NORWICH CTU

INHALE WP3 Trial: Health Economic Analysis Plan (HEAP) – Version 1.4, 11.04.2022

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1. Summary of clinical trial

INHALE WP3 is a multi-centre, open-labelled, parallel, randomised controlled trial exploring the potential impact of the FilmArray rapid molecular diagnostics coupled with a prescribing algorithm, aiming for non-inferiority in clinical cure of pneumonia and superiority with regard to antimicrobial stewardship, compared with standard care. The following summary of the trial is taken in abbreviated form from the published protocol (1).

Hospital-acquired and ventilator-associated pneumonias (HAP and VAP) are medically important owing to their frequency, high mortality, and because they drive the use of broad-spectrum antibiotics. In the United Kingdom (UK), VAP occurs in 9-27% of ventilated patients, with an incidence of 5 cases/1000 ventilator days (2). The cost is high: Edwards et al. (3) estimated around £19-20K per patient for severe pneumonia, even at 2008 prices.

Timely treatment is crucial to outcome in HAP and VAP, with mortality increased if antibiotics are withheld or delayed (4). Accordingly, antimicrobial chemotherapy is begun empirically, at clinical diagnosis, with the agents used being selected based on guidelines, local resistance rates and patient risk factors for resistant bacteria (e.g. other recent antibiotics and duration of hospitalisation/s). This approach reflects the fact that it takes 48-72h to grow and test the bacteria causing the infection by standard of care microbiology, delaying the opportunity to match the antibiotic to the pathogen present.

Treatment inadequacy, because the pathogen proves resistant to the empirical agent(s), is associated with increased mortality (5). Consequently, fears of resistance-associated failure create pressure to empirically prescribe the broadest-spectrum antibiotics, including carbapenems (6), as recorded in a recent NHS longitudinal analysis (7). This approach is argued to increase survival and to have health economic benefits (e.g. shorter time in ICU), including in NHS settings (3), but amounts to poor stewardship. Many patients with susceptible pathogens are given unnecessarily broad-spectrum antibiotics, and these exert pressure on the gut flora, favouring overgrowth of drug-resistant bacteria, which 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 Enterobacterales with NDM carbapenemases in the Indian subcontinent (8). Most carbapenemase producers are susceptible in vitro only to a few antibiotics, e.g. colistin and tigecycline, that have significant toxicity and efficacy limitations.

The conventional approach to 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. As recognised in the Chief Medical Officer's (CMO) Report (9), it is vital to find alternative, evidence-based, models to guide the use of both new and established antibiotics. Whilst this timeline has not been met, the need for better informed prescribing continues to be widely agreed.

In principle, and even without rapid diagnostics, the broad-spectrum empirical therapy initiated when HAP or VAP is clinically diagnosed should be de-escalated to narrower-spectrum therapy once the pathogen is identified and its resistances determined by the microbiology laboratory, a process that typically takes 48-72 hours. This strategy, sometimes dubbed 'start smart, then focus', has developed over 70 years, and its timescales are contingent upon speed of bacterial growth and testing in the microbiology laboratory. Although sound in principle, this approach has three major limitations.

First, it leads to over-treatment of the many patients with susceptible pathogens, unnecessarily increasing pressure on their gut flora.

Secondly, many patients with clinically diagnosed infection have no pathogen grown. Since their pathogen(s) remains undefined, and with the threat of increased mortality due to under-treatment, these patients often spend prolonged periods on broad-spectrum empirical agents, including empirical carbapenems. This raises the contingent risk of side effects, and selection of a resistant gut flora.

Thirdly, even with broad-spectrum agents empirical therapy is likely to prove inadequate in patients with unusually resistant pathogens, whose mortality risk is thereby increased in severe infection (10).

Molecular microbiological diagnostics offer a potential route to overcoming these limitations by identifying pathogens and their resistances in hours instead of days, allowing immediate targeted therapy or, at least, much earlier therapeutic refinement. Several automated, Polymerase Chain Reaction (PCR)-based pathogen and resistance detection platforms are now available for microbiological evaluation of HAP and VAP patients, but no data exist on whether these offer advantages in respect of clinical outcomes, or if they are cost effective.

