Statistical Analysis Plan (SAP) : work package 3

Full title of trial: 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 (INHALE)

Version of SAP: 1.0
Date: 22nd February 2022
Prepared by: Julie Barber & Sue Stirling
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Authors	Title	Signature	Date
Dr Julie Barber	Trial Statistician		22nd Feb 2022
Susan Stirling	Statistician		22nd Feb 2022
Reviewers	**Title**	**Signature**	**Date**
Juliet High	Senior Trial Manager		24th Feb 2022
Dr Vicky Enne	Programme Manager		28th Feb 2022
Approver	**Title**	**Signature**	**Date**
Dr Vanya Gant	Chief-Investigator		8th March 2022
Prof David Livermore	Chief-Investigator		8th March 2022

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Version	Date	Details of change
1 DRAFT	8th July 2021	
1 DRAFT	30th September 2021	Updated to include comments from DMEC, Vicky Enne & Juliet High

1 DRAFT	1st December 2021	Updated to include further comments from DMEC, Vicky Enne & Juliet High
1.0	22nd February 2022	Updated to include comments from Vicky Enne, Juliet High, David Livermore & Vanya Gant and to meet JAMA guideline requirements

ABBREVIATIONS

AE	Adverse Event
APACHE	Acute Physiology, Age, Chronic Health Evaluation score
c.	Circa
CCU	Critical Care Unit
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
DDD	Defined Daily Dose
DMC	Data Management Committee
EQ-5D	EuroQol questionnaire, 5 levels
GCP	Good Clinical practice
GCS	Glasgow Coma Scale
h/ hrs	Hours
HAP	Hospital Acquired Pneumonia
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
ID	Patient identifier
IQR	Interquartile range
ITT	Intention to Treat
LRTI	Lower Respiratory Tract Infection
MAR	Missing at random
MNAR	Missing not at random
N / n	number
NCTU	Norwich Clinical Trials Unit
NHS	National Health Service
PELOD-2	Paediatric Logistic Organ Dysfunction Score
PI	Principal Investigator
PIM	Paediatric index of mortality
PPA	Per-protocol analysis
PSC	Programme Steering Committee
pSOFA	Paediatric Sequential Organ Failure Assessment
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
SOPs	Standard Operating Procedures
UCLH	University College London Hospital
VAP	Ventilator Acquired Pneumonia
VFD	Ventilator Free Days
WP	Work Package

1 TRIAL SUMMARY

The summary given in this section is based on the most recent trial protocol. For full details see the protocol (version 3).

Note that through discussion with the study team, there have been some changes to outcomes and outcome definitions since protocol version 3. These are detailed below in section 1.6.3.

1.1 BACKGROUND

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.

Immediate antibiotics are crucial to outcome in HAP and VAP, with mortality increased if these are withheld or delayed (Iregui et al 2002). Empirical treatment is therefore given, 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 (Kollef et al 2008), and the risk of inadequacy inevitably grows as the resistance prevalence increases. This generates pressure to empirically prescribe the broadest-spectrum antibiotics. This approach, is argued to increase survival and to have health economic benefits, including in NHS settings (Edwards et al 2012). 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 practice has developed over 70 years but is inadequate on 3 counts: i) many patients may have no pathogen grown, possibly due to suppression of growth by antibiotics already given; ii) empirical therapy may be inadequate in patients with unusually resistant pathogens; and iii) risk of mortality through under-treatment leads to increasing use of broad-spectrum treatments.

Faster recognition of pathogens and profiling of their resistances could 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.

Molecular diagnostics potentially offer improvement by identifying pathogens and resistances in hours, thereby allowing early therapeutic refinement. In INHALE WP1, the FilmArray Pneumonia Panel test (the "FilmArray test") was selected as the best performing test for a two-armed trial (WP3): in one arm, therapy for HAP/VAP will be guided by the FilmArray test plus trial-based prescribing algorithm and by conventional culture-based tests in the second arm.

1.2 OBJECTIVES (AS FROM PROTOCOL)

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.

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 a 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.

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 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

1.3 TRIAL DESIGN

A multicentre, 2-arm, parallel randomised controlled trial of the FilmArray test Molecular Diagnostics for pneumonia, plus trial-based prescribing algorithm, versus standard care among ICU/CCU patients about to receive a new antimicrobial to treat a suspected LRTI for the first time, or a change in antimicrobial for LRTI because of deteriorating clinical condition. Full details of the intervention are available in the protocol.

1.4 INCLUSION/EXCLUSION CRITERIA (AS FROM PROTOCOL)

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. *T*his 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

1.5 RANDOMISATION

Eligible participants are randomised on a 1:1 basis to one of two trial arms (A & B) using a web-based randomisation system. Allocation is blocked (using blocks of randomly varying block length) and stratified by site.

1.6 OUTCOMES

[Note: superscripts given in sections 1.6.1 & 1.6.2 below are explained in section 1.6.3]

1.6.1 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 pneumonia was considered causative or 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. Superiority in antimicrobial stewardship at 24 h post randomisation.

Defined as participants on active and proportionate antimicrobial therapy within 24 h of randomistion[1], 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.

1.6.2 Secondary Outcomes

1. ICU/CCU length of stay – time from randomisation to discharge from ICU/critical care (days)

2. Number of ventilator-free days over 21 days post randomisation

> *Note of calculation of VFD: In creating the VFD variable for analysis, days on non-invasive ventilation will be regarded as ventilator-free. Number of ventilator free days (VFD) will be calculated for all subjects[2], taking guidance from published methodology (Yehya et al 2019), where:*
> *VFD = 0 if subject dies within 21 days of randomisation*
> *VFD = 21 – x if successfully liberated from invasive ventilation x days after randomisation*
> *VFD = 0 if subject is invasively ventilated for more than 21 days*

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 and 14 days post randomisation (adults)[3,4]

