Molecular Diagnostics plus trial based prescribing algorithm versus standard care, with the aim of showing non-inferiority in participant outcomes and superiority in antimicrobial stewardship. Participants will be randomised in the ratio of 1:1 to the control and intervention arms.

5.3.1 Internal Pilot Phase

An internal pilot phase has been designed to allow an assessment of criteria for progression to a full trial to confirm that the trial is safe and feasible. At the end of this phase a decision will be made by the funder, in consultation with the TSC and DMC, on whether or not to proceed with the trial. Recruitment will continue while data on patients in the internal pilot are analysed and reviewed by the committees and a funder decision is obtained. As an internal pilot, all data collected on trial participants will be included in the final trial analyses.

The pilot phase will run for 6 months, reporting on data collected from the first 50 participants randomised.

It is anticipated that recruitment will take 1-2 months to stabilise and reach required levels, therefore criteria surrounding recruitment of sufficient participants will be based on recruitment in months 3-8 (inclusive) and reported at the end of month 8 along with the analysed data from the first 50 participants (who it is expected will have been recruited starting from month 1).

The objectives of the internal pilot phase are to confirm trial safety and feasibility. These will be assessed through a 'traffic light' grading system [20] as follows:

Pilot objective to be assessed	RED	AMBER	GREEN
Recruitment of sufficient participants: randomisations per site/per month including all open sites in months 3-8	0.33	0.34-1	>1
	Additionally, sites have been set their own targets based on the size of the ITU/patient population. These targets will be reviewed with each site individually.		
% of eligible participants randomised per site/per month and overall	No specific target set for this. Each site will be reviewed individually and any site with a low % of eligible patients recruited (in comparison to other sites) will be investigated. There are a number of factors that could impact this number, so we will constantly review and may consider providing further training or support.		
Intervention adherence, defined as the proportion of participants in the intervention arm who have a molecular diagnostic result (overall)	<50%	51-74%	>75%
	Any individual site with less than 50% will be investigated and may be closed		
Proportion of participants in the intervention arm whose specimen has been tested on the FilmArray machine within 8h of being taken from the participant	<20%	20-60%	>60%
That data on primary and key secondary outcome measures are entered into the trial database within 14 days	Data completeness and quality will be reviewed by the DMC and TSC. If less than 50% of data is in the database (that should be there, per site, for analysis at data cut off) this will be considered as needing significant remedial action before proceeding.		
Safety	To be assessed by the DMC		

A Statistical Analysis Plan for the feasibility analysis will be drafted based on the criteria above and the analyses will be performed at the end of the pilot phase. This will not involve a formal comparison of the primary and secondary outcomes between groups. The DMC opinion, combined with an assessment by the TSC on recruitment rate, protocol feasibility, data completeness and safety will inform the decision to continue to the full trial as planned, whether there should be modifications to the protocol, or whether the trial should end.

6 Methods

6.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to the CI and the NCTU.

6.1.1 Trial Setting

The trial will take place across adult and paediatric ICUs/CCUs in England.

The NHS evaluation sites are selected to represent diverse patient mix and resistance epidemiologies. They comprise regional university hospitals anticipated to have little resistance and a stable local population; large city-based university hospitals with higher resistance and serving a more diverse and mobile population, and specialist children's centres. A private hospital located in London that receives many patients from the Middle East with highly resistant pathogens is also included.

6.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with: (i) a copy of this protocol, (ii) the prescribing algorithm (which will be subject to agreed local adaptation), (iii) a FilmArray machine and (iv)a lab manual for the machine.

To participate in the INHALE WP3 trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the INHALE Trial Management Group (TMG). These are defined below.

Eligibility criteria:

- A named clinician willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff available to recruit participants, enter data and collect specimens
- An area near to the point of care that can house the molecular diagnostic (i.e. within the ICU/CCU or adjacent to it)
- Adequately trained staff available to test specimens ideally within 8 hours of collection
- Space to store consumables and freezer space to store specimens awaiting despatch for central testing (this can be at an appropriate nearby location if not on ICU/CCU)
- Collaboration of ICU/CCU and microbiology staff to agree any local variation of treatment algorithm

Trial sites meeting eligibility criteria will be issued with the INHALE WP3 Investigator Site File (ISF) and a pack of documentation needed by the Research and Development Department (R&D) of their Trust to enable the Trust to provide confirmation of capacity and capability to undertake the trial.

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must sign an investigator statement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, familiarity with the appropriate use of the intervention, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return to the NCTU.

6.2 Site approval and activation

When agreed between the trial management group and local trust R&D that a site will take part in the INHALE study, a FilmArray test machine and consumables will be shipped. This machine should be set up and run according to the manufacturers' manual, with staff trained in its use by member of the INHALE team, the manufacturer, or both. Sites will need to confirm that the machine is ready to use, but it must not be used until activation of the site is agreed by NCTU.

The trial manager or delegate will notify the PI in writing of the plans for site initiation.

On receipt of the signed investigator statement, approved delegation of responsibilities log, staff contact details and any other pre-specified information, written confirmation of site activation will be sent to the site PI. Sites are not permitted to recruit any participants until a letter for activation has been issued. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor, HRA and Research Ethics Committee (REC). This includes not using the machines for any testing other than of pre-specified INHALE participant specimens. The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at the NCTU.

A list of active sites can be obtained from the Trial Manager.

6.3 Participants

6.3.1 Eligibility Criteria

6.3.1.1 Participant selection

There will be no exceptions or waivers to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be directed to the Trial Manager, who will escalate to the CI as required, prior to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered. They ensure that only appropriate participants are entered.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

1 About to receive an antimicrobial to treat a suspected lower respiratory infection (LRTI – including suspected HAP/VAP) for the first time, or a change in existing antimicrobial for LRTI because of deteriorating clinical condition. This relates both to spontaneously breathing patients and those who are intubated for any reason
2 In-patients in a participating ICU/CCU
3 Hospitalised for >48 hours
4 Sufficient volume of airway specimen obtained for routine testing at site plus 200μL for the FilmArray test

6.3.1.3 Participant Exclusion criteria

1 Previous inclusion in WP3
2 Concurrent participation in the active phase (defined as within 30 days of primary end point) of an interventional trial not agreed as acceptable for co-enrolment by the local PIs of both trials. Participants will be permitted to co-enrol in studies that do not involve an intervention (e.g. observational studies).
3 Moribund and/or not expected to live more than 48 h
4 Presence of an existing directive to withhold life-sustaining treatment in relation to antibiotic use
5 Prisoners or young offenders currently in custody of HM Prison Service or supervised by the probation service

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

The Trial intervention and research team must be identified on the delegation log and must have received trial-specific training to ensure consistency in the way the algorithm is used, the specimen is tested and the data are collected at all sites. Training will be delivered through a training package delivered by the relevant experts. Types of training include: an initial face-to-face session, refresher meetings, agreement of a specific version-controlled algorithm and a laboratory manual.

Only those trained and listed on the delegation log to do so, and who have a login in their name, may test the specimens on the machine.

6.3.1.5 Co-enrolment Guidance

A list of trials where co-enrolment has been agreed will be held in a separate document (including any where co-enrolment would not be acceptable). This is not an exhaustive list: if the patient has participated in another trial (within 4 weeks of entering this trial) not listed, please contact the Trial Manager to discuss this, prior to their recruitment.

Co-enrolment will be considered for all trials where the local PIs of both trials do not consider there to be a risk to the participant or outcomes of either trial. Participants are permitted to co-enrol on observation only studies, as long as the PI does not consider this too great a burden. If in doubt decisions should be escalated to the Chief Investigator or Trial Management Groups.

