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Inhale work package 3 – rapid versus standard testing to diagnose lung infections in intensive care, including COVID-19 observational sub-study

Submission date
15/07/2019

Recruitment status
No longer recruiting

Registration date
05/08/2019

Overall study status
Completed

Last Edited
12/08/2025

Condition category
Respiratory

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Severely ill hospital patients often develop lung and respiratory infections such as pneumonia. Such infections are life-threatening and must be treated as soon as possible with antibiotics. It is well known that not all antibiotics are working as well as they used to, this is largely due to resistance of the bacteria that cause the infections and has been listed as a major public health concern by the UK Department of Health and many other countries around the world. Current practice in hospitals, when a patient is suspected of having a lung infection, is to send a sample of their sputum (spit and phlegm mixture collected from their airways) to the microbiology lab for analysis. This takes 2-3 days, during that time the suspected infection is treated with a broad range of antibiotics. It has been found that this approach means around 67% of people with pneumonia receive antibiotics that they do not need, thus creating resistance risk and can cause unnecessary and unpleasant side effects to the patients themselves. The INHALE trial tests a rapid diagnostic machine (the Biofire "FilmArray") to see if sample results can be provided quicker than lab sample testing and if this leads to the best and most appropriate antibiotics being prescribed sooner.

Added 11/06/2020: During the COVID-19 pandemic, the main INHALE trial recruitment has had to be suspended. Staff at several participating ICUs have suggested results from the Pneumonia Panel could prove extremely useful in the management of COVID-19 patients who would otherwise be treated with non-specific antibiotics to treat possible secondary bacterial pneumonias. They have requested access to machines and reagents, which are approved ("CE marked") for clinical use. To accommodate this, and to maximise clinical potential, the researchers have designed an observational sub-study for current INHALE sites, to allow evaluation of the clinical use of the tests. This is distinct from the INHALE trial, providing useful data for patient and antibiotic management during the COVID-19 epidemic, allowing sites to remain open and engaged, ready to re-commence randomisation to the trial when necessary. Accordingly, the aim of the sub-study is to describe clinically, how useful the rapid Pneumonia Panel test is for the management of ICU patients during the COVID-19 outbreak.

Who can participate?
In-patients in a participating ICU/CCU with suspected Lower Respiratory Tract Infections (LRTIs) including Hospital Acquired Pneumonia (HAP) or Ventilator Acquired Pneumonia (VAP) will be potentially eligible to participate.

What does the study involve?
As part of usual care participants will provide samples of sputum for analysis. Participants will either have their samples tested in the usual way or in the usual way and with a new test which is being trialled in this study. Machine results should be available and reviewed within 8 hours of collection. All participants will have their sample sent to the lab regardless of whether it is also tested on the new machine, so all standard care options are also available to their doctor. Treatment will proceed as usual for all participants. To guide doctors in prescribing the most appropriate antibiotic according to resistance 'stewardship' guidelines, trial-specific guidance will also be provided.

Added 11/06/2020: Doctors will have the option to use the BioFire machine for patients in ICU who test positive for Covid-19. A small amount of anonymous data (they cannot be identified) is collected from their medical records to help understand how best to treat patients who have COVID-19 and secondary pneumonias.

What are the possible benefits and risks of participating?
There are no direct benefits to patients in hospital today but they will be playing an important part in helping the NHS to treat adults and children with pneumonia in the next few years. The risk is considered to be no higher than the normal care that they would receive if they do not take part in this study. No new drug is being tested and their doctor can prescribe all of the same medicines regardless of how their sample has been tested. The antibiotics given to help fight the participant’s lung infection can be changed if the results show this might help them get better quicker or that they don’t need the antibiotics. While the machine can identify the most common causes of pneumonia, there are some rare bacteria it cannot find. Therefore there is a small risk that participants might have one of these rare bacteria, in which case treatment may have to be changed again after 2-3 days, once the bacteria from their phlegm have been grown in the lab.