6. Change in PELOD-2 (ΔPELOD) score from randomisation to 7 and 14 days post-randomisation (children)[3, 4]

7. Change in pSOFA (ΔpSOFA) score from randomisation to 7 and 14 days post randomisation (children)[3, 4]

> *Note on calculation of SOFA/pSOFA/PELOD-2 scores: These scores will be calculated using published approaches (Vincent et al, Matics et al, Leteurtre et al). Some missing items/scores are expected and through discussion with the research team the following approach for these cases was agreed.*
> - *Missing day 7 or 14 scores (or missing items needed for calculating scores) will be replaced with values from the previous day. If the previous day's values are not available those from the following day will be used. Values will remain missing if all three days (e.g. day 6, 7 and 8) have missing values unless the missing score is due to incomplete Glasgow Coma Scale scores/items where these will be replaced with "normal values" (Normal scores: eye opening = 4; verbal = 5; motor = 6).*
> - *'Missing' items/scores at 7 or 14 days will not be replaced for cases where the scores are unavailable because of patient discharge or death before that day (see analysis section for more detail about these).*
> - *For baseline clinical scores which are missing due to incomplete Glasgow Coma Scale, missing GCS items/scores will be replaced with "normal" values (Normal scores: eye opening = 4; verbal = 5; motor = 6).*

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 72h from randomisation

10. % of participants on narrow-spectrum antimicrobials at 24 and 72 h from randomisation[5]

11. % of participants with hypersensitivity, induced diarrhoea and C difficile[6] associated with antibiotics within 21 days from randomisation

12. % of participants that contract a secondary pneumonia (caused by a different pathogen than the primary pneumonia) within 21 days from randomisation

13. Total antibiotic usage in Defined Daily Dose (DDDs) per ICU day over 21 days post randomisation (all conditions)[7]

1.6.3 Outcomes: updates to protocol version 3

This section lists changes to outcome definitions given in protocol version 3 that have subsequently been agreed by the study team. Each point below refers back to an outcome described in sections 1.6.1 and 1.6.2 using superscript numbers.

[1] The definition of antimicrobial stewardship given in the protocol refers to 'active and proportionate antimicrobial therapy within 24 h of clinical diagnosis'. 'clinical diagnosis' was subsequently clarified to mean randomisation and changed in the definition given in section 1.6.1.

[2] The protocol states that VFD would be calculated 'only for VAP participants who survive for 21 days post randomisation'. A decision was subsequently made to calculate this for all patients.

[3] Day 14 outcomes for clinical scores are not listed as secondary outcomes in the protocol, but were added by the research team for this SAP.

[4] Protocol (footnote table P34) states that scores would be collected "[1]Every day until 14 days after randomisation or until clinical cure of pneumonia, whichever is first. Assessments only required on these days if in ICU/CCU and not cured of pneumonia". The team subsequently agreed that this footnote had been included in error and that the intention was to collect these scores for the whole period in ICU regardless of clinical cure. This intention is reflected in the CRFs and thus appropriate data has been collected for analysis.

[5] Narrow-spectrum v broad-spectrum antimicrobials are not clearly defined in the protocol. Data collected refers to 4 categories: narrow/not on antibiotics/broad/old. The team agreed that for analysis narrow-spectrum category will include 'not on antibiotics' and broad-spectrum will include 'old' antibiotics.

[6] Referred to as Specific adverse events' in the protocol, but defined by the team as occurrence of Hypersensitivity, Induced diarrhoea and C difficile.

[7] Protocol refers to 'DDD at 21 days', subsequently defined by the team as DDD per ICU Day.

1.7 SAMPLE SIZE (SUMMARY FROM PROTOCOL)

A sample size of 552 patients (randomised 1:1) will provide at least 90% power for analysis of the trial's co-primary outcomes. This is a larger sample size than originally planned, following inflation to allow for inclusion of COVID-19 patients. Detail of the revised sample size justification was added in protocol version 3.

The original calculation required at least 466 participants to achieve 91% power with a significance level of 5% and assumed a cure rate of 70% in both arms, a non-inferiority limit of 13% and allowed for 5% attrition. Since including COVID-19 patients, the cure rate of pneumonia decreased. The sample size calculation was therefore updated (protocol version 3) to reflect a new assumed cure rate of 55% in both arms. Under this assumption, and still with a non-inferiority limit of 13%, at least 528 participants are needed to achieve 91% power with significance level 5%. In previous work (INHALE WP2) we found that, under standard care 53% of patients received antibiotics that were both appropriate and proportionate within 24 hours of clinical diagnosis. The sample size of 528 participants required for the non-inferiority outcome provides 99% power to detect an improvement in the co-primary outcome of microbial stewardship (that is, receipt of appropriate and proportionate antibiotics within 24 hours of clinical diagnosis) of at least 20%. To allow for 5% attrition it is planned to randomise at least 552 patients, or 276 per randomised arm. See section 6.7 of the protocol for full details.

1.8 ASSESSMENTS

All 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. Where possible (i.e.: the participant is conscious, has capacity, has consented and their treating doctor agrees it appropriate), an EQ-5D-5L will also be collected from participants in hospital at 21 days. 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 to obtain outcome data regarding: 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).

1.9 STATISTICAL ANALYSIS PLAN (AS IN PROTOCOL)

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' and following the SOPs of the NCTU. A summary of the planned analyses is provided below.

Outline of main analysis
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, 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.

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.

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.

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.

2 INTRODUCTION TO SAP

2.1 PURPOSE OF THE SAP

This document contains details of the main quantitative, statistical analyses for the INHALE trial and has been prepared following the brief plan provided in the protocol and in advance of making any formal comparisons between the randomised groups.

This SAP addresses the primary and secondary objectives but excludes analyses of patient costs, which will be detailed in a separate Health Economics Analysis Plan produced by the health economics team. The plans for analysis given in this document do not preclude the undertaking of further ad-hoc analyses, although the results of any such further analyses would be interpreted carefully. Furthermore, the SAP does not prevent the adaptation of any part of the trial analysis and reporting, should situations arise in which such adaptation is necessary. Any such adaptation will be fully justified and transparent. This SAP includes suggested formats for tables to display results from the main analyses.

2.2 TIMING OF STUDY ANALYSIS

The final analysis will take place once the SAP is formally signed off and the database has been locked.