The list of pre-agreed co-enrolment trials can be obtained from the Trial Manager.

6.3.1.6 Screening Procedures and Pre-randomisation Investigations

This trial is designed as a trial of emergency medicine. As such, potential participants will be identified and randomised prior to full informed consent being taken. Screening of a participant may proceed on this basis providing there is nothing to suggest that they or their consultee do not assent or otherwise agree to this. For more detailed information about consent, see Section 7.5. Enrolment of a participant in the trial (in order that randomisation can occur) should be recorded on the study database and in the patient notes.

6.4 Interventions

There are two trial arms, (A) Intervention and (B) Control, both with usual clinical care. This trial is not blinded, so treating clinicians will be aware of the allocation and treatment will be arranged accordingly. Eligibility must be agreed by a clinician who is delegated this activity on the trial delegation log.

An appropriate routine respiratory specimen (sputum, endotracheal aspirate or BAL) for microbiological investigation of HAP/VAP must be obtained according to normal processes. This specimen should be taken around the time the antibiotic leading to inclusion in the study is administered, specimens taken before antibiotic administration are admissible and must be within ±12 hours of antibiotic administration. If a specimen cannot be obtained the patient is not eligible, though the patient can be re-considered once a suitable specimen is obtained as long as all other eligibility criteria are still met. The specimen should either be split immediately into Sample 1 and Sample 2, or collected into two separate containers. Routine containers should be used; sample 1 will follow the usual pathway for routine respiratory specimens and sample 2 should be labelled as 'INHALE WP3 study specific', with the INHALE trial identifiers. Please refer to "INHALE WP3 Laboratory Manual" for full instructions on specimen workflow.

In all cases, Sample 1 should be sent to the usual microbiology testing facility for the site.

Some basic details must be added to the database to identify that this is a new participant, the option to randomise will then become available. Enrolment should be recorded in the participants' hospital notes.

Consent should now be sought from the participant or relative/consultee according to Section 7.5. As this is a trial of emergency medicine, it is the intention that the above intervention steps will have been undertaken prior to consent.

6.4.1 Arm A - Intervention

6.4.1.1 FilmArray test Molecular Diagnostic machine

For participants randomised to the Intervention arm (only), Sample 2 should be prepared and analysed according to the INHALE WP3 Laboratory Manual. Testing should be carried out by appropriately-trained and delegated staff as soon as is possible after the specimen has been taken.

When the FilmArray test run is complete, approximately an hour after the sample run is initiated, and once the corresponding report is available (generated by Film Array software) this must be printed and saved/uploaded to REDCap for INHALE WP3 according to the INHALE WP3 Laboratory Manual, as well as documented in the participant medical notes.

When results are available they should be reviewed by the treating clinician together with the trial-specific algorithm and local prescribing guidelines. It is intended that this happens as soon as possible after the results are available and the time that the results were acted upon should be recorded in the database.

It is anticipated that intervention participants will receive either only one dose of empirical treatment, or perhaps none, before the FilmArray test result and its interpretation become available. If this target is not achieved, the participant should continue receiving normal clinical care, including empirical antibiotics until the clinician has suitable results to consider tailoring the treatment. Number, time given, name and doses of empirical and targeted treatments given should all be recorded on the database.

Future specimens from the same participant may be tested using the FilmArray test provided the following conditions are met:

- The participant was randomised to the intervention arm and has not withdrawn from the trial
- The specimen is being taken as part of routine care and a matching specimen (“sample 2”) has also been sent to microbiology
- Testing is no less than 72h apart from previous specimens
- The specimen would have been taken regardless of the participants involvement in the trial and there is enough spare specimen for the machine testing
- Only staff delegated to do so use the machine and interpret the result and the sample is logged as a second/third etc. trial sample.
- The participant was randomised to the trial ≤21 days ago.

6.4.1.2 Treatment algorithm

This document is version controlled and trial specific. It should be used together with the machine result and local prescribing guidelines to decide what (if any) treatment modifications should be made. It is to be used in addition to any known local requirements and based on clinical symptoms/patient contra-indications. The clinician should always use their clinical judgement as to the best course of action for the individual participant and can choose to accept or disregard the machine results or treatment suggestions. The decision as to what treatment is given (and if relevant, why the machine result was disregarded) should be recorded on the database. The participant can remain in the trial for follow up, regardless of treatment decisions.

Once routine microbiology results are available they should be recorded on the database and used to further modify treatment if necessary and the reasons for modification recorded.

6.4.1.3 Accountability and compliance

The FilmArray test machine must only be used on specimens from participants who are eligible, enrolled in INHALE WP3, and randomised to Arm A (intervention arm). The machines must not be used in any other circumstance or for other patients. Machine use will be closely monitored by the INHALE trial team; site staff have FilmArray test specific logins, and diagnostic pouch numbers are captured on the trial database alongside a paper accountability log. The accountability procedures for INHALE are documented in the INHALE WP3 Laboratory Manual.

Staff not trained and not on the trial delegation log must not operate the machine.

Although the treatment algorithm is based on standard local practice, it is a trial- specific document and, as such, should not be used to guide the treatment of non-trial participants.

If, for any reason (e.g.: machine failure, clinician decision, new information becoming available) the machine result for an intervention participant is not or cannot be used, this should be noted and normal clinical practice and trial procedures should continue.

Compliance to the intervention and reasons for non-compliance will be reviewed as part of the behavioural study, see Section 8.

6.4.1.4 Standard care in the intervention group

All participants randomised to the intervention group will continue to receive standard care alongside the additional intervention testing. Their specimen will be sent to microbiology and all other aspects of clinical management should continue as normal throughout. When the culture results become available the participant's treatment may be tailored according to usual practice at the site and based on any reported susceptibilities.

6.4.2 Arm B – Control

6.4.2.1 Standard Care

Once the respiratory specimen has been split and sample 1 sent to microbiology, clinical management of the HAP/VAP participant should continue as normal for the site.

Sample 2 should be frozen at -20°C (or lower) according to the INHALE WP3 Laboratory Manual, within 8 h of collection. This should be documented on the INHALE Specimen Log. These samples will be shipped to a central facility for INHALE for additional analysis. Additional collection, processing and storage instructions are documented in the INHALE WP3 Laboratory Manual.

6.4.3 Concomitant Care

All participants will receive treatment as usual for their diagnosis or condition regardless of randomisation into this trial. If this includes antibiotics for other indications, this should be recorded and clearly distinguished by completing the correct section on the database.

6.4.4 Protocol Discontinuation

This trial is designed as a trial of emergency medicine. Participants will be randomised and receive the intervention prior to full informed consent being taken. This will be followed up with consent or assent by participants (where they have capacity) or consultees (relative or professional) if they do not regain capacity during their time in the trial.

In consenting to the trial, participants are consenting to follow-up and data collection. However, in exceptional circumstances their clinician may decide that treatment according to the protocol must be stopped early, the reason for this should be documented.

As participation in the trial is entirely voluntary, the participant or their consultee may decline to give consent to their continuing participation or choose to withdraw at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants or their parents or consultees who decline to consent or wish to withdraw will be asked to decide if they wish to withdraw from:

- trial intervention, but participate in all further data collection
- active follow -up but allow existing data and medical records to be used
- specimen storage for future studies
- data linkage for future studies
- all aspects of the trial, and require all data collected up to the point of withdrawal to be excluded from analysis

In all instances for those participants whose consent is subsequently withdrawn, the end of study page must be completed by the research staff, based on information provided by the participant or consultee. The PI in each site should ensure that the relevant page is completed as fully and as soon as possible. Any queries relating to potential withdrawal should be forwarded to the Trial Manager.