The INHALE Randomised Controlled Trial (RCT) is Work Package 3 (WP3) of the NIHR-funded INHALE Research Programme. In WPs 1 and 2, three rapid diagnostic systems – the PCR-based BioFire FilmArray, the Curetis Unyvero platforms and rapid sequencing with the Oxford Nanopore Technologies MinION – were evaluated on respiratory specimens from ICU patients (11, 12). Based on these results, the FilmArray Pneumonia Panel (the "FilmArray test") was selected as the best performing test to carry forward into the present RCT.

Accordingly, the INHALE RCT is a two-armed study with two co-primary outcomes: non-inferiority in clinical cure of pneumonia at 14 days post randomisation, and superiority in antimicrobial stewardship at 24 hours post randomisation (published protocol: (1)). In the intervention arm, therapy for HAP/VAP is guided by the FilmArray test, undertaken within ICUs rather than in a laboratory; results are linked to an algorithm to translate its outputs into treatment guidance. In the control arm patients receive standard empirical antibiotics, according to the local prescribing policy. Patients are randomised to the arms on a 1:1 basis. Both arms have standard microbiology culture and susceptibility testing performed,

according to local laboratory procedures, with results typically available after 48-72 hours. These results allow further refinement of therapy in both arms.

The inclusion criteria for INHALE are:

1. About to receive an antimicrobial to treat a suspected LRTI – being either (i) first treatment of a newly-suspected HAP/VAP; or (ii) a change in previous antimicrobials for an LRTI owing to deteriorating clinical condition.
2. In-patient in a participating ICU/CCU.
3. Breathing spontaneously, or intubated for any reason.
4. Hospitalised for >48 hours.
5. Able to provide sufficient volume of airway specimen obtained for routine testing, plus 200 µL for the FilmArray test.

Patients are excluded if they: have previously been enrolled in INHALE; are enrolled in another trial not deemed suitable for co-enrolment with INHALE; moribund or not expected to live more than 48 hours; have an existing directive to withhold life-saving treatment or are currently in the care of the prison service or being supervised by probationary services.

Data are collected up to 21 days post-randomisation. For patients discharged before 21 days there is a telephone interview between 20 and 24 days post-randomisation to collect follow-up data.

1.1 Aim

The overall trial aim is to show that clinical and safety outcomes for patients whose treatment is guided by the FilmArray test molecular diagnostic are non-inferior compared to standard care, but that altered prescribing leads to improved antimicrobial stewardship.

1.2 Objectives

1.2.1 Co-primary objectives

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 an improvement in antimicrobial stewardship at 24 hours post randomisation for participants treated according to the FilmArray test versus those treated with standard care. In context, antimicrobial stewardship is defined as receipt of active and proportionate treatment.

The study will be declared to have met its primary objectives 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.

1.2.2 Secondary objectives

FilmArray and standard care arms additionally will be compared to determine whether:

1. There is a difference in the number of participants receiving an appropriate antibiotic at 24 and 72 hours post randomisation
2. There is a difference between the two groups in total antibiotic use over the 21-day study period

3. The FilmArray test plus algorithm is more cost-effective than standard care at 21 days post randomisation
4. There are any differences in antibiotic-associated adverse events (e.g. *C. difficile* infection) between the two groups within 21 days of randomisation
5. There are changes in organ dysfunction scores between the two groups at day 7 post randomisation
6. ICU/ Critical Care Unit (CCU) length of stay, septic shock rates, or mortality rates are decreased (or increased) by the intervention compared to the standard care
7. There is an increase in ventilator-free days for ventilated participants in the intervention group
8. There are any differences between the groups in the number of participants contracting secondary infections

To address objective 3, we will conduct an economic evaluation alongside the clinical trial to examine the cost-effectiveness implications of the FilmArray compared to standard care. The methods used in this economic evaluation are outlined in the health economics analysis plan (HEAP) presented here.

1.3 Registration, funding and sponsor details

Trial registration: ISRCTN16483855, retrospectively registered 15th July 2019

This project is funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research (project reference RP-PG-0514-20018). The trial Sponsor is University College London (UCL).