2.3 STATISTICAL SOFTWARE

The analysis will be undertaken by Susan Stirling and Julie Barber using Stata version 17 (StataCorp 2021) (or later), however, other packages such as R or SAS may be used if necessary (with justification). The Stata commands to be used for the main analyses are included in the text that follows.

3 STATISTICAL PRINCIPLES

3.1 GENERAL

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' and following the SOPs of the NCTU. Results will be reported following CONSORT guidance.

3.2 ASSOCIATED DOCUMENTS

NCTU working practice document: Statistical Principles – NCTU_M_WPD_1_v1.4

Preparation of REDCap data for analysis: This document gives a detailed description of how measures and clinical scores to be used in analysis will be obtained from the collected data. These details have been predefined and agreed by the research team.

3.3 CONFIDENCE INTERVALS AND P-VALUES

Confidence intervals will be presented at the 95% level and will be 2 sided. Interpretation will focus on the upper limit for non-inferiority investigations. P-values will be 1-sided for tests of non-inferiority and 2 sided for superiority.

3.4 ANALYSIS POPULATIONS

In all superiority analyses eligible participants will be analysed on an intention-to-treat basis comparing outcome data between the groups as randomised, regardless of clinicians' decisions, use of the FilmArray test results or antibiotics prescribed, and regardless of test failures or timing of tests. All analyses will exclude any patients found to be ineligible after randomisation.

Per protocol analysis will provide the primary results for the non-inferiority outcome. These analyses will compare randomised groups, but exclude:

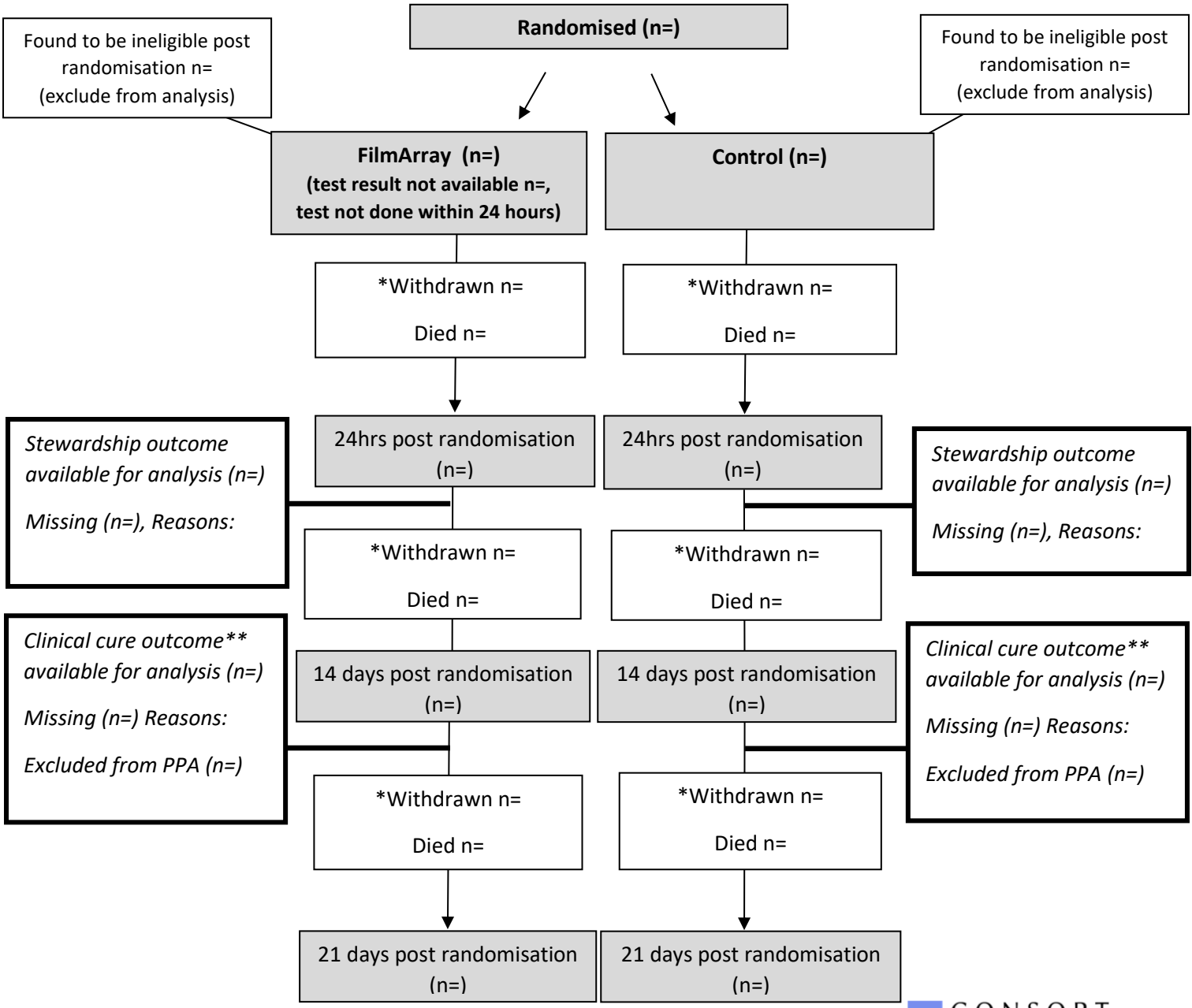
- Those in the intervention arm where FilmArray test results were not obtained
- Those in the intervention arm where a FilmArray run was not initiated within 24 hours of sample collection

Those with missing outcome data will be excluded from analyses, but extent, reasons and characteristics of those with missing data will be examined, and sensitivity analyses used to consider the impact of missing values on the results (described in more detail below).

4 DESCRIPTION OF STUDY SAMPLE

4.1 CONSORT DIAGRAM (FIGURE 1)

A consort diagram will be constructed, describing, by randomised group, the numbers of patients randomised, receiving allocated intervention, withdrawing or lost to follow-up and with data available for primary analysis. Reasons will be included where relevant.
The number of ineligible patients randomised, if any, will be reported with reasons for ineligibility.