In the event that a participant dies during their time in the study, all data will be retained up to date of death, unless they have previously indicated or their representative requests otherwise.

6.5 Outcomes

6.5.1 Primary Outcomes

1. Non-inferiority in clinical cure of pneumonia at 14 days post randomisation.

   Cure of pneumonia defined as: Absence of (i) death where the pneumonia was considered causative or at least contributory, (ii) septic shock (except when associated with a documented non-respiratory infection) and (iii) relapse of the pneumonia. Relapse is defined as an infectious pulmonary event, associated with clinical and radiological signs of HAP or VAP, or a worsening of 2 points of the baseline multiple organ dysfunction score (SOFA or PELOD-2) or (iv) other evidence that the original pneumonia is not cured.

2. Improvement in antimicrobial stewardship at 24 h post randomisation. Defined as:

   Participants on active and proportionate antimicrobial therapy within 24 h of clinical diagnosis, where active therapy is defined as receiving an antimicrobial active against the organism(s) in vitro and proportionate as defined in the prescribing algorithm specific to that site.

6.5.2 Secondary Outcomes

- ICU/CCU length of stay – time from randomisation to discharge from ICU/critical care
- Number of ventilator-free days over 21 days post randomisation (VAP participants only surviving 21 days post randomisation)
- Mortality - death from any cause within 28 days of randomisation
- Incidence of septic shock – within 21 days of randomisation.
- Change in SOFA (ΔSOFA) score from randomisation to 7 days post-randomisation (adults)
- Change in PELOD-2 (ΔPELOD-2) score from randomisation to 7 days post-randomisation (children)
- Change in pSOFA (ΔpSOFA) score from randomisation to 7 days post-randomisation (children)
- % of participants on antibiotics active/inactive against the pathogen(s) found at 24 and 72h from randomisation
- % of participants on proportionate/disproportionate antibiotics in relation to pathogen(s) found at 24 and 72h from randomisation
- % of participants on narrow-spectrum antimicrobials at 24 and 72 h from randomisation
- % of participants with specific adverse events associated with antibiotics within 21 day from randomisation
- % of participants that contract a secondary pneumonia within 21 days from randomisation
- Total antibiotic usage in Defined Daily Dose (DDDs) at 21 days post randomisation (all conditions)
- In patient stay related costs

6.6 Participant Timeline

Visit	Screening and Baseline (may occur on D1)	Day 1	Day 2	Day 3	Day 4	Daily assessment	Day 14	Daily assessment[5]	Day 21 (-1/+3 days)	Day 28

Clinician makes decision to include participant	X									
Eligibility	X									
Demographics added to database	X									
Routine specimen taken for HAP/VAP, split to provide 2 samples		X								
Randomisation		X								
Sample 1 sent for routine microbiology testing		X								
Sample 2 (intervention arm) tested on FilmArray machine		X								
Sample 2 (control arm) stored in -20^{o}C (or lower) freezer		X								
Review and act on machine result when available (intervention only)		X*								
Review and act on microbiology result (both groups) when available			←	—	—	→				
Medical history including current antibiotic use[3]		X								
Apache2/PIM3[2] (as recorded on admission for current admission)	X									
SOFA/Paediatric SOFA/PELOD-2[2]		X	X	X[1]	X[1]	X[1]	X[1]		X	
Adverse events (including c.diff) septic shock (if relevant)[5]		X	X	X	X	X	X	X	X	
Mortality to be recorded (if relevant)		X	X	X	X	X	X	X	X	X
Ventilation details (if relevant)[5]		X	X	X	X	X	X	X	X	
Antimicrobial prescriptions given[5]		X	X	X	X	X	X	X	X	
Pneumonia status[5]		X	X	X	X	X	X	X	X	
Is Routine chest x-ray and/or CT scan available and does it show pneumonia?	X						X		X	
EQ-5D-5L									X	
Hospital resource use[3]	X								X	
Follow up phone call									X[4]	

*Later on day 1 and as soon as possible after decision to test for pneumonia. Further specimens from the same participant may be tested on the machine, within the 21 day trial period, only if clinically indicated and a sample has also been sent routinely to the microbiology laboratory

[1]Every day until day 14 or until clinical cure of pneumonia, whichever is first. Assessments only required on these days if in ICU/CCU and not cured of pneumonia

[2]Which assessment is used depends on whether participant is a child or adult. Clinical teams record these routinely and will know which is used

[3]Data collected may pre and post date the trial period, but this will be collected from clinical records by hospital staff

[4]Window for "day 21" phone call to occur is from days 20-24 post randomisation

[5]Record if relevant until day 21 (even if pneumonia is cured sooner)

6.6.1 Participant Assessments

All consented/assented participants will be enrolled in the trial from the point of randomisation until the Day 21 visit (or phone call). An additional check of their medical records will be carried out at day 28 to answer the question about mortality

Participant-specific demographics, clinical and cost data will be collected from routine medical records.

Information collected from clinical records will be:

- reasons for ICU/CCU admission, including dates of ICU/CCU and hospital admission and discharge (this may pre and post date the trial period)
- type of LRTI/pneumonia (HAP, VAP)
- demographics (including age, gender)
- hospital and ICU/CCU stays in the 3 months prior to the current admission
- patient functional measures (Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Paediatric Index of Mortality 3 (PIM3), which are recorded on admission)
- Sequential Organ Failure Assessment (SOFA) score, paediatric SOFA score and Paediatric Logistic Organ Dysfunction (PELOD-2) score which are recorded daily while in ICU/CCU), data will be collected for the trial for up to 14 days after randomisation or until discharge from ICU, whichever is sooner
- ventilation status (daily)
- need for and type of ventilation (if relevant)
- septic shock (as defined by Singer, M et al) [21]
- mortality (all cause, up to 28 days after randomisation)
- details of pathogens identified by routine microbiology from all body sites, from 7 days prior to randomisation to 21 days after
- antimicrobial prescriptions (including antibiotics administration in the 7 days prior to the study enrolment and antibiotics used to treat HAP/VAP) and reasons for stopping the antibiotic, where the course is not completed, and including number of doses of empirical treatment given
- presence or absence of any significant co-morbidities
- time of specimen collection and time that results were reviewed in ICU/CCU
- results from routine microbiology (all participants) and machine (for intervention group)
- whether a routine x-ray and/or CT scan was carried out and if so the dates closest to screening, day 14 and day 21 and whether it showed evidence of pneumonia
- Clostridium difficile infections and any other adverse events potentially related to antibiotic use
- health service resource use data relating to cost of the ICU/critical care/hospital stay

Participants will have data collected from their routine care records, for assessments as shown in the participant timeline table in section 6.6. Data collection will continue from day 1 until 21 days after randomisation or death. Daily assessments will stop at day 14 and also if the participant is discharged from ICU/CCU or dies before day 14.

For participants discharged home prior to 21 days post randomisation, a brief telephone interview will be conducted at a time convenient to the participant between days 20-24 (providing consent has been given for this). The condition of participants still in hospital at 21 days will be assessed from their notes. Where possible (ie: the participant is conscious, has consented and their treating doctor agrees it appropriate), an EQ-5D-5L will also be collected from participants in hospital at 21 days.

During the telephone call, discharged participants will be asked to provide information on their

- Current health (focusing on breathing, fever and pneumonia)
- Current need for antibiotics or other medications for pneumonia
- GP resource use
- Quality of life questionnaire (EQ-5D-5L).

Note: Day 1 is the calendar day on which the participant has a specimen collected making them eligible for this trial. Daily records refer to a calendar day 24 h period. Day 1 will be the day of randomisation.