2. Economic objective and context

The objective is to determine the cost-effectiveness of intensive care unit (ICU) treatment of HAP/VAP guided by the FilmArray test molecular diagnostic compared to standard care alone in ICU patients with suspected HAP or VAP utilising data from INHALE WP3, a multi-centre, open labelled, parallel, randomised controlled trial.

To determine whether the trial outcomes justify costs, a cost-effectiveness study will be conducted using the main trial's co-primary outcomes (see Section 1.2.1 for further detail):

1. Clinical cure of pneumonia at 14 days post-randomisation;
2. Antimicrobial stewardship at 24 hours post-randomisation.

A cost-effectiveness analysis will be undertaken for both outcomes – respectively, these will evaluate i) the incremental cost per additional clinical cure (at 14 days) and ii) the incremental cost per additional patient receiving active and proportionate antibiotics within 24 hours of clinical decision to prescribe antibiotics for HAP/VAP. Where non-inferiority in clinical cure is not established, or if cost-effectiveness results for the primary outcomes are contradictory (i.e., if one favours the FilmArray arm and if the other favours the control), interpretation of findings will be more difficult – a decision-tree model will be used to explore the implications.

In order to inform decision-making regarding the optimum testing strategy for HAP/VAP in UK hospitals, the primary costing perspective will be that of hospital intensive care. This is in part driven by the restriction that data collection regarding resource use will be limited to the patients' hospital stay, meaning that an 'NHS and personal social services perspective', as recommended by NICE (13), will not be possible. Additionally, this is a narrower perspective than proposed in the protocol (1), in which we

proposed to take the wider costing perspective of costs to the whole hospital. We think this change to an intensive care perspective is an improvement and justified as:

- The 'signal' of effect/impact will be clearest and least impacted from this perspective: the intervention is focused on the context of intensive care – adopting a wider perspective increases the risk of contributing confounders (such as the underlying cause of patients being at hospital) and 'noise' that may then reduce precision with which we can measure the economic impact of the intervention;
- Intensive care is typically the most expensive component of hospital stays so, in line with the advice by Ramsey, Willke (14), it is sensible to focus on this main cost driver/source (as evidenced in Wagner, Turner (15));
- Data completeness should be greater: adopting a wider hospital perspective requires costs for the whole stay of participants – this may not be fully available at time of analysis for participants who are yet to be discharged. However, with the narrower intensive care perspective we *can* include participants who have been discharged from intensive care *but* are yet to be discharged from hospital.

Thus, the primary analysis (the 'base case') will focus on ICU based costs. However, for those participants with sufficient data, we will explore the impact on our conclusions of adopting the wider hospital perspective within sensitivity analyses (see Section 10).

The time horizon of the base case cost analysis will be that of each participant's duration of contiguous ICU care, commencing from the intensive care episode in which they are recruited. Consequently, it is important to note that the period for which we consider costs and outcomes differ – for example, clinical cure is considered at 14 days post-randomisation. This approach has been adopted so that we do not understate the cost difference between those with clinical cure and those without, since the latter are likely to have longer periods of care (assuming they do not die). The previously mentioned sensitivity analysis looking at the wider hospital perspective (Section 10) will also allow us to further explore these issues.

3. Data collection methods

The majority of data are collected from routine care records by trial research staff. Data collection continues from day 1 until 21 days after randomisation or until death if earlier. Daily assessments stop at day 14, or earlier if the participant is discharged from ICU/critical care unit (CCU) or dies before day 14. For participants discharged home prior to 21 days post randomisation, a brief telephone interview is conducted between days 20-24, providing consent is given. The condition of participants still in hospital at 21 days is assessed from their notes. A medical record check is carried out for the patient's final date of discharge, or death noted up to day 28. The data are collected and managed using REDCap (16, 17) electronic data capture tools hosted at Norwich Clinical Trials Unit (NCTU).

Additional data for the health economic analysis (such as durations [and associated dates] of ICU stay and index admission, and associated health resource groups [HRGs]) are additionally collected through liaison with each site's finance/business team. Any further required information was based on expert opinion.