CONSORT TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

* Detailed cause of death in table 1b & reasons for withdrawal in table 1a (note patients where consent for use of any data was withdrawn are represented as withdrawn immediately after randomisation)** note: death within 14 days of randomisation does not impede 14 day outcome from being determined

Table 1a: *Detailed reasons for withdrawal from follow-up*

	ID	Reason for withdrawal	Time since randomisation (days)*
FilmArray			
Control			

* Specified as 0 for all those who withdrew consent to use any of their data after randomisation

Table 1b: *Cause of death by randomised group as recorded in the database*

FilmArray			
ID	**Cause text (verbatim from database)**	**Days from randomisation**	**Age**
Control			
ID	**Cause text**	**Days from randomisation**	**Age**

4.2 BASELINE PATIENT CHARACTERISTICS

Baseline characteristics will be summarised by randomised group using appropriate summary measures: mean and standard deviation or median with interquartile range for continuous measures (as appropriate), and frequency and percentage for categorical data. The number of observations for each variable will also be reported. Histograms will be provided to show the distribution for continuous measures. Table 2a gives details of the data that will be presented.

Table 2a: Baseline characteristics by randomised group. All given as frequency (%) unless specified otherwise.

	FilmArray (N=)	Control (N=)
Male participants		
Age at randomisation		
Adults (18+ years)		
Adults: Mean (SD) [median (IQR)](years)		
Children (<18 years)		
Children: Mean (SD) [median (IQR)] (years)		
Children (< 2 years)		
Ethnicity		
White – British		
White – Irish		
White – Other		

White and Black Caribbean		
White and Black African		
White and Asian		
Mixed – Other		
Indian		
Pakistani		
Bangladeshi		
Chinese		
Asian – Other		
Caribbean		
African		
Black – Other		
Any other		
Not stated		
Missing		
Site		
Aintree		
Birmingham Children's' Hospital		
Brompton		
Brompton Children's Hospital		
Chelsea and Westminster		
Cromwell		
Dudley		
Great Ormond Street		
James Paget		
Liverpool		
Royal Free		
Stoke		
UCLH		
Watford		
Comorbidities		
COVID infection at randomisation:all patients		
COVID infection at randomisation: recruited prior to Jan 2020*		
COVID infection at randomisation: recruited after July 2020		
COVID infection at randomisation: recruited between Jan 2020*-July 2020 (test based on frozen sample)		
Historical COVID infection severe enough to require hospitalisation		
Bloodstream infection in 7 days prior to randomisation		
COPD		
Cancer – haematological		
Cancer - solid tumour		

Post bone-marrow/ Stem cell transplantation		
Post solid-organ transplantation		
Chromosomal abnormality		
Chronic kidney disease/renal failure		
Chronic lung disease		
Severe neurodevelopmental delay		
Neurological		
Congenital cardiac malformation (excluding PDA, secundum ASD)		
Chronic liver disease/ cirrhosis		
Diabetes		
Cardiovascular		
Immunocompromised		
Inherited metabolic disease		
Known colonisation by MRSA		
Known colonisation by ESBL producer		
Known colonisation by carbapenemase producer		
Post-operative		
Haematological - non malignant		
Rheumatological		
Mental Health		
Abdominal		
Congenital		
Premature birth (only if relevant to current stay i.e., if baby born during this admission)		
CAR T cell therapy		
Other pre-existing conditions (provide list)		
Patient admitted to hospital from:		
Elective admission		
A&E		
Transfer from another hospital		
Missing		
Reason for ICU admission:		
Medical		
Surgical		
Trauma		
Other		
Missing		
Type of LRTI/pneumonia		
HAP		
VAP		
Missing		
ICU admission from:		
Elective admission		
A&E		

Elsewhere in hospital		
Another hospital		
Missing		
Ventilation status at randomisation**		
Not ventilated		
Ventilated: non- invasive		
Ventilated: invasive		
Missing		
Taking of prescribed antimicrobials for any indication in 7 days prior to randomisation		
Sample type		
Endotracheal Tube Exudate		
Bronchoalveolar lavage		
Non-directed Bronchoalveolar lavage		
Sputum		
Other		
Missing		
APACHE II score at ICU admission (adults) (Range: 0 (good) – 55 (poor) N Mean (SD) Median (IQR) N Missing		
SOFA Score at randomisation (adults) (Range: 0 (good) – 24 (poor))** N Mean (SD) Median (IQR) N Missing		
PIM3 at ICU admission (children) (probability of death: 0 – 1.0) N Mean (SD) Median (IQR) N Missing		
PELOD score at randomisation (children) (Range: 0 (good) – 33 (poor))** N Mean (SD) Median (IQR) N Missing		
pSOFA score at randomisation (children) (Range: 0 (good) – 24 (poor))** N Mean (SD) Median (IQR) N Missing		

Hospital stays in 90 days prior to current admission Yes – one or more		
ICU stay in 90 days prior to current admission Yes – one or more		

* Date to be confirmed. All those prior to this date will be assumed COVID negative.

**Refers to status/score on Day 1 for those participants randomised on Day 1, and Day 2 for those participants randomised on Day 2

Table 2b: Baseline characteristics by per protocol groups for those with clinical cure outcome available (*table format similar to 2a)*

Table 2c: Baseline characteristics by group for those with stewardship outcome available (if needed depending on extent of missing data) (*table format similar to 2a)*

Figure 2a,b,c,d,e,f : Histograms for age and continuous clinical scores

4.3 Detail on compliance (based on criteria for PPA comparison) & other summary information

Table 3a: *Proportion of participants in the intervention arm who have a molecular diagnostic result*

Number in group (FilmArray only)	Number (%) with molecular diagnostic result	Number (%) without molecular diagnostic result		
		Analysis failure (%)	Information missing (%)	Total no result (%)

Table 3b: *Intervention timing - Time from specimen being taken to initiation of FilmArray testing (minutes) & proportion where FilmArray run was not initiated within 8/24 hours of sample collection*

Number in group (FilmArray only)	Mean (SD)	Median [interquartile range] [range]	N (%) with time > 8 hours	N (%) with time > 24 hours

Table 3c: *Proportion of participants in the control arm who have a molecular diagnostic result*