6.6.2 Human Tissue Samples

A laboratory manual will be provided to all sites detailing specimen collection and handling procedures. 'Tissue' in this trial will solely comprise respiratory specimens. As, however, these contain human DNA they will nonetheless be subject to handling, storage and future testing according to the Human Tissue Act.

'Sample 2', for participants randomised to the routine care arm, will be stored at -20^{o}C (or lower) at the source sites, or the microbiology laboratories serving them, according to the provided manual. When requested these will be transferred to the Biorepository or other agreed and appropriate laboratory for interim storage. Samples will then be transferred to the agreed laboratories in London or Norwich for analysis. Detailed written instructions and appropriate tissue transfer agreements will be put in place prior to the transfer of relevant material.

Participants are being asked to consent to their anonymous surplus sample being stored for potential future testing in other ethically approved studies. Where consent is given for this, samples will be stored as above.

6.6.3 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they are no longer receiving the trial treatment. If, however, the participant exercises the view that they no longer wish to be followed up, this view must be respected and the participant will be withdrawn entirely from the trial. For further details see Section 6.4.4.

Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow-up early.

Randomised participants who stop trial follow-up early will not be replaced.

6.6.4 Participant Transfers

Occasionally, participants may be transferred to other hospitals or wards. Once they leave ICU/CCU several components that are being collected such as SOFA/PELOD will no longer be available. In these instances, we will only collect data that are accessible on less intensive wards, such as cure of pneumonia, antibiotic prescriptions where available and other infections.

If a participant is transferred to a hospital not participating in INHALE, making continued follow -up at their consenting site inappropriate, every effort should be made for them to be followed at the new hospital.

6.6.5 Loss to Follow-up

In the unlikely event of loss to follow up, the participant will not be replaced.

For participants who are discharged prior to day 21, contact details will be stored in the patient records at the treating hospital and if consent has been given, usual hospital procedures will be used to contact the participant at day 21. If this is without success (after reasonable attempts) then this will be recorded in the database as 'unable to complete the visit'. Number of participants where this has occurred will be monitored by the TMG. The "day 21" call should take place on one occasion between days 20-24.

6.6.6 Trial Closure

The end of the trial is defined as 3 months following the last follow-up of the last participant randomised, to allow for data entry and data cleaning activities to be completed.

6.7 Sample Size

Calculation of the required sample size is based on the co-primary outcomes of clinical cure at 14 days and antimicrobial stewardship within 24 hours (defined above). The trial will investigate non-inferiority in terms of clinical cure and superiority for antimicrobial stewardship. Calculations aim to achieve 90% power and 5% significance for the co-primary analyses, under the conservative assumption of no correlation between them.

Data for the first 100 patients from WP2 has provided estimates for this sample size calculation. For the non-inferiority outcome, the clinical cure rate observed in WP2 was 70%. Assuming a rate of 70% in both arms and defining a non-inferiority limit of 13% [22-26] the trial will require at least 442 participants to achieve 91% power (chosen to ensure 90% power for the co-primary analyses) with a significance level of 5% [27]. From WP2 data we found, under standard care, that 53% of patients received antibiotics that were both appropriate and proportionate (i.e. narrow spectrum wherever possible) within 24 hours of clinical diagnosis. It is clinically important to improve this latter proportion by at least 20% (to 73%). With the sample size of 442 participants required for the non-inferiority outcome, such a difference will be detected with 99% power at a 5% significance level. This sample size will allow overall power for the co-primary analysis to be maintained at 90% (0.91x0.99=0.9), under the conservative assumption of no correlation between the outcomes. To allow for 5% attrition we aim to randomise at least 466 participants (approximately 233 per randomised group). We have not inflated for non-compliance, as none is expected.

The WP2 estimates used for both cure rate and antimicrobial stewardship are consistent with those reported in published studies [21, 23], [28]

6.8 Recruitment and Retention

6.8.1 Recruitment

Recruitment of participants is from pre-approved intensive care/critical care units who have met the INHALE WP3 site selection criteria.

Results from the trial feasibility aspects of WP2 indicated that more than the originally-planned 4 sites would be required to meet the recruitment targets. We will therefore start the trial with around 13 hospital sites open to recruitment. Further sites may be considered in future, if agreed by the TMG and further machines are available and supportable.

On average sites will be required to recruit 2 participants per month. This will be achievable based on recruitment to the earlier work packages. The exact recruitment rate will vary depending on the size of the hospital (number of ICU/CCU beds). Recruitment of hospitals that differ in size and type is intentional and aims to achieve a representative and generalizable range of patients and specimens for the final analysis.

All participants must be assessed as eligible by a clinician delegated to undertake this activity on the trial delegation log. Participation in this trial should be recorded in their patient notes and on the trial database.

No advertisements for participants will be required and patients cannot self-refer. Non-trial doctors and nursing staff may become aware of potentially eligible participants, these patients should be notified to staff listed on the INHALE delegation log. Sites should document locally how this process will work as it may vary by site, depending on total numbers of ICU/CCU staff and number and types of intensive and critical care units within a hospital.

6.8.2 Retention

Retention is unlikely to be challenging in this population. All participants will be visited on the ICU/CCU ward on which they are treated. The only visits which may take place elsewhere are for those who are discharged to another ward or home within 21 days of randomisation. Where this is the case, they will either be visited on the new ward if possible or (with consent) receive a telephone call at 20-24 days (see further details in section 6.6.1).).

The majority of 'visits' are for collection of data from routine medical records. This will be undertaken by research staff at no inconvenience to participants.

6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation

Eligible participants will be randomised on a 1:1 basis to one of the two trial arms (A & B) using a web based randomisation system. Allocation will be blocked (using blocks of randomly varying block length) and stratified by site. The randomisation lists will be generated by the NCTU data manager.

6.9.1.2 Allocation concealment mechanism

At the point of randomisation the member/s of staff responsible for trial enrolment will enter some basic participant eligibility data and demographics into an online randomisation system. An

immediate allocation will be provided by the system to the person entering the data and the PI at site. A confirmatory email will be sent to the trial team.

The database generates a participant identification number, and this should be used on all trial documents.

Concealment of allocation will be guaranteed by using this central web-based randomisation process.

6.9.1.3 Allocation Implementation

Named clinicians at each site (PI and sub-Investigators (Sub-I)) are responsible for ensuring that a participant is suitable to be randomised. In collaboration with the nursing staff, the PI or sub-I will ensure specimens are taken and the participant treated according to the assigned intervention.

The PI at site has ultimate responsibility for ensuring that no other patients are treated using the trial intervention and that randomised participants receive the correct treatment allocation.

6.9.2 Blinding

Not applicable – study is not blinded

6.9.3 Emergency Unblinding

Not applicable – study is not blinded

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Each participant will be given a unique trial Participant IDentification (PID) Number at the point of generating a new study record on the database shortly before randomisation. Data will be collected at the time-points indicated in the Trial Schedule (6.6).

The preferred method of data collection is direct online entry of data onto the central database – which is stored on servers based at the NCTU – by members of the local research team working at each site. Data may be entered onto paper Case Record Forms (CRFs) prior to entry onto the database though this is not an essential step. Staff will receive training on data collection and use of the online system during the Site Initiation Visit (SIV).

As most data to be used in this trial are collected routinely in patient notes, these data can be entered into the trial database by research staff during normal working hours. All data should be entered into the database within 7 days of the timepoint occurring.

Data collection, data entry and queries raised by a member of the INHALE WP3 trial team will be conducted in line with the NCTU and trial specific Standard Operating Procedures and Work Instructions.

Screening logs and enrolment logs will be kept at the trial site in a locked cabinet according to local procedures.