We proceed by considering each of the main resource use and outcome categories important for the health economic analysis, noting for each how it was measured, the source of information, and where relevant, the method of completion. The items focused on are informed by the guidance that one

should focus on the large cost drivers and those resource items that have the potential to differ between study arms (14). The data to be used, and its methods of collection, were explored and trialled in the earlier INHALE WP2.

NOTE: *In what follows, we separate out details of intensive care use, and general admission information. Given intensive care is so resource intensive, it is one of the elements of care that is reimbursed separately, along with reimbursement for a patient's general admission (i.e. there are separate HRGs for intensive care and the general admission). Thus, in what follows, we separate out resources/information around intensive care, and those related to the general admission. As noted above, the primary economic analysis ('base case') focuses on ICU costs, but wider hospital costs are considered in sensitivity analysis (see Section 10) and so, below, we additionally cover details on general admission etc.*

3.1 Resource use

3.1.1 Intensive care use

Data collected from routine care records by trial research staff (primarily from day 1 until 21 days after randomisation or until death if earlier):

- Dates of intensive care admission and discharge, from which intensive care length of stay (LoS) can be calculated;
- Daily details on:
    - For adults: the organ systems being supported;
    - For children: the critical care level;
    - Details of whether the patient is being ventilated.

Through liaising with site finance/business teams, we have also collected for each intensive care episode[1] during the hospital admission:

- Dates of intensive care admission and discharge, from which intensive care length of stay (LoS) can be calculated;
- Associated health resource group (HRG);
- Corresponding income for the hospital (see subsequent sections for more detail).

3.1.2 Information on the use of standard microbiology culture and susceptibility testing

We will note the use of standard microbiology for culture and susceptibility testing. Associated details collected by trial research staff includes:

- Number of cultures conducted (derived from number of cultures recorded).

Other information on resources used (e.g. consumables needed and staff time/grade required) in the testing will be sought from expert opinion.

3.1.3 Information on use of BioFire FilmArray

We will note use of the BioFire FilmArray. Details collected from routine care records by trial research staff includes:

[1] There may be multiple admissions to ICU, beyond the one focused on in the trial. For each of these ICU admissions, there may be multiple episodes associated with them: site finance/business teams were asked to provide details of *all* ICU episodes occurring during each participant's admission.

- Number of machine runs needed to process initial sample (takes account of occasions when the FilmArray test has to be run again due to sample processing failure; this figure will be derived from the number of tests recorded).

Other information on resources used (e.g. staff time needed to use the machine and grade of staff etc) in application of the FilmArray test will be sought from expert opinion and informed by data collected in earlier INHALE WPs (including a questionnaire of research staff using this and other machines to understand resources involved in their use – such as staff time).

3.1.4 Prescribed antimicrobials

Details collected from routine care records by trial research staff on *all*[2] antimicrobials prescribed and/or administered to patients from 7 days before enrolment to 21 days after, includes:

- Antimicrobial name;
- Dose;
- Treatment frequency;
- Route (e.g. oral, intravenous, etc);
- Start and end dates of treatment (including if patient was still receiving at end of the follow-up period).

3.1.5 (Hospital) Admission details

Data collected from routine care records by trial research staff (primarily from day 1 until 21 days after randomisation or until death if earlier):

- Dates of admission to and discharge from hospital, from which overall hospital length of stay (LoS) can be calculated.

Through liaising with site finance/business teams, we have also collected:

- Dates of admission and discharge to hospital, from which overall hospital length of stay (LoS) can be calculated;
- Associated core health resource group (HRG);
- Associated hospital income for the hospital.

3.1.6 Use of chest X-ray or CT scans

Data collected from routine care records by trial research staff (primarily from day 1 until 21 days after randomisation or until death if earlier):

- Type of scan (X-ray or CT scan);
- Number of each type of scan (derived from numbers of tests recorded).