Number in group (control only)	Number (%) with molecular diagnostic result	Number (%) without molecular diagnostic result		
		Analysis failure (%)	sample missing (%)	Total no result (%)

Table 3d: *Time from sample taken to being frozen in control arm*

Number in group (Control only)	Mean (SD)	Median [interquartile range] [range]	N (%) with time > 72 hours

Table 3e: *Time from sample taken to microbiology result available (hours)*

Group	Number in group	Mean (SD)	Median [interquartile range] [range]
FilmArray			
Control			

Table 3f: *Time from sample taken to FilmArray result being available (hours)*

Number in group (FilmArray only)	Number in group	Mean (SD)	Median [interquartile range] [range]
Calculated using date/time of result supplied by site			
Calculated as FilmArray initiation date/time + 1 hour 15 mins			

Table 3g: *FilmArray arm: Time from sample being taken to decision being made (hours)*

Group	Number in group	Mean (SD)	Median [interquartile range] [range]
FilmArray			

Figure 3a: FilmArray arm: Histogram of time from specimen being taken to initiation of FilmArray testing (minutes)

Figure 3b: Control arm: Histogram of time from specimen being taken to being frozen (hours)

Figure 3c: Histogram of time from specimen being taken to microbiology result available (hours) – by randomised group

Figure 3d: FilmArray arm: Histogram of time from specimen being taken to FilmArray result being available (hours)

Figure 3e: FilmArray arm: Histogram of time from specimen being taken to decision being made (as reported by site)

5 ANALYSIS

5.1 ANALYSIS FOR PRIMARY OUTCOMES

5.1.1 Clinical cure: Non-inferiority objective

For each randomised group we will summarise the primary outcome as the proportion of participants where clinical cure was achieved within 14 days after randomisation, both for the per protocol and intention to treat comparisons.

Main analysis

Based on the per protocol population, the effect of the intervention will be described using a difference in proportions with a one sided 97.5% confidence interval. The treatment effect estimate will be obtained using a mixed effects binomial generalised linear model with identity link (Stata command *gllamm (*http://www.gllamm.org/) specifying options *family(binomial) link(id)*). The model will include an indicator for treatment group as a fixed effect. Site will be included as a random effect.

Non-inferiority will be concluded if the upper limit of the confidence interval is less than 13% (the prespecified non-inferiority margin).

Analysis will exclude those with missing data for clinical cure.

5.1.2 Active and proportionate antimicrobial therapy given within 24 h of randomisation: superiority objective

Main analysis

Based on the ITT population, for each randomised group we will summarise the proportion of participants where active and proportionate antimicrobial therapy has been given within 24 h of randomisation.

The effect of the intervention will be described using a difference in proportions with a 95% confidence interval and P-value. The treatment effect estimate will be obtained using a mixed effects binomial generalised linear model with identity link (Stata command *gllamm (*http://www.gllamm.org/) specifying options *family(binomial) link(id)*). The model will include an indicator for treatment group as a fixed effect. Site will be included as a random effect.

Analysis will exclude those with missing data for this outcome.

A descriptive summary of finer categorisations made by the microbiology committee for this binary outcome will also be given by randomised group –including frequency (%) of those with a negative result, considered treated (i.e. antibiotics not deemed necessary) or with virus only result.

5.1.3 Non convergence: Alternative main analysis for primary outcomes

In the event that the main models proposed for either of the primary outcomes do not converge, the analysis will instead be carried out with adjustment for site as a fixed effect (using command *glm* specifying options *family(binomial) link(id)*). If this second model doesn't converge a model excluding site will be used (using command *glm* specifying options *family(binomial) link(id)).*

5.1.4 Supportive/Sensitivity analyses

For both primary outcomes, the following additional analyses will be conducted:

Sensitivity analyses

1) The main model will be extended to adjust for the following set of baseline prognostic factors (as fixed effects): age (in years), SOFA/PSOFA (continuous score), COVID infection at randomisation (yes/no), blood stream infection in 7 days prior to randomisation (yes/no). SOFA and pSOFA scores will be rescaled and combined for analysis using z score transformation ((observed score – mean score)/standard deviation).
2) The main model will be extended to adjust for any concerning imbalances in baseline characteristics.
3) The model in sensitivity analysis 1) will be refitted excluding adjustment for COVID status (as this may not be reliably known for a significant proportion of patients).

Supplementary analyses

1) An odds ratio describing the intervention effect will be estimated (with 95% confidence interval). This will be obtained from a mixed effects logistic regression model with a random effect for site (using Stata command *melogit*). A model including adjustment for age (in years), SOFA/PSOFA (continuous z scores), COVID infection at randomisation (yes/no), blood stream infection in 7 days prior to randomisation (yes/no) will also be fitted.
2) For clinical cure outcome only - the main model, logistic model and associated adjusted model (adjusted for age (in years), SOFA/PSOFA (continuous score), COVID (yes/no), blood stream infection in 7 days prior to randomisation (yes/no)) will be refitted to compare groups defined by intention to treat
3) Supplementary analyses 1) and 2) will be rerun without adjustment for COVID (as this may not be reliably known for a significant proportion of patients).

Missing outcome data

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

If the level of missing data for either of the primary outcomes exceeds 1% of randomised patients, the following sensitivity analyses for that outcome will be carried out to explore robustness of the primary results:

- Estimation under MAR assumption: 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 associated with missingness identified. Treatment effects will be re-estimated with additional adjustment for baseline predictors of missingness (under MAR assumption these analyses will provide unbiased estimates (Groenwold 2012)).

- Estimation under MNAR assumption: In this sensitivity analysis δ_0 will represent the assumed event rate amongst patients with missing outcome data in the control arm and δ_1 will be the assumed event rate amongst patients with missing outcome data in the treatment arm.