If participants provide consent to the phone call and/or wish to receive the trial newsletter, their contact details will be recorded on the database by site staff to enable this additional contact. There will be a clear logical separation of participant-identifiable data from the trial data and the former

will be deleted prior to archiving. If participants opt out of the phone call or newsletters, their details will not be stored.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act and the General Data Protection Regulation (GDPR) (EU) 2016/679. University College London, as the sponsor, is the Data Controller for this trial.

The data collected in this trial will not be transferred to any third party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the participants' consent.

6.10.2 Data Management

Data will be entered, under the participant's PID number, onto the central database stored on the servers based at the NCTU. Access to this database will be via unique, individually assigned (i.e. not generic) usernames and passwords, and only accessible to members of the INHALE WP3 trial team, and to external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected physically and environmentally in accordance with University of East Anglia's General Information Security Policy 3 (GISP3: Physical and Environmental Security).

The database and associated code have been developed by NCTU Data Management, in conjunction with the INHALE WP3 trial team. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests and search facilities allowing identification of validation failures and/or missing data.

After completion of the trial, the database will be retained on the NCTU servers for on-going analysis of secondary outcomes.

The screening and enrolment logs, linking participant identifiable data to the pseudoanonymised PID, will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the screening and enrolment logs will be stored securely by the sites for 20 years unless otherwise advised by NCTU.

6.10.3 Non-Adherence and Non-Retention

Participants will be analysed on an intention-to-treat basis, regardless of clinicians' decisions in use of the FilmArray test results or antibiotics prescribed.

Reasons for non-adherence and non-retention (both clinician decision and if relevant, participant decision to withdraw) will be recorded.

6.10.4 Statistical Methods

Analyses will follow a predefined detailed statistical analysis plan (SAP), drafted by the NCTU statistician under the guidance of Dr Julie Barber and approved by the PSC and DMC. Analyses will

be planned and conducted according to the principles of GCP, the research governance framework, and ICH topic E9 'Statistical Principles for Clinical Trials' [29] and following the SOPs of the NCTU. A summary of the planned analyses is provided below.

6.10.4.1 Outline of main analyses

Patient-level baseline data will be summarised by treatment group using means (with standard deviations), medians (with interquartile ranges), counts and proportions, as appropriate, to gauge the balance in characteristics between the randomised groups. A CONSORT diagram will describe the flow of participants through the trial including numbers eligible, randomised, consenting and with data for the primary outcomes.

For each randomised group we will summarise the primary outcomes as the proportion of participants where:

- Active and proportionate antimicrobial therapy has been given within 24 h of clinical diagnosis
- Clinical cure was achieved by 14 days after randomisation

For both outcomes the effect of the intervention will be described using a difference in proportions and an odds ratio, each calculated with a 95% confidence interval. For the non-inferiority analysis of clinical cure, confidence intervals will be one sided. Estimates will be obtained from regression models that allow for study site; a binomial generalised linear model with identity link will provide an adjusted difference in proportions and a logistic regression model will estimate an adjusted odds ratio.

Similar approaches will be used for binary secondary outcomes. For continuous secondary outcomes data will be summarised by group using means (SD). Standard regression models will be used (where normality assumptions are satisfied) to obtain differences in means allowing for site and adjusting for baseline values where these are available.

6.10.4.2 Statistical Analysis Plan

Analyses will follow a predefined detailed statistical analysis plan (SAP), drafted by the NCTU statistician following NCTU SOPs under the guidance of Dr Julie Barber and approved by the PSC and DMC.

6.10.4.3 Additional Analyses

The following supportive analyses will be carried out for the primary and secondary outcomes using the same modelling approaches as described previously:

- Estimation of an unadjusted treatment effect estimate
- Further adjusted analyses allowing for other predefined factors related to the outcome.
- Estimation of the treatment effect adjusting for any concerning imbalances in baseline characteristics.

6.10.4.4 Analysis Population

We do not expect non- compliance to be an issue in this trial; however, in the event that non-compliance occurs, a per protocol analysis will provide the primary results for the non-inferiority

outcome. An ITT analysis will be conducted alongside this as a sensitivity analysis and any discrepancies closely examined. For the superiority analysis ITT analysis will provide the primary results.

6.10.4.5 Missing Data

Reasons for missing outcome data will be described and frequency (%) of subjects with missing data, by reason will be provided for each randomised group (and for each outcome).

Characteristics of participants with and without missing outcome data will be compared using logistic regression models (with missing yes/no as the outcome) and characteristics that predict missingness identified. In a sensitivity analysis, the treatment effect will then be re-estimated with additional adjustment for baseline predictors of missingness. Further analyses based on multiple imputation methods will be considered if appropriate.

6.10.5 Economic evaluations

A cost-effectiveness study will be conducted from a hospital perspective. The alternatives being compared will be the same as for the main clinical study, as detailed in Sections 6.4.1 and 6.4.2. Briefly, the intervention arm involves the use of the FilmArray test Molecular diagnostic machine within 8 hours of randomisation plus microbiology laboratory result at 2-3 days. The control group comprise microbiology laboratory result at 2-3 days only. The outcome measure used in the economic evaluation will be the study co-primary outcome measure (Section 6.5.1). If the two arms of the study are found to be equivalent in terms of clinical cure of pneumonia at 14 days post randomization, we will conduct a cost-effectiveness study evaluating the incremental cost per additional patient receiving active and proportionate antibiotics within 24 hours of clinical decision to prescribe antibiotics for HAP/VAP. If there is not equivalence in clinical cure but there is an improvement in antibiotic stewardship, then interpretation will be more difficult and we will use the decision tree model to explore the consequences of this situation – see Section 6.10.5.2. As this trial will involve very ill patients in ICU/CCU, collection of patient reported measures, such as the EQ-5D-5L, [30] will not be possible for all patients. For individuals discharged before 21 days health related quality of life will be assessed by means of EQ-5D-5L, administered by telephone interview. However, as EQ-5D-5L completion will not be possible for individuals still in ICU/CCU it will not be used as the outcome measure in the within trial evaluation. Additionally, it would be expected that the characteristics of those who have EQ-5D-5L at 21 days will be different from those who do not. This is because we would only be collecting EQ-5D data from individuals who were able to be discharged. We would expect that on average, these individuals would have better health than individuals who were not able to be discharged at 21 days. EQ-5D-5L data will be collected to help inform the economic model (section 6.10.5.2); these data will be used alongside EQ-5D-5L data already collected as part of WP2 of INHALE.

Resource use data collection in this study will be limited to the inpatient stay. Therefore, an NHS and social services perspective, as recommended by NICE, will not be possible, costs will be estimated from the perspective of the hospital. We will collect all resources required for microbiological diagnosis in both arms of the RCT. This will include costs of routine laboratory culture as well as the molecular diagnostic machine. The costs of the molecular diagnostic machine will build on work undertaken in WP1 to identify an indicative cost of the machine and will include costs associated

with: equipment; consumables; and staff time. As this technology is new there may not be definitive market prices at the time of analysis and we will conduct sensitivity analysis around assumptions made in the costing process as well as assumptions relating to throughput. Data will also be collected on antibiotic prescribing in both arms of the RCT, and this will be costed using appropriate unit cost data. Data relevant to hospital resource use will be obtained from participating hospitals by means of healthcare resource group codes (HRGs). This would include length of stay in the ICU/CCU and also total hospital length of stay. Data on in hospital use of antibiotics will also be recorded. Cost year will be the most up to date available costs at time of analysis, and will be reported in pounds Sterling.