3.2 Outcomes

3.2.1 Non-inferiority of clinical cure of pneumonia at 14 days post-randomisation

Cure of pneumonia is defined as: absence of (i) death where pneumonia was considered causative or contributory, (ii) septic shock, except when associated with a documented non-respiratory origin of infection and (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

[2] This will include details of antimicrobials not related to the treatment of pneumonia.

organ dysfunction score (SOFA or PELOD-2)), or (iv) other evidence that the original pneumonia is not cured.

3.2.2 Superiority in antimicrobial stewardship at 24 hours post-randomisation

This is defined as: participants on active and proportionate antimicrobial therapy within 24 hours of clinical diagnosis, where active therapy is defined as receiving an antimicrobial active against the organism(s) in vitro and proportionate as active and not excessively broad spectrum for the pathogen(s) identified. A Microbiology Committee, comprising three independent members and one member of the study team, has been set up to review prescribing decisions. The Committee assesses whether prescribing is active and proportionate at 24 hours and 72 hours post randomisation for each patient, and is blinded to the study arm.

3.2.3 EuroQol EQ-5D-5L

In line with the National Institute for Health and Clinical Excellence (NICE) methods guide (13), quality of life was measured using the EQ-5D-5L, where respondents are asked to report the level of problems (none to extreme/unable) they have on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression)(18). This was sought from patients aged over 5 and alive at 21 days (permitted: 20-24 days). If the patient is still in hospital, review is carried out in person; if they have been discharged, they are telephoned (where the patient is a child, the parents are called). It is recorded where the patient is not well enough to complete the measure and where a proxy completes on behalf of the patient.

4. Costing: Assigning unit costs to resources

We proceed to describe how the resource use items were costed.

4.1 Costing intensive care and overall hospital admissions

As a proxy for the costs of these admissions, we will utilise hospital income associated with the HRGs for intensive care and overall hospital admissions[3]. In the base-case analysis, we will utilise local income values sourced from site finance/business teams. Currently, there are no nationally agreed incomes for intensive care HRGs – these are negotiated locally at each site. However, for the 'core' HRGs[4] – associated with the overall hospital admission – which have nationally agreed incomes, this corresponds to applying the local market forces factor[5] to the nationally agreed tariffs (20). We will explore the impact of using national estimates of HRG unit costs/incomes sourced from the National Schedule of Reference Costs (21) in sensitivity analyses (see Section 10).

In the above costing, it is worth noting that we are potentially going beyond the 14/21-day collection focus of the broader trial – see Section 1.2 – depending on how long participants are in intensive care and/or admitted to hospital.

We have liaised extensively with participant hospitals to ensure this data is as complete as possible. Where we have been unable to obtain this data, or where data is missing for other reasons, we will estimate this value using other collected data. In adults, the daily income rate for an ICU HRG depends on the number of organ systems being supported. Thus, where there is missing ICU admission income data, we will explore mapping from the REDCap recorded number of supported organ systems to infer a potential daily income and multiply by the number of days that this number of systems is being supported. For those hospitals that are privately funded – expected to only treat adults – we will use the same approach to estimate what income would be expected were this treatment to have been provided by the NHS. In children, a similar approach will be explored with critical care level.

The NHS cost inflation index (NHSCII) will be used to inflate locally sourced values to the most up to date cost year at the time of analysis (22). We expect it to be rare, but there may be some admissions that are longer than a year (particularly in the specialist paediatric sites); their incomes/cost values will be appropriately discounted at a rate of 3.5% (the rate endorsed by NICE (13)) to give a present value.

4.2 Costing microbiology culture and susceptibility testing – deriving cost-per-test

We consulted INHALE team members who were familiar with these techniques to establish the likely resource required to provide them. Drawing on this expert opinion it was established that the

[3] Thus, we exclude other incomes hospitals may receive for treating patients, such as additional income where high-cost drugs are needed. However, for the large majority of patients we expect this to capture the majority of income received. Additionally, from the earlier work packages and elsewhere, we know the main cost driver, and thus main source of income, is the intensive care provision.

[4] Each admission has one 'Core' HRG associated with it.