Where is the study run from?
University College London Hospital, UK

When is the study starting and how long is it expected to run for?
July 2019 to April 2022

Who is funding the study?
National Institute for Health Research (NIHR), UK

Who is the main contact?
Dr Vicky Enne
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Study website
http://www.ucl.ac.uk/inhale-project

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
41211

Study information

Scientific Title
The impact of using film array 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 and a COVID-19 related observational sub-study

Acronym
INHALE

Study objectives
Rapid diagnostics will be at least equivalent to standard care for clinical and safety outcomes in this trial and show improvement in antimicrobial stewardship

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/03/2019, NHS REC London-Brighton & Sussex (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT; 0207 104 8241; NRESCommittee.SECoast-BrightonandSussex@nhs.net), ref: 19/LO/0400

Study design
Randomized; Interventional; Design type: Treatment, Complex Intervention

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Pneumonia

Interventions
Patients in intensive care presenting with suspected Lower Respiratory Tract Infections (LRTIs) including Hospital Acquired Pneumonia (HAP) or Ventilator Acquired Pneumonia (VAP) will be potentially eligible to participate.

Intensive Care Unit (ICU) staff will be responsible for identifying potentially eligible patients. The trial has been designed as a trial of emergency medicine and as such participants samples will be tested and where relevant results acted upon before they have been approached for consent. The sample itself will be an airway specimen (sputum), collected routinely as recommended for all patients who have a suspected LRTI. 200 microlitres of spare sample would be retained and, depending on which group the participant has been randomised to, will either be tested straight away on a new machine, or frozen.

When an eligible patient is identified, the site staff will need to add some basic details to the trial database (in order that it can generate a participant ID number and avoid adding the same person twice) they will then be able to press a button which randomly selects which group that participant will be in. Those in group A will have their sample tested on the new machine straight away, whilst also receiving all other treatment as usual and those in group B will have only treatment as usual. There is a 50:50 chance of being in either group. A total of 466 participants will be included, 233 in each group.

The machine under test is a Biofire "FilmArray" molecular diagnostic machine. This works by identifying the genetic material of the bacteria (DNA) present in a sample and thereby identifying what is causing the infection, within 1-2 hours. In this trial this will be in addition to treatment as usual (microbiology culture preparation) which will also return a result to the treating doctor within 2-3 days. To enable the treating doctor and trial team to agree that the most appropriate antibiotic have been given according to stewardship guidelines, an "algorithm" document has been produced. This has been prepared for the trial but is intended to be adapted

to individual site requirements. When data are analysed, it will be against the agreed algorithm for that site that stewardship will be determined.
The treating doctor has all the usual antibiotics available to them and can choose to disregard the algorithm if appropriate. All treatments given will be recorded in the trial database.

If a sample is tested on the new machine straight away and results acted upon, it will be possible to tailor treatment with antibiotics much sooner (within 1-2 hours, although the study allows up to 8 hours) than when using standard microbiology techniques (2-3 days). It is not known whether this will lead to improvements in antibiotic stewardship - for example whether doctors will feel confident with the machine result and change the treatment sooner and if so choose a single appropriate antibiotic rather than continue to treat with a broader ranging dose of different antibiotics. The trial also aims to confirm that there is at least equivalence in cure rates of pneumonia when using the machine. Other outcomes will compare safety signals such as adverse events, septic shock and mortality rates and two other key aspects of the programme of research include a cost/benefit analysis and a behavioural study, to look at the likely success of introducing such a change to routine practice in future. To understand this it is necessary to include a control group which receives only treatment as usual. No participants in either group will have any standard treatment options withheld, those in the machine group will have the trial test in addition to standard care microbiology and their treating doctor will have all of the usual treatment options available to them.

All participants will have sample sent to the local microbiology lab as usual for standard care, but their sample will have been split at collection to retain a portion of spare sample. Those in group A will have their spare sample run on the new machine, located in or near to ICU as soon as possible. Those in group B will have their spare sample frozen for future shipping and centralised analysis. (The results of the central testing will never be reported to site and are not intended to influence local treatment in any way). From that point forwards group B participants will follow only standard care.

As soon as a machine result is available for group A participants, the treating doctor should review and together with the trial specific treatment algorithm (which may be agreed and adapted to take into account local variations) will decide whether antibiotic treatment should be modified. Further modification may be required when the lab results are known and these will be reviewed and acted upon regardless of which group the participant is in.