Estimates of costs and effects will be used to calculate incremental cost-effectiveness ratios (ICERs) evaluating the incremental cost per additional patient receiving active and proportionate antibiotics within 24 hours of decision to prescribe antibiotics for HAP/VAP diagnosis. Where appropriate, regression- based methods will be used to allow for differences in baseline characteristics. Uncertainty in data will be allowed for by the use of cost-effectiveness acceptability curves (CEACs), which estimate the probability that the intervention is cost-effective at different monetary valuations of the outcome measure. As costs will be estimated from routinely collected hospital data we would not expect high levels of missing data. However, the extent of missing data will be evaluated. This will be conducted by the study health economics team, in consultation with the study statistician and CI. If deemed appropriate, this will be allowed for using appropriate methodology, such as multiple imputation. The above economic analysis constitutes a 'within trial' analysis, as it would be conducted within the time frame of the clinical trial. This will constitute the primary economic analysis.

6.10.5.1 Health Economic Analysis Plan

In line with Norwich CTU practice a health economics analysis plan will be developed. This will be discussed with the study chief investigator and trial statistician, and other INHALE investigators.

6.10.5.2 Model based analysis

As the study population will be highly heterogeneous, interpretation of the economic evaluation from the RCT may not be straightforward. Additionally, the trial occurs within a short period of time and hence long-run outcomes from treatment will not be available as part of the study. Therefore, in order to explore the effect of assumptions and potential variability we will further develop the decision tree model being developed as part of the INHALE health economics work package (WP5). Furthermore, data from the literature will be used to estimate the potential long run HRQoL effects of HAP/VAP, as well as estimating a cost/QALY approach. Assumptions as to the health benefits of different pathways and outcomes will allow us to explore scenarios relating to potential longer term effects (e.g. potential effects on antibiotic use, resistance and related health outcomes). Literature data and clinical opinion will be incorporated where necessary. This decision tree model will be used to explore a range of 'what if' scenarios evaluating different consequences of results produced from the trial. The exact nature of scenarios to be explored will be discussed with study clinicians and pre-specified in the HEAP. Assumptions about the consequences of care provided and of improved antimicrobial stewardship will be formulated. This approach is speculative but will potentially inform

decision makers as to the potential consequences of different diagnostic regimes. The results of this model will constitute a secondary analysis to the primary analysis detailed in Section 6.10.5.

The model will be constructed in Microsoft Excel. This will be a probabilistic model, where model inputs will constitute random draws from pre-specified distributions. The structure of the model has been established in consultation with clinical experts from the INHALE study. Results will be taken from a probabilistic sensitivity analysis (PSA), which constitutes repeatedly running the model to obtain a large number of separate sets of results (samples). PSA will be used for both cost per additional patient receiving active and proportionate antibiotics within 24 hours of decision to prescribe antibiotics for HAP/VAP diagnosis. Results will be presented in the form of mean estimate of effect and 95% percentiles from PSA results. Also presented will be CEACs. Data for the model will be drawn from a variety of sources. This will include: data obtained from other INHALE work packages; data obtained from INHALE WP3; other published literature sources; and where necessary, expert opinion.

6.10.6 Analysis of Qualitative Information

Qualitative information will be collected as part of a sub-study, this will be detailed in a separate protocol and this is described briefly in section 8.1.

6.10.7 Analysis of Tissue Samples

A laboratory manual will be developed and agreed by the TMG prior to any analysis of samples. 'Tissue' in this trial will solely comprise respiratory specimens.

6.11 Data Monitoring

6.11.1 Data Monitoring Committee

An independent data monitoring committee (DMC) is in place for this trial. They are independent of the sponsor, sites and trial team as per NIHR (funder) requirements.

Further details of the roles and responsibilities of the DMC, including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the INHALE WP3 DMC Terms of Reference (ToR).

6.11.2 Interim Analyses

No efficacy interim analyses are planned. However, a description of recruitment rates, withdraw rates, completeness of primary and secondary outcomes and safety information will be prepared based on data from the internal pilot.

6.11.3 Data Monitoring for Harm

Monitoring for harm will be conducted continually, as part of normal clinical practice. The intervention in this trial does not include any new medications and, accordingly, any reactions to medications prescribed should be treated according to standard local procedures for escalation/de-escalation and change of therapy.

The treating clinician does not have to change therapy based on the intervention if they do not believe it would be in the participant's best interest. Data on such decisions is recorded.

Serious adverse events that require monitoring for harm are described in section 6.12. These will be reviewed regularly by the Trial Management Group (TMG) and during DMC meetings.

6.12 Safety reporting

The trial population includes very sick, hospitalised children and adults being treated in Intensive Care Units where they are under close monitoring at all times. The trial intervention involves testing routinely collected specimens using a CE-marked molecular diagnostic device to determine antibiotic sensitivity and resistance.

Table 1: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with the trial interventions.
Serious Adverse Event (SAE)	Results in death, prolongation of hospitalisation, is life threatening, leads to persistent or significant disability or incapacity or to a congenital anomaly or birth defect

The following adverse and serious adverse events are secondary outcomes of the trial:

- life-threatening events (including septic shock, secondary infections)
- changes in laboratory parameters indicative of organ failure (SOFA and PELOD scores)
- receipt of inactive antibiotic/inappropriate step-down of therapy
- adverse reactions to antibiotics including severe hypersensitivity, antibiotic induced diarrhoea and *Clostridium difficile* infection
- death

They are recorded as part of routine data collection in clinical notes and on the eCRF, and are not subject to expedited reporting on an SAE form.

Predominant adverse outcomes of concern that require expedited reporting to the CI via the Norwich CTU within 24 hours:

- Machine error and laboratory errors producing misleading or wrong results, leading to inappropriate antibiotic prescribing with serious adverse consequences e.g. death, life threatening event, hospitalisation or prolongation of hospitalisation
- Any other situation that the site PI feels requires expedited reporting to the CI

6.12.1 Investigator responsibilities relating to safety reporting

The PI at each site is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

Non-serious AEs should be recorded in the patient's medical notes and in relevant section of the eCRF. Reportable SAEs should be notified to NCTU immediately the investigator becomes aware of the event, in no circumstance should this notification take longer than 24 hours.

6.12.1.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must assess whether or not the event is serious using the definition given in Table 1. If the event is classified as 'serious' and reportable in this trial then an SAE form must be completed and NCTU (or delegated body) notified immediately.

6.12.1.2 Severity or grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity gradings in the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) June 14, 2010 criteria using the following definitions:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3: Severe or medically significant but not immediately life threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**
Grade 4: Life threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE

A semi colon indicates 'or' within the description of the grade.
* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.
** Self care Activities of Daily Living (ADL) refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bed-ridden.

6.12.1.3 Causality

The principal investigator at the site must assess the causality of all serious events in relation to the trial intervention using the definitions in Table 2.

Table 2: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (eg the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (eg the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (eg because the event occurs within a reasonable time after the trial intervention). However, the influence of other factors may have contributed to the event (eg the participant's clinical	Related SAE

	condition or other concomitant treatment)	
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	Related SAE
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Related SAE

6.12.1.4 Expectedness

Because of the difficulty in developing a list of expected adverse events in this complex clinical environment, expectedness will be reviewed by the CI against the machine operating characteristics for the intervention arm and against normal lab performance indicators for the control arm. Expectedness will be confirmed with the local PI. Any events which are deemed unexpected and related to treatment in either group will be reported as Suspected Unexpected Serious Adverse Reactions (SUSARs).

6.12.2 Notifications

6.12.2.1 Notifications by the Investigator to the NCTU

The NCTU must be notified of all reportable SAEs within 24 h of the investigator becoming aware of the event. This will include SAEs reported from time of randomisation until day 28 for individual participants in the study.