[5] The market forces factor 'is an estimate of unavoidable cost differences between Health Care Providers, based on their geographical location' [19. NHS Data Model and Dictionary. Market Forces Factor. 2021.]. For example, part of the MFF will be used for adjusting for the greater cost of employing staff in London etc. See [20. NHS England and NHS Improvement. Consultation on 2021/22 National Tariff Payment System: A guide to the market forces factor. 2021.] for more information.

associated resources differed relatively little across sites, so a common unit cost will be utilised. The resources/costs, and sources of information considered:

- Consumables – costs sourced from expert opinion;
- Biomedical scientist time to perform testing:
    - Duration provided by expert opinion;
    - Corresponding grade of staff provided by expert opinion;
    - Associated cost of staff time taken from Curtis and Burns (22).

For each participant, we will include the cost of culture and susceptibility testing for samples recorded as having been processed by microbiology (see Section 3.1.2).

4.3 Costing use of the Biofire FilmArray – deriving cost-per-test

Costing the resources utilised in using the FilmArray was informed from work in earlier work packages. From expert opinion it was established that the associated resources differed relatively little across sites, so a common unit cost will be utilised. The resources/costs, and sources of information considered:

- Acquisition of machine – costs sourced from Biofire;
- Consumables – costs sourced from Biofire;
- Staff time to use machine:
    - Duration provided by expert opinion;
    - Corresponding grade of staff provided by expert opinion;
    - Associated cost of staff time taken from Curtis and Burns (22).

A key parameter in determining the cost-per-test is throughput: for example, in sites with a higher throughput, the impact of acquisition costs will be lower, as this can be 'split' across more tests. However, from the earlier costing work, the main driver is expected to be the costs of consumables which is unimpacted by throughput rate (our consumable costs do not assume any discount for buying in bulk – to our knowledge, no such discounts are commonly available). Sensitivity analyses (Section 10) will include exploration of the impact of varying cost-per-test.

For each patient we will multiply the cost-per-test by the number of machine runs required to process the initial study sample to estimate costs of using the FilmArray.

4.4 Costing prescribed antimicrobials

Costs for antimicrobials will be taken from NHS Business Services Authority (23). We will cost antimicrobial use from randomisation until 21 days later (the end for which this data is collected) for each patient.

4.5 Base case (intensive care) total treatment costs

Total costs for each patient for the base case (intensive care costing perspective) will then be the sum of:

- ICU admission income/cost;
- Microbiology culture and susceptibility testing use;
- Biofire FilmArray use;
- Prescribed antimicrobials.

4.6 Total overall treatment costs (utilised in sensitivity analyses)

Total costs for all treatment (intensive care AND general admission, utilised in sensitivity analyses) for each patient will be the sum of:

- Base case component costs (as in Section 4.5)
- General admission income/cost.

4.7 Costing use of chest X-ray or CT scans

Cost for the use of chest X-ray or CT scans will be sourced from the National Schedule of Reference Costs (21).

For each patient we will:

- Multiply X-ray costs by the number of x-rays conducted;
- Multiply CT scan costs by the CT scans conducted.

These will be summed together to give the costs of imaging/scanning.

The inclusion of these costs will be explored in sensitivity analyses (see Section 10).

5. Outcomes:

As only those able to complete the EQ-5D-5L will provide a value at 21 days, we will not have values from all participants. Furthermore, those providing a value will tend to be those who have made fuller recoveries. For this reason it is not possible to conduct a cost-utility analysis on study participants, as results will not be representative of the whole INHALE sample. Thus, we will conduct a cost-effectiveness analysis, as outlined below. However, for those participants where an EQ-5D-5L is collected, the crosswalk mapping function (24) (as recommended in the NICE position statement (25)) will be used to convert responses into utility scores, where a score of zero corresponds to death and one to full health (26). Dependent on the analysis question, those who die will also be assigned a utility score of zero. This data will be used to help inform the decision analytic model.

The outcome measures used for the cost-effectiveness analysis will be the same as the main study co-primary outcomes (see Section 1.2.1 for further detail):

1. Non-inferiority in clinical cure of pneumonia at 14 days post-randomisation;
2. Superiority in antimicrobial stewardship at 24 hours post-randomisation.