As soon as appropriate (recommended within 48 hours) the local research staff should approach the patient or their relatives or representatives (parent for children in specialist paediatric hospitals) to explain about the trial and seek their consent. They will be given as long as they need to decide and the participant will continue to be treated according to the protocol during this time, as long as they assent. This whole process will be undertaken by specially trained staff with agreement from the local treating clinician. We have undertaken extensive pre-trial consultation on this process, including with our patient and public involvement team (PPI) and clinicians from a range of hospitals, including GOSH, who have a lot of experience with such trial designs. We have their support and the consensus is that such a trial would not produce representative results if we were to include only participants who were able to give consent at time of randomisation.

For all participants, demographic, clinical and cost data will be collected and scores of disease progression and severity will be measured for up to 14 days following recruitment. This will be collected from medical records by site staff at no inconvenience to the participant.

For participants discharged home within 21 days following recruitment, a brief telephone interview will be conducted on day 21 (window of day 20-24), providing consent has been given to this. This will include the EQ-5D-5L questionnaire and some simple questions about their current condition. Other than consent, this is the only information collected directly with the participant.
There will also be a review of mortality at 28 days, a simple yes/no collected from medical records and again at no inconvenience to the participant.

Information collected from clinical records will be:
• Reasons for ICU admission, including dates of ICU 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) and 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),
• Ventilation status (daily)
• Need for and type of ventilation (if relevant)
• Septic shock
• 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 21and 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/hospital stay
• On day 14 (all participants) the database will ask for the clinician's view on whether the pneumonia is cured
• For the second primary outcome (anti-microbial stewardship) this will be calculated by a dedicated panel of staff based on doses prescribed given and when and compared to the local version of the prescribing algorithm.

Added 11/06/2020: COVID-19 observational sub-study
The sub-study will not run in parallel to the main trial, only during the suspension of recruitment to the main trial during the COVID-19 pandemic, from March 2020.

The sub-study, conducted only in INHALE RCT sites, allows evaluation of the clinical utility of the tests in patients with COVID-19 and suspected secondary pneumonias. This is distinct from the INHALE RCT and aims to provide useful data for patient and antibiotic management during the COVID-19 epidemic, and allows sites to remain open and engaged, ready to re-commence randomisation to the RCT at the appropriate time.

Accordingly, the main objective of the study is to describe the clinical utility of rapid Pneumonia Panel testing on the management of ICU patients during the COVID-19 outbreak.
Patient will be eligible if they have clinically diagnosed or suspected pneumonia (HAP, VAP or CAP), test positive for COVID-19 and are able to produce sufficient surplus lower respiratory tract sample (200 µl) for testing on the Biofire Pneumonia Panel.

Methods of machine testing will be the same as the RCT, but with special consideration given to additional Personal and Protective Equipment requirements as described by Public Health England (PHE) during the pandemic. There will be no randomisation and no central laboratory testing. The algorithm will still be available to guide treatment decisions.

Anonymous data is collected from patient records by research staff at the sites. The data collected is: age, sex, comorbidities, dates of COVID-19 diagnosis, admission (including transfers from other hospitals), ICU admission and all pneumonia panel tests performed, date discharged from ICU or date of death.

For each test, the clinical reason for requesting the test will be noted, along with an upload of the machine result and routine microbiology results available in the same time period. Name of antibiotics will be collected and start and stop dates for 7 days before and 7 days after BioFire test and indication of whether antibiotic initiation, change or cessation was based on the Pneumonia Panel result.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Biofire "FilmArray" molecular diagnostic machine

Primary outcome measure
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), or (iii) relapse of 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).
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.