The SAE form must be completed by the local investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care) with attention paid to the grading, causality and expectedness of the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to NCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the trial number (PID) and month and year of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

The SAE form must be scanned and sent by email to the trial team at NCTU:

nctu.safety@uea.ac.uk

Participants experiencing SAEs must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue beyond completion of protocol treatment and/or trial follow-up if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to NCTU as further information becomes available. Additional information and/or copies of test results etc may

be provided separately. The participant must be identified by trial number, month and year of birth and initials only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

6.12.2.2 NCTU responsibilities

Medically-qualified staff at the NCTU and/or the Chief Investigator (CI or a medically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality assessment given by the local investigator and the CI, both opinions and any justifications will be provided in subsequent reports.

The CI will also review the assessment of expectedness and if their decision is different to that of the PI, the event will be reported as a SUSAR, with both explanations provided to the REC.

NCTU is responsible for the reporting of relevant SAEs and all SUSARs to the Sponsor and REC. Fatal and life threatening SUSARs must be reported to the Sponsor within 5 days of NCTU becoming aware of the event and to the REC within 7 days.

NCTU will keep investigators informed of any safety issues that arise during the course of the trial.

6.13 Quality Assurance and Control

6.13.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the INHALE WP3 trial are based on the standard NCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial, likelihood of detectability of risks and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

6.13.2 Central Monitoring at NCTU

NCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database will be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the INHALE WP3 trial Data Management Plan.

6.13.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the INHALE WP3 Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority, NCTU must be notified as soon as possible.

6.13.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

6.13.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the INHALE WP3 Quality Management and Monitoring Plan.

6.13.4.1 Trial Team

The Chief Investigator, Trial Manager, Trial Statistician and the Norwich CTU are responsible for the day to day running of the trial as detailed in trial working practice documents and implementing processes described in the Quality Management and Monitoring Plan and Safety Management Plan. They will work together as the Trial Management Team (TMT).

6.13.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

6.13.4.3 Independent Programme Steering Committee

An Independent Programme Steering Committee (PSC) was set up to oversee the programme in its entirety. The PSC will undertake functions of the TSC as the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The PSC will provide advice to the CI, NCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in an updated PSC, or separate TSC terms of reference.

6.13.4.4 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to unblinded accumulating comparative data. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

6.13.4.5 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. When an institution is the trial sponsor and has delegated some and/or the totality of Sponsor's activities to the CI and the NCTU, the Sponsor's form for delegated activities should be completed and signed by all parties before the start of the trial.

7 Ethics and Dissemination

7.1 Research Ethics and Health Research Authority Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC and to HRA for approval. Any subsequent amendments to these documents will be submitted for further approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow -up and data analysis according to the treatment option to which they have been allocated.

7.2 Competent Authority Approvals

Not applicable

7.3 Other Approvals

Documentation will need to be submitted to the R&D Department at each NHS Site in order to gain confirmation of capacity and capability prior to the trial being initiated at that site. Confirmation from the site will take the form of a site agreement signed by both the Sponsor/NCTU and the relevant site.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the NCTU Protocol Review Committee.

7.4 Amendments

Amendments to the Protocol and other documents (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be agreed by the TMG. Such amendments will be forwarded to the Sponsor for confirmation as to whether it is either substantial or non-substantial and will then be submitted to the Health Research Authority or Ethics Committee for categorisation and approval. Once the amendment has been categorised it will be sent to relevant sites for consideration in accordance with standard HRA processes and timescales. Amendments must not be implemented until HRA approval is received and sites have either confirmed acceptance or, no objection has been received within the defined timescale. Notification will be sent by NCTU to trial personnel to confirm when an amendment can be implemented.

7.5 Consent or Assent

INHALE is a trial in an emergency setting; pneumonia and respiratory infections are life threatening and a decision to treat is taken very quickly, this standard care should not be delayed because of the trial. This will make any attempt to collect fully informed consent inappropriate prior to treatment, nor would it be appropriate to provide the information to distressed relatives prior to inclusion in the trial. Consent will therefore not be taken before randomisation and the intervention is delivered but instead will follow a retrospective process. This is recognised in European Law [31] and this decision has been made in consultation with the trial PPI panel and a review of the literature [32-34].

The trial is not looking at an invasive treatment or medicine, the same antibiotics and decisions are available to clinicians at all times.

Consent or assent will be taken at the earliest or most appropriate opportunity after the initial treatment on day 1 and preferably within the next 48 hours. Participants or consultees should be given as long as needed to make an informed decision and the participant should remain in the trial whilst a decision is sought and as long as there is no objection.

Participants will be consented by delegated members of the Trial Team. It is anticipated that a consultee will give assent to participate in most cases due to the expected incapacity of most ICU/CCU patients. To enable such patients' participation in clinical research, the Mental Capacity Act (2005) [35] allows a consultee to grant/withhold permission until the participant recovers capacity. The consultee may be a personal consultee or independent professional consultee. Consultees will be approached by a member of the Trial Team, who will explain the trial and provide an information sheet (produced in consultation with the PPI panel). The consultee will be able to discuss and ask questions before being asked whether they wish to sign agreement. Should the participant recover capacity, with clinical team agreement, the research nurse at site will approach them directly: their consent/refusal over-rides consultee agreement.

For children (aged 15 years or under), the parent(s) or guardian of a child will be approached to give consent for their child to participate. Paediatric information sheets are provided for a variety of levels of understanding and an appropriate form (PI discretion) should be given to children or adolescent participants. They must be asked to assent or agree. Participation must be refused in the event that a child is distressed by participation, or does not assent.

Participants or their consultee will be provided with a Participant Information Sheet (PIS) and given time to read it fully. Following discussion with a medical-qualified investigator or suitably trained and authorised delegate, any questions will be answered and if the person is willing to participate, written informed consent will be obtained. During the consent process it will be made completely and unambiguously clear that the participant or consultee is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment (or that of their child).

In private London hospitals, the majority of International patients speak either English or Arabic. Arabic translations of participant information sheets and informed consent forms will be provided. Non-English speaking participants will be consulted via translators. It is not anticipated that additional translations in other languages will be required.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the participant information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use. Consent will also be re-sought in the event that a child's carer changes.

A copy of the approved consent documents are available from the NCTU trial team.

7.6 Confidentiality

Any paper copies of personal trial data will be kept at the participating site in a secure location with restricted access.

Confidentiality of participant's personal data is ensured by not collecting participant names on CRFs and limiting access to personal information held on the database at NCTU. At trial enrolment the participant will be issued a participant identification number and this will be the primary identifier for the participant, with secondary identifiers of month and year of birth and initials. Initials will be deleted after the main trial has finished and not be sent with other trial information for analysis. Month and year of birth will not be collected on samples, only initials and initials will also be removed from samples that are stored for future analysis.

The participant's consent form will carry their name and signature. These will be kept at the trial site, with a copy sent to NCTU for monitoring purposes. This copy will be destroyed once checks are complete. Consent forms will not be kept with any additional participant data.

7.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

7.8 Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the trial. University College London 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.

Participants may also be able to claim compensation for injury caused by participation in this trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this trial shall provide negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

7.9 NHS Trust Incidents and Near Misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.
A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.

It puts Trust property or assets in an adverse position or at risk of loss or damage

7.10 Finance

The whole of the INHALE Programme, including this trial, is fully funded by the NIHR, through an NIHR PGfAR grant with the reference number RP-PG-0514-20018

It is not expected that any further external funding will be sought for the trial.

7.11 Archiving

At the end of the trial, all essential documentation will be archived securely by the CI for a minimum of 20 years from the declaration of end of trial.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

7.12 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG. Considerations for approving access are documented in the TMG Terms of Reference.

7.13 Ancillary and Post-trial Care

Machines only to be used for trial participants. They will not be available after the trial to participating units.