  Analyses will be carried out with δ_0 taking values 0.45, 0.5, 0.55, 0.60, 0.65 or 0.70, and for each value of δ_0, δ_1 will take values $\delta_0 + 0.2$, $\delta_0 + 0.1$, $\delta_0 + 0.05$, δ_0, $\delta_0 - 0.05$, $\delta_0 - 0.1$, $\delta_0 - 0.2$

  For each different combination of δ_0 and δ_1 an estimated treatment effect and 95% confidence interval will be obtained based on 10 imputed datasets. For each combination of δ_0 and δ_1 missing data will be imputed as follows:
  - Patients with missing outcome data in the control arm will be randomly ordered within the dataset; the first δ_0 of patients will be set to experiencing an event, and the remaining 1- δ_0 of patients will be set to not having experienced an event.
  - The same approach will be used to impute missing data in the intervention arm.
  - Each imputed dataset will be analysed using the primary analysis model (described in the sections 5.1.1 & 5.1.2). Estimates of the treatment effect and their standard errors will be combined across the 10 imputed data sets using Rubin's rules (Rubin 2004).

Table 4a: Summary of Clinical cure outcome n/N [with available data] (%)

Number (%) of participants with clinical cure of pneumonia at 14 days post randomisation		
	FilmArray (n/N)	**Control (n/N)**
Intention to treat		
Per protocol		
Excluded from analysis		
Missing clinical cure outcome		
'Non-compliant' (excluded from PPA only)		

Table 4b: Analyses for clinical cure outcome. All models include random effect for site. Adjusted results from models including: age, SOFA/PSOFA, COVID, Bloodstream infection in 7 days prior to randomisation

Per protocol analysis (N=)		
	Estimate	**95% confidence interval**
Unadjusted		
MAIN ANALYSIS: Difference in proportions		
Odds ratio		
Adjusted		
Difference in proportions		
Odds ratio		
Intention to treat analysis (N=)		
	Estimate	**95% confidence interval**
Unadjusted		
Difference in proportions		
Odds ratio		

Adjusted		
Difference in proportions		
Odds ratio		

Figure 4: Check of assumptions - Normal plot of level 2 residuals for main analysis

Table 5a: Summary of stewardship outcome n/N [with available data] (%)

Number (%) of participants on active and proportionate antimicrobial therapy within 24 hours of randomisation		
	FilmArray (n/N)	**Control (n/N)**
Intention to treat		
Excluded from analysis		
Missing stewardship outcome		

Table 5b: Analysis of stewardship outcome. Unadjusted results include random effect for site. Adjusted results from models including: age, SOFA/pSOFA, COVID, other infection (except HAP/VAP) in 7 days prior to baseline

Intention to treat analysis (N=)			
	Estimate	**95% confidence interval**	**P-value**
Unadjusted analysis			
MAIN ANALYSIS: Difference in proportions			
Odds ratio			
Adjusted analysis			
Difference in proportions			
Odds ratio			

Figure 5: Check of assumptions - Normal plot of level 2 residuals for main analysis

5.2 ANALYSIS FOR SECONDARY OUTCOMES (SUPERIORITY OBJECTIVES)

Analysis for all secondary outcomes will be carried out on an ITT basis comparing groups as randomised.

5.2.1. Binary secondary outcomes

- Mortality - death from any cause within 28 days of randomisation
- Septic shock within 21 days of randomisation.
- On antibiotics active/inactive against the pathogen(s) found at 24h from randomisation
- On antibiotics active/inactive against the pathogen(s) found at 72h from randomisation
- On proportionate/disproportionate antibiotics in relation to pathogen(s) found at 72h from randomisation
- On narrow-spectrum antimicrobials at 24 h from randomisation
- On narrow-spectrum antimicrobials at 72 h from randomisation

- Adverse events associated with antibiotics within 21 days from randomisation: Antibiotic induced diarrhoea
- Adverse events associated with antibiotics within 21 days from randomisation: C-diff infection
- Adverse events associated with antibiotics within 21 days from randomisation: Hypersensitivity
- Secondary pneumonia within 21 days of randomisation

Main analysis

For these binary secondary outcomes we will calculate the proportion of participants experiencing the defined outcome within each randomised group.

The effect of the intervention will be described using a difference in proportions with a 95% confidence interval. The treatment effect estimate will be obtained using a mixed effects binomial generalised linear model with identity link (Stata command *gllamm* (http://www.gllamm.org/) specifying options *family(binomial) link(id)*). The model will include an indicator for treatment group as a fixed effect. Site will be included as a random effect.
Analysis will exclude those with missing data for the outcome.

Non convergence : Alternative main analysis for primary outcomes
In the event that the proposed main model does not converge the analysis will instead be carried out with adjustment for site as a fixed effect (using command *glm* specifying options *family(binomial) link(id)*). If this second model doesn't converge a model excluding site will be fitted (using command *glm* specifying options *family(binomial) link(id)*).

Supplementary analysis / description
1. An odds ratio describing the intervention effect will be estimated (with 95% confidence interval). This will be obtained from a mixed effects logistic regression model with a random effect for site (using Stata command *melogit*).
2. Frequency (%) of finer categorisations provided by the micro committee will be summarised by randomised group (e.g. for test results, including categories: negative result, considered treated or with virus only result, and for categories of antibiotic: Narrow, broad, Old, Not on antibiotics)

5.2.2. Continuous secondary outcomes: clinical scores

- Change in SOFA score from randomisation to day 7 post-randomisation (adults)
- Change in PELOD-2 from randomisation to day 7 post-randomisation (children)
- Change in pSOFA score from randomisation to day 7 days post-randomisation (children)
- Change in SOFA score from randomisation to day 14 post-randomisation (adults)
- Change in PELOD-2 from randomisation to day 14 post-randomisation (children)
- Change in pSOFA score from randomisation to day 14 days post-randomisation (children)

Main analysis
Histograms and normal plots will be used to show the distribution of continuous scores. They will be summarised by group using means (SD) and medians (IQR).

Mixed effects regression models will be used to obtain differences in means (with 95% confidence interval) to describe the effect of the intervention. The model will include an indicator for treatment

group and the score at randomisation as a fixed effects. Site will be included as a random effect (Stata command *mixed*).

Where scores at day 7 or day 14 are not available due to ICU discharge, the last observed value prior to discharge will be used in analysis. If values are not available due to death, scores will be set to the maximum daily value provided by the patient during their ICU stay. A summary will be given of the number of deaths and discharges scored in this way.