6. Data cleaning procedures

Ahead of analysis, source data will be reviewed with plausibility checks (eg that admission and discharge dates tally with the period of data collection). For sites where there is a cross-over in data between that collected in REDCap and that provided by site finance/business teams, we will compare for consistency. In particular, we expect the dates of admission to and discharge from both intensive care unit and hospital to be consistent between the two data sources. In cases where these do not match we will seek to resolve discrepancies between sources, but expect to prioritise that from finance records, given these are the data/dates used to determine costs/income.

7. Analyses undertaken to estimate the incremental cost and incremental effect

In the base case analysis, costs will be estimated from the hospital intensive care's viewpoint, to include (as specified in Section 4.5) the costs of: intensive care admissions; culture and susceptibility testing; using of the FilmArray test and prescribed anti-microbials. We will exclude those participants – expected to be very few – who are still in ICU at time of analysis, and so not have complete intensive care cost data.

A within-trial analysis will be undertaken. In the base-case analysis, participants will be analysed within the group to which they were allocated, regardless of whether they adhered to the regime in question – in line with the intention to treat (ITT) approach adopted in the trial. As the data for the main primary outcome analysis is from routine sources, levels of missing data are expected to be low, although we have designed an approach to missing data which is outlined in the SAP and the study protocol (1)/Statistical analysis plan (SAP). In the economic analysis, we need to use a wider range of data, increasing the risk of missing data; however, we will seek to use all sources of data to maximise sample size in the economic analysis (as described in Section 4) and check the impact of such assumptions in sensitivity analyses (see Section 10). Should rates of missing data be high enough to warrant use of more formal missing data procedures (e.g. multiple imputation), we will consult with the study statistician.

Two cost-effectiveness analyses will be carried out, to reflect the dual co-prime outcomes of the study – these will evaluate the incremental cost per additional:

- clinical cure within 14 days post randomisation;
- additional patient receiving active and proportionate antibiotics within 24 hours of randomisation.

Where between-arm estimates of difference are required, these will be adjusted using standard regression approaches in line with the protocol/SAP (this will include site adjustment, as specified by the SAP).

Where non-inferiority in clinical cure is not established, or if cost-effectiveness results for the primary outcomes are contradictory (i.e., if one favours the FilmArray arm and if the other favours the control), interpretation of findings will be more difficult – a decision-tree model will be used to explore the implications.

Subgroup analyses: We will conduct separate pre-specified sub-group analyses:

- HAP versus VAP infections – work elsewhere highlights treating VAP specific patients is more resource intensive and costly (e.g. (27) and (15)). Definitions for these cohorts will accord with those derived by the study statistician.
- Prescence or not of COVID infection – limited research has been conducted on the economic impact of COVID on HAP/VAP treatment. Definitions for these cohorts be based on those used by the study statistician. Definitions for these cohorts will accord with those derived by the study statistician.
- Adults and children (participants of less than 18 years of age at time or randomisation).

Analysis will be conducted using a mix of R, Stata and Excel.

8. Interpretation

Two outcomes are to be considered, in line with the dual primary outcomes of the trial:

- clinical cure within 14 days post randomisation;
- additional patient receiving active and proportionate antibiotics within 24 hours of randomisation.

For each of these outcomes, we will conduct separate cost-effectiveness analyses.

Within each analysis, we will consider costs and impact on the appropriate outcome. If either arm is found to have lower costs and improved outcome (either: improved clinical cure rate; or receiving more active and proportionate antibiotics at 24 hours) compared to the other, that option is described as being 'dominant' and estimated to be cost-effective based on available evidence. If dominance does not occur, the incremental cost-effectiveness ratio (ICER; mean incremental cost/mean incremental effect) associated with FilmArray informed treatment compared to treatment as usual will be calculated (either: cost per additional cure; or cost per additional patient treated with active and proportionate antibiotics at 24 hours). We are unaware of appropriate cost-effectiveness thresholds for such ICERs.