7.14 Publication Policy

7.14.1 Trial Results

The results of the INHALE Trial will be disseminated via conferences and journal publications.

The UCLH press office will prepare press releases summarising key results, when these are about to be published or presented.

National dissemination will be achieved through multiple approaches. A website designed to inform professionals and the public about the trial exists (www.ucl.ac.uk/inhale-project) and will be regularly updated. The INHALE project Twitter feed (@HAP_Diagnostics) is regularly updated with trial news and progress. Local PIs will be encouraged to organise lectures and symposia to aid dissemination within their NHS trusts and the trial team will be pleased to assist with this if requested.

Towards the end of the trial dissemination workshops will be organized, with invitations to key national NHS stakeholders, e.g. diagnostics, clinical microbiology, infectious disease, intensive care and health economics, alongside members of the public.

Key decision- making bodies will be engaged through existing PHE, Department of Health and NHS structures, also via ARHAI. We will work with these organisations to produce a framework for the widespread release of the key messages of our programme's conclusions.

The results of the trial will be disseminated regardless of the direction of effect.

7.14.2 Authorship

The results of the INHALE trial will be written in collaboration between research scientists and clinicians participating in the trial. Professional writers will not be used. Authorship and order of authors will be decided based on merit according to an individual's contribution to the trial. In the event of conflict in authorship the TMC and Chief Investigator will undertake decisions and resolve disputes. A copy of the full INHALE publications policy can be obtained from the Trial Manager on request.

7.14.3 Reproducible Research

The INHALE WP3 trial protocol will be published and made available for public access.

8 Ancillary Studies

8.1 Behavioural Sub-Study

This integrated sub-study fits within the broader INHALE research programme and will identify barriers and facilitators to molecular diagnostic-guided treatment and antimicrobial prescribing. It is designed to develop methods to reduce barriers and enhance facilitators, thereby linking diagnostic results to good prescribing. Specifically, the work will:

a) Examine why ICU/CCU-based molecular diagnostics are taken up (or not) from an individual and systems perspective. This will establish relevant individual factors (e.g. perceptions and capabilities of individual prescribers) and system factors (e.g. within hours vs. out-of-hours prescribing) and evidence whether and how molecular diagnostic information might be applied in practice
b) Using data from (a) above, develop materials supporting appropriate and optimal use of molecular diagnostics in RCT's intervention arm (including the prescribing algorithms).
c) Assess how molecular diagnostic are used in the INHALE trial to establish the fidelity of the intervention and the efficacy of the support materials developed in (b) above.
d) Develop a broad, far-reaching, strategy for implementation of molecular diagnostics across the NHS, if appropriate. This will incorporate a behaviour change component, derived from our experience in this study. Elements of antimicrobial stewardship will represent the Exemplar in this context.

The work will build on that already undertaken during the pre-trial phase. The research will take place within some of the ICUs/CCUs taking part in the trial, but only involving members of staff as participants. No patients are included in this sub-study.

Separate consent forms will be provided for staff and a separate document will describe the plans for this work in more detail.

A summary of the trial phase work of this sub-study is as follows:

"Embedded qualitative study of molecular diagnostic use in INHALE to identify the drivers for, and elements of, normative antibiotic prescribing decisions (guideline concordant) and exceptions (guideline discordant) antimicrobial prescribing decisions".

Antibiotic prescribing will continue to be studied and its determinants during the WP3 trial, in both the intervention and control arms. Exceptions will be carefully investigated - whether to normative prescribing in the control arm or to the treatment guided by the algorithm and supportive material in the intervention arm. Exceptions will be subjected to Root Cause Analysis to understand the factors influencing discordant prescribing.
In the Intervention arm, how the molecular diagnostic is used in practice will be documented and factors identified that impede or enhance its influence on prescribing. This will help to:
(1) Understand reasons why the trial succeeds or fails (i.e. fidelity questions). For example, whether behavioural factors compromise the potentially positive effect of the molecular diagnostics on antibiotic stewardship (e.g. if its results were not trusted by prescribers, who continued to prefer broad-spectrum antibiotics).

(2) Identify opportunities and potential methods to improve the acceptance of molecular diagnostic results by observing prescribing exceptions as they occur. This will also enable identification of the salient barriers and drivers to guideline-concordant prescribing and their antecedents (e.g. the relative roles of motivation and/or capability/opportunity). This will prompt and guide modification of support materials and how they are delivered.

In the Control arm, researching antibiotic prescribing behaviour and its antecedents will be continued. It provides a direct comparison of antibiotic prescribing behaviour without molecular diagnostics, but under trial conditions. This will add to the longitudinal comparison of antibiotic stewardship before and after the introduction of molecular diagnostics and associated guidance. Because randomisation is at the patient level, it will be possible to assess whether antibiotic prescribing behaviour in the Control arm is influenced by clinicians developing different approaches as a result of the availability of the diagnostic and related information within the Intervention arm (even though molecular diagnostics will not, of course, be used in the control arm). This will provide insight into trial processes within the Control arm and will provide intelligence on any wider changes that arise following receipt of the algorithm and support materials by clinicians, identifying additional opportunities for maximizing adoption. To this extent, the study will identify opportunities for improving antibiotic stewardship whether or not the molecular diagnostic adds value.

Sampling

Sampling will be the same as in the pre-trial work. The approach resembles purposive sampling, in that prescribing events, identified daily, trigger interviews. The aim will be to 'sample to completion', achieving saturation (i.e. 3 consecutive interviews without new themes emerging). In the pre-trial work it was estimated that completion would be achieved by 25 interviews (critical incident prescribing episodes).

In this 'during trial phase' work there is capacity for more interviews (up to a total of 100 critical incident prescribing episodes across the two conditions), this is important because the introduction of molecular diagnostics may create a range of additional issues influencing prescribing behaviour that need to captured and understood. For this reason, it is likely that more critical incident prescribing episodes will need to be assessed to reach saturation. Sampling capacity has therefore been increased to 50 episodes within each arm of the trial.

Analysis

The semi-structured interviews will be recorded and transcribed verbatim. A framework analysis will be applied based on the Theoretical Domains Framework as used in the pre-trial work.

9 Protocol Amendments

9.1 Summary of changes for v1.1

1. Version and date details updated
2. Correction to state only month and year of birth of participants will be collected, in line with what is described in the patient information (previously stated as date of birth)
3. The following statement has been added to section 7.6 (confidentiality) to match the patient information: "Initials will be deleted after the main trial has finished and not be sent with other trial information for analysis. Month and year of birth will not be collected on samples, only initials and initials will also be removed from samples that are stored for future analysis."

9.2 Summary of changes for v1.2

1. Version and date details updated
2. NRES reference number updated (because protocol was originally submitted to a different REC and then transferred prior to review and approval)
3. Exclusion criteria number 4 amended to clarify that the definition of "withholding life sustaining treatment" refers only to whether antibiotics would still be prescribed
4. An additional exclusion criteria (number 5) has been added to be clear that prisoners currently in custody are excluded
5. Start date updated to reflect current likely recruitment start date
6. Updates to reflect changes in oversight group members
7. Added "or lower" after -20^{o}C freezer conditions
8. Primary outcome full definition has added wording to further clarify "cure of pneumonia"
9. On page 34, definition of "day 1" of the trial has been updated and a sentence removed to avoid ambiguity. Day 1 will now always be defined as day of randomisation, which will also be the day when the participant becomes eligible
10. SAE reporting window clarified as not previously explicit in the protocol (no change in practice and follows guidelines for this type of trial)
11. Minor typographical errors and minor amendments for consistency and clarity added throughout

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11 Appendices

None