Sensitivity analyses

1. Sensitivity analyses will be used to consider the impact on results of assumed values for scores after death and discharge. Models will be rerun replacing 'missing' day 7 and 14 scores for those who died or were discharged from ICU by:
    - Carrying forward last recorded observation
    - For 'missing' due to discharge applying the minimum score ever obtained by the patient, and if due to death applying the maximum score ever obtained by that patient
    - For 'missing' due to discharge carrying forward the last recorded observation, and if due to death applying the maximum score possible (i.e.. SOFA =24, PELOD=71, pSOFA=24)

2. A second sensitivity analysis will use daily clinical scores to provide estimates of the treatment effect at 7 and 14 days using alternative assumptions for missing values. Daily scores over 14 days will be described with summary statistics and graphs by randomised group. A three level mixed model will be fitted for the repeated measurements, including covariates for randomised group, baseline score, time and a random effect for site (Stata command: *mixed*). Models will include an interaction between randomised group and time to provide treatment effect estimates at day 7 and 14. These analyses will use daily scores that are available <u>without</u> imputation for discharge/death/missing scores. All patients who have at least one post randomisation measurement will be included. Using this model, missing values up to day 14 will be considered missing at random.

   To address potential concerns that data 'missing' due to discharge/death may be missing not at random, a joint competing risks model for time until death/discharge and daily scores will also be considered, as recommended by Harhay et al (Stata command *stjm.* Crowther et al).

5.2.3. Total antibiotic usage (for all conditions) in Defined Daily dose (DDDs) per ICU day

Main analysis

Histograms and normal plots will be used to show the distribution of Total DDD, number of ICU days and DDD per ICU day. These will be summarised by group using means (SD) and medians (IQR).

A mixed effects regression model will be used to obtain an estimate (with 95% confidence interval) to describe the effect of the intervention. The model will include an indicator for treatment group as a fixed effect. Site will be included as a random effect (Stata command *meglm*).

Supplementary analysis / description

DDD by antibiotic will also be summarised for each randomised group

5.2.4. Time to event outcomes : Survival up to 28 days

Main analysis
Death within 28 days will also be analysed as a time to event outcome, where those alive at 28 days (and any subject lost to follow up) are censored. This outcome will be described using a Kaplan-Meier plot and analysed using a Cox survival model with gamma distributed shared frailty for site (Stata command *stcox* with option *shared(site)*). The treatment effect will be estimated using a hazard ratio with 95% confidence interval.

Analysis will exclude those with missing survival information.

5.2.5. Time to event outcomes : ICU/CCU length of stay

Main analysis
Time from randomisation to discharge to a non-ICU, or death whichever is sooner will also be analysed as a time to event outcome where those alive and in ICU at 28 days (and any lost to follow up) will be considered censored. These outcomes will be described using a Kaplan-Meier plot and analysed using a Cox competing risks survival model for discharge and death (Stata command *stcrreg* with option *vce(cluster, site)* to account for clustering by site, chosen as no option for a mixed effects competing risks model in Stata) .

Analysis will exclude those with missing length of stay information.

5.2.6. Number of ventilator-free days (VFD) over 21 days post randomisation

Main analysis
VFD will be summarised by randomised group using tables, summary statistics and plots.

[note – the distribution of VFD is expected to include a stack of zero values (representing those who are invasively ventilated for the whole period and those who died (see section 1.6.2) and a smaller stack of values at 21 days. There will be a smaller representation for VFD between 1 and 20. Given this expected distribution an ordinal regression is planned for this outcome]

An odds ratio (and 95% confidence interval) to describe the intervention effect will be obtained from a multilevel ordinal logistic regression model (Stata commend: *meologit*, option *or*) fitted for all 22 ordered VFD groups. This model will include an indicator for treatment group as a fixed effect and site as a random effect.

Analysis will exclude those with missing VFD.

Sensitivity analyses
1. An odds ratio (and 95% confidence interval) will also be obtained from a multilevel ordinal logistic regression (Stata commend: *meologit*, option *or*) fitted with 4 ordered VFD groups: 0, 1-10, 11-20, 21.
2. The main model will be refitted based only on those who survived to 21 days

Supplementary analysis / description

1. For those on a ventilator at randomisation a supplementary analysis will be carried out comparing time until extubation over 21 days, using a competing risks regression model for death/extubation. Those who remain on a ventilator at 21 days will be censored. (Yehya *et al*) (Stata command *stcrreg* with option *vce(cluster, site)* to account for clustering by site, chosen as no option for a mixed effects competing risks model in Stata)
2. The number (%) of non-ventilated, invasively ventilated and non-invasively ventilated patients at 7 and 14 days after randomisation will be summarised.

5.2.7 Additional sensitivity analyses for all secondary outcomes

The following sensitivity analyses will be carried out for all secondary outcomes using the same modelling approaches as described previously for the main outcome analyses:

1. Further analyses adjusting for the following set of baseline prognostic factors (fixed effects): age (years), SOFA/pSOFA, COVID infection at randomisation, Bloodstream infection in 7 days prior to baseline (as previously defined for primary outcome analysis)
2. Estimation of the treatment effect adjusting for any concerning imbalances in baseline characteristics.
3. Additional analyses 1) above will be rerun without adjustment for COVID status (as this may not be reliably known for a significant proportion of patients).

Missing outcome data

For each secondary outcome, reasons for missing outcome data will be given and frequency (%) of subjects with missing data, by reason will be summarised for each randomised group.

Sensitivity analyses to consider impact of missing secondary outcome data on the main results will be carried out. Detail of approaches to be used for each outcome will be decided on blind review of the data to examine extent and reasons for missingness.

To obtain unbiased treatment effect estimates under missing at random assumptions, the main analysis model may be refitted including adjustment for any baseline factors related to missingness (identified using logistic regression) (Groenwold 2012).

Multiple imputation may be used to further investigate the impact of missingness and any concerns about data missing not at random.