Secondary outcome measures
1. ICU length of stay – time from randomisation to discharge from ICU
2. Number of ventilator-free days over 21 days post randomisation (VAP participants only surviving 21 days post randomisation)
3. Mortality - death from any cause within 28 days of randomisation
4. Incidence of septic shock – within 21 days of randomisation.
5. Change in SOFA (ΔSOFA) score from randomisation to 7 days post-randomisation (adults)
6. Change in PELOD-2 (ΔPELOD-2) score from randomisation to 7 days post-randomisation

(children)
7. Change in pSOFA (ΔpSOFA) score from randomisation to 7 days post-randomisation (children)
8. % of participants on antibiotics active/inactive against the pathogen(s) found at 24 and 72h from randomisation
9. % of participants on proportionate/disproportionate antibiotics in relation to pathogen(s) found at 24 and 72h from randomisation
10. % of participants on narrow-spectrum antimicrobials at 24 and 72 h from randomisation
11. % of participants with specific adverse events associated with antibiotics within 21 day from randomisation
12. % of participants that contract a secondary pneumonia within 21 days from randomisation
13. Total antibiotic usage in Defined Daily Dose (DDDs) at 21 days post randomisation (all conditions)
14. In patient stay related costs

Added 11/06/2020: COVID-19 observational sub-study:
1. Amongst those who received at least one prescription of antibiotics for a respiratory infection, the proportion of patients on narrow (vs broad) antibiotics at 24 h and 72 h from the start of respiratory antibiotics, comparing Biofire versus non Biofire groups
2. Amongst those who received at least one prescription for antibiotics for a respiratory infection, the proportion of patients on active and proportionate antibiotics at 24 h and 72 h from the start of respiratory antibiotics, comparing Biofire versus non Biofire groups
3. Amongst patients who had a Biofire test, length of stay in ICU, mortality and ventilator-free days within 28 days from ICU admission, comparing those with a positive Biofire test versus those with a negative test
4. Amongst patients with a pathogen detected by Biofire and/or routine microbiology, length of stay in ICU, mortality and ventilator-free days within 28 days from ICU admission, comparing those treated with active antibiotics versus those treated with inactive antibiotics

Overall study start date
01/10/2018

Completion date
30/04/2022

Eligibility

Key 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 200 microlitres for the FilmArray test

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 552; UK Sample Size: 552

Total final enrolment
558

Key exclusion criteria
1. Previous inclusion in work programme 3
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
5. Prisoners or young offenders currently in custody of HM Prison Service or supervised by the probation service

Date of first enrolment
01/07/2019

Date of final enrolment
31/10/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University College London Hospitals NHS Foundation Trust
235 Euston Road
London
United Kingdom
NW1 2BU

Study participating centre
Aintree Hospital
Lower Lane
Liverpool
United Kingdom
L9 7AL

Study participating centre
Chelsea and Westminster Hospital NHS Foundation Trust
Chelsea and Westminster Hospital
369 Fulham Road
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SW10 9NH

Study participating centre
Russells Hall Hospital
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Study participating centre
Great Ormond Street Hospital
Great Ormond Street
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WC1N 3JH

Study participating centre
James Paget University Hospitals Nhs Foundation Trust
Lowestoft Road
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NR31 6LA

Study participating centre
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre

Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
Staffordshire and Stoke on Trent Partnership NHS Trust
Haywood Hospital
High Lane
Burslem
Stoke on Trent
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ST6 7AG

Study participating centre
BUPA Cromwell Hospital
164-178 Cromwell Road
London
United Kingdom
SW5 0TU

Study participating centre
Birmingham Children's Hospital
Steelhouse Lane
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B4 6NH

Study participating centre
Watford General Hospital
Vicarage Road
Watford
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WD18 0HB

Study participating centre
Royal Brompton Hospital
Sydney Street

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Sponsor type
University/education

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: RP-PG-0514-20018

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
31/12/2022

Individual participant data (IPD) sharing plan
The data will be available on reasonable request to the study team (inhale.study@uea.ac.uk).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version v1.2	11/07/2019	16/08/2019	No	No
HRA research summary			28/06/2023	No	No
Other publications		07/06/2021	06/09/2023	Yes	No
Protocol article		07/10/2021	06/09/2023	Yes	No
Other publications	ICU prescribers' views on the application of molecular diagnostics in HAP/VAP patients	16/11/2023	17/09/2024	Yes	No
Other publications	The influence of clinicians' beliefs on the application of rapid molecular diagnostics in intensive care	05/02/2025	07/02/2025	Yes	No
Results article	Secondary outcome on patient resource use and costs	08/08/2025	12/08/2025	Yes	No