Where non-inferiority in clinical cure is not established, or if cost-effectiveness results for the primary outcomes are contradictory (i.e., if one favours the FilmArray arm and if the other favours control), interpretation of findings will be more difficult – a decision-tree model will be used to explore the implications.

9. Analysis of uncertainty

Uncertainty around cost-effectiveness conclusions in terms of i) clinical cure and ii) receiving active and proportionate antibiotics will be explored using separate cost-effectiveness acceptability curves (CEACs). CEACs estimate the probability that the intervention is cost-effective at different monetary valuations of the outcome measure. The CEACs will be derived using non-parametric bootstrapping of the trial's data.

Where non-inferiority in clinical cure is not established, or if cost-effectiveness results for the primary outcomes are contradictory (i.e., if one favours the FilmArray arm and if the other favours control) and a decision-tree model is used, probabilistic sensitivity analysis will be used to characterise uncertainty.

10. Sensitivity analyses

Sensitivity analysis will be undertaken in order to assess the robustness of conclusions to changes in key assumptions:

1. Explore the impact of extending regression adjustment with covariates identified in the Supportive/Sensitivity analyses of the SAP (SAP Section 5.1.4).
2. Explore the impact of only considering costs up to 14 days post randomisation, so that costs align with the clinical cure outcome at 14 days post randomisation.
3. Explore the impact of extending costs to include separate costs for X-rays and CT scans.
4. Exploring the effect of including all admissions costs (e.g. including general admission costs – see Section 4.6). We will exclude those patients who are still hospitalised at the time of analysis (since we will not have appropriate costing data for them – e.g. general admission HRG).

5. Use national HRG costs: explore whether our conclusions differ if national values are used, rather than locally sourced values.
6. Explore the impact of varying costings for microbiology culture and Biofire Filmarray use (e.g. by varying different throughput rate).
7. Complete case analysis to explore the impact of approaches for dealing with missing data/augmenting data from the different sources.

11. Decision analytic modelling

As the study population is highly heterogeneous in respect of the underlying illness/trauma precipitating the ICU admission, economic evaluation may not be straightforward. The cost-effectiveness analysis described above will look at both main trial outcomes. As specified in Section 2, these will be the:

i) incremental cost per additional clinical cure (at 14 days);
ii) incremental cost per additional patient receiving active and proportionate antibiotics within 24 hours of clinical decision to prescribe antibiotics for HAP/VAP.

These outcomes may be contradictory – for example, the rate of clinical cure may be worse in one arm, but with an improvement in antibiotic stewardship. Additionally, the trial takes place within a short timeframe, making long-run outcomes unavailable. To address such issues, a decision-tree model will be used to further analyse the data produced by INHALE. The cost perspective of the model will be the same as the within trial analysis, i.e., NHS secondary care costs. Outcomes considered will be expected life years gained and quality adjusted life years (QALYs).

The model will allow us to estimate a cost per life year saved and a cost per QALY, additional to the results produced by the within trial analysis. Primarily this will be carried out by modelling the expected gain in life years and QALYs associated with different outcomes, such as clinical cure at 14 days. These assumptions as to the health benefits of different pathways and outcomes will allow an exploration of potential longer-term effects.

It is expected that the primary source of data for the model will be generated from the INHALE clinical trial and its parallel economic evaluation. This will include the following: cost of the FilmArray test; costs of ICU stays; other hospital-based costs; and the trial's co-primary outcome measures. These data will be supplemented by data from literature (27), and expert clinical opinion incorporated as necessary. Inherently, this process will be speculative as the longer-term outcomes are not evaluated in the trial. Consequently, the decision-tree model will be used to explore a range of 'what if' scenarios, evaluating different consequences of results from the trial. Specifically, these will include the sub-group analyses outlined in Section 7 and the sensitivity analyses outlined in Section 10. Assumptions about the consequences of care provided, and of improved antimicrobial stewardship, will be formulated. This approach will inform decision makers as to the potential longer-term consequences of rapid microbiological diagnostics, beyond that which is presented in the within trial analysis. The results of this model will constitute a secondary analysis.

12. Reporting results

Resulting analysis will be reported with reference to the CHEERS Checklist for Economic Evaluations (28).

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