Table 6a: Summary of secondary outcomes (frequency (%), unless otherwise stated)

	FilmArray (N=)	**Control (N=)**
Participants on active antibiotics at 24 hours post-randomisation [Number (%)]		
Participants on active antibiotics at 72 hours post-randomisation [Number (%)]		
Participants on proportionate antibiotics at 72 hours post-randomisation [Number (%)]		
Participants on narrow-spectrum antimicrobials at 24 hours post-randomisation [Number (%)]		
Participants on narrow-spectrum antimicrobials at 72 hours post-randomisation [Number (%)]		

Participants experiencing an antibiotic associated adverse event within 21 days of randomisation [Number (%)]		
Severe Hypersensitivity		
Antibiotic induced diarrhoea		
C difficile infection		
Participants contracting a secondary pneumonia within 21 days of randomisation [Number (%)]		
Participants dying of any cause within 28 days of randomisation [Number (%)]		
Participants with septic shock within 21 days of randomisation [Number (%)]		
Length of stay in ICU/CCU (days) since randomisation [Median (IQR)]		
Length of stay in ICU/CCU (days) since randomisation amongst survivors [Median (IQR)]		
Length of stay in ICU/CCU (days) since randomisation amongst non-survivors [Median (IQR)		
Number of ventilator free days over 21 days post-randomisation amongst those on ventilator at baseline [Median (IQR)]		
Ventilator free days categories:		
0		
1-10		
11-20		
21		
Total antibiotic use per patient in Defined Daily Dose (DDDs) at 21 days post randomisation		
SOFA score day 7 [Mean (SD)]		
Change in SOFA score: day 7 - randomisation [Mean (SD)]		
PELOD-2 score day 7 [Mean (SD)]		
Change in PELOD-2 score: day 7 - randomisation [Mean (SD)]		
pSOFA score day 7 [Mean (SD)]		
Change in pSOFA score: day 7 – randomisation [Mean (SD)]		
SOFA score day 14 [Mean (SD)]		
Change in SOFA score: day 14 – randomisation [Mean (SD)]		
PELOD-2 score day 14 [Mean (SD)]		
Change in PELOD-2 score: day 14 – randomisation [Mean (SD)]		
pSOFA score day 14 [Mean (SD)]		
Change in pSOFA score: day 14 – randomisation [Mean (SD)]		

Figure 6: Histogram of number of ventilator free days over 21 days post-randomisation by group

Figure 7: Histogram of a) total antibiotic use per patient in Defined Daily Dose (DDDs) over 21 days post randomisation by group b) number of ICU days by randomised group c) DDD per ICU day by randomised group

Figure 8: Histogram of a) day 7 SOFA score by group b) day 7 pSOFA score by group c) 7 day PELOD score by group

Figure 9: Histogram of a) change in SOFA score (day 7-baseline) by group b) change in pSOFA score (day 7 – baseline) by group c) change in PELOD score (day 7 – baseline) by group

Figure 10: Histogram of a) day 14 SOFA score by group b) day 14 pSOFA score by group c) 14 day PELOD score by group

Figure 11: Histogram of a) change in SOFA score (day 14-baseline) by group b) change in pSOFA score (day 14 – baseline) by group c) change in PELOD score (day 14 – baseline) by group

Figure 12: Average SOFA scores over time by group

Figure 13: Average pSOFA scores over time by group

Figure 14: Average PELOD scores over time by group

Figure 15: Kaplan Meier estimate of the probability of survival to day 28 by randomised group

Figure 16: Kaplan Meier estimate of time until discharge from ICU by randomised group

Table 6b: Treatment effect estimates for secondary outcomes (OR = odds ratio, RD = difference in proportions, DM = difference in means, HR = hazard ratio – all estimates from models allowing for a random site effect. Models for clinical scores (SOFA & PELOD) include adjustment for baseline score)

	Estimate		**95% confidence interval**
On active antibiotics at 24 hours post-randomisation	OR		
	RD		
On active antibiotics at 72 hours post-randomisation	OR		
	RD		
On proportionate antibiotics at 72 hours post-randomisation	OR		
	RD		
On narrow-spectrum antimicrobials at 24 hours post-randomisation	OR		
	RD		
On narrow-spectrum antimicrobials at 72 hours post-randomisation	OR		
	RD		
Antibiotic associated adverse events within 21 days of randomisation	OR		
	RD		
Secondary pneumonia within 21 days of randomisation	OR		
	RD		
Death within 28 days of randomisation	OR		
	RD		
Septic shock within 21 days of randomisation	OR		
	RD		
Change in SOFA score: day 7 - randomisation	DM		
Change in PELOD-2 score: day 7 - randomisation	DM		
Change in pSOFA score: day 7 - randomisation	DM		
Change in SOFA score: day 14 - randomisation	DM		
Change in PELOD-2 score: day 14 - randomisation	DM		
Change in pSOFA score: day 14 - randomisation	DM		
28 day Survival	HR		
Length of stay in ICU/CCU (days) since randomisation	HR		
ventilator free days over 21 days post-randomisation	OR		
Antibiotic use in Defined Daily Dose(DDDs) at 21 days post randomisation per ICU bed day	RD		

5.3 ADDITIONAL SUMMARIES

5.3.1 Additional safety items not reported as secondary outcomes

Receipt of inactive antibiotic/inappropriate step-down of therapy [identified when raised as concern by study microbiology committee]

Table 7 : *Recorded instances of concerning antimicrobial therapy, noted by the microbiology committee*

		FilmArray	Control
Recorded instances of concern amongst those currently assessed by committee		N=	N=
	Yes		
	No		

Adverse outcomes requiring expedited reporting

Table 8 : *Machine error*

	FilmArray N=	Control N=
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		

Table 9 : *Any other situation requiring expedited reporting*

	FilmArray N=	Control N=
Any other situation that the site PI feels requires expedited reporting to the CI		

Table 10: *Listed Adverse Events (text as recorded in the database) up to 28 days*

Intervention					
ID	**MedDRA term**	**AE details**	**AE Grade**	**Serious?**	**Requires urgent report?***
Control					
ID	**MedDRA term**	**AE details**	**AE Grade**	**Serious?**	**Requires urgent report?***

*Requires urgent report was defined as: 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. Unrelated SAEs did not require expedited reporting in this trial.

5.4 SUBGROUP ANALYSES

None specified in protocol

5.5 REFERENCES

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