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HAPFAST- A feasibility study incorporating qualitative, mechanistic and costing sub-studies alongside a randomised pilot trial comparing chest x-ray to low-dose CT scan and empirical antibiotics to antibiotics guided by the BIOFIRE® FILM ARRAY® pneumonia panel in adults with suspected non-ventilator acquired Hospital-acquired Pneumonia (nv-HAP)

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HAPFAST- A feasibility study incorporating qualitative, mechanistic and costing sub-studies alongside a randomised pilot trial comparing chest x-ray to low-dose CT scan and empirical antibiotics to antibiotics guided by the BIOFIRE® FILM ARRAY® pneumonia panel in adults with suspected non-ventilator acquired Hospital-acquired Pneumonia (nv-HAP)

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ABSTRACT

Introduction

Non-ventilator associated Hospital-acquired Pneumonia (nv-HAP) is the most common health care associated infection (HCAI), has high associated mortality and morbidity and places a major burden on healthcare systems. Diagnosis currently relies on chest x-rays to confirm pneumonia and sputum cultures to determine the microbiological cause. This approach leads to over-diagnosis of pneumonia, rarely identifies a causative pathogen and perpetuates unnecessary and imprecise antibiotic use. The HAP-FAST study aims to evaluate the feasibility of a randomised trial to evaluate the clinical impact of low dose, non-contrast enhanced thoracic CT scans (CT) and rapid molecular sputum analysis using the BIOFIRE® FILMARRAY® pneumonia panel plus (FAPP) for patients suspected of nv-HAP.

Methods & Analysis

The HAP-FAST feasibility study consists of a pilot randomised trial, a qualitative study, a costing analysis, and exploratory analyses of clinical samples to investigate the immune-pathophysiology of HAP. Participants are identified and recruited from 4 acute hospitals in the Northwest of the UK. Using a Research Without Prior Consent (RWPC) model, the pilot trial will recruit 220 adult participants, with or without mental capacity, and with suspected HAP. HAP-FAST is a non-blinded, sequential, multiple assignment, randomised trial (SMART) with two possible stages of randomisation: firstly, chest x-ray (CXR) or CT; secondly, if treated as nv-HAP, FAPP or standard microbiological processing alone (no FAPP). Pathogen-specific antibiotic guidance will be provided for FAPP results. Randomisation uses a web-based platform and follow-up is for 90 days. The feasibility of a future trial will be determined by assessing trial processes, outcome measures, and patient and staff experiences.

Ethics & Dissemination

This study has undergone combined review by the UK NHS Research Ethics Committee (REC) and Health Research Authority. Results will be disseminated via peer-reviewed journals, via the funders website and through a range of media to engage the public.

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ARTICLE SUMMARY:

Strengths & Limitations of the Study

- HAP-FAST will be the largest randomised trial of nv-HAP in the UK and will provide valuable insights into this patient population beyond the feasibility objectives.
- Includes a qualitative sub-study into participant and carer experiences of the trial and its interventions that will inform a subsequent trial powered for clinical endpoints and future studies of nv-HAP.
- Decentralised, clinician-led randomisation facilitates continual recruitment on all wards of participating hospitals, improving the representativeness of the study population, and providing insights into expected recruitment patterns in future trials.

- Sequential, multiple assignment design coupled with low rates of self-expectorated sputum sample submission, may mean study will provide limited assessment of use of FAPP platform.
- The denominator for eligibility is hard to assess prospectively. Mitigations are in place using data from an ongoing nv-HAP quality improvement programme. (1)

INTRODUCTION:

Non-ventilator associated Hospital-acquired Pneumonia (nv-HAP) is the most common healthcare associated infection (HCAI).[2] UK in-patient mortality following nv-HAP is 24% and it extends length of hospital stay by, on average, 9 days.[1,3] Among those who survive to discharge, compared to other HCAIs, nv-HAP has the highest level of disability adjusted life years (DALYs) (ref). Nv-HAP therefore represents a major risk for patients and places a huge burden on healthcare systems.

Diagnostic Uncertainty in nv-HAP

Pneumonia is a syndrome that is diagnosed based on a case definition with three components: signs and symptoms of a lower respiratory tract infection, evidence of a systemic inflammatory response and radiological change compatible with infection on chest imaging.[4] Defining the specific aetiological cause requires microbiological tests. Traditional diagnostic methods, relying on chest x-rays for syndromic diagnosis of nv-HAP and sputum cultures for microbiological diagnosis of cause, often lead to over-diagnosis, delayed treatment decisions and inappropriate antibiotic use.[5,6] Together these diagnostic inadequacies contribute to poor clinical outcomes, and the UK National Institute for Health and Care Excellence (NICE) have called for a research focus on diagnostics.[7]

Addressing this evidence gap, the HAP-FAST study aims to evaluate the use of low dose, non-contrast enhanced CT scans as an alternative to chest x-rays, and the BIOFIRE® FILMARRAY® Pneumonia Panel Plus (FAPP) as an alternative to standard microbiological testing, both individually and in combination in patients suspected of nv-HAP.

Rationale for Chosen Diagnostics in this Study

CT scans in nv-HAP

Chest x-rays (CXR) have limitations when diagnosing pneumonia.[8-13] Using a CT scan as the gold standard, CXR had a positive predictive value of 27% in 3423 US patients with possible Community acquired Pneumonia (CAP).[10] Claessens et al demonstrated that performing a CT after a CXR in suspected CAP might avoid antibiotics in 14%.[11] The diagnostic inaccuracy of CXR is further exacerbated in bedridden patients, as is often the case in nv-HAP, with CT scan reports changing management plans based on CXR diagnosis in nearly half of patients.[13] Prendki et al found that using a CT scan instead of a CXR avoided antibiotic use in 8.5% of elderly Swiss patients with suspected pneumonia.[9] These non-randomised, observational studies are prone to bias and we need a randomised controlled trial to demonstrate the impact of CT scans on clinical outcomes following nv-HAP.

Rapid Microbiological Testing in nv-HAP

Empirical antibiotic treatment of nv-HAP is imprecise and hampered by conflicting evidence about the potential pathogens. A Spanish study demonstrated 60% of bacterial detections were Gram-positive and a retrospective Scottish study found 71% were Gram-negative.[14,15] Neither study tested for viruses but subsequent studies have detected viruses in up to 22% of patients with HAP.[16,17] Clinical guidelines often extrapolate recommendations from literature about ventilator associated pneumonia (VAP), but a comparative study suggests this comparison is invalid.[18] Most recently, the

INHALE research group compared two rapid molecular diagnostic tests to conventional microbiological testing of respiratory samples from patients with pneumonia on critical care. They reported superior sensitivity for pathogen detection for the new rapid tests when compared to conventional methods and viruses were implicated in a significant proportion of cases.[19]

The BIOFIRE® FILMARRAY® Pneumonia Panel (FAPP) is a CE marked, United States Food and Drug Administration (FDA) approved point-of-care test that can simultaneously detect 18 bacteria, 9 viruses and 7 antimicrobial resistance genes from a respiratory sample in 75 minutes.[19] Compared to the traditional culture based methods, the speed, sensitivity and specificity of this diagnostic test has the potential to dramatically change the way nv-HAP is managed. However, before it is widely implemented, questions relating to the interpretation of results and cost-effectiveness within the NHS setting need to be addressed.[20] There are also key questions relating to: the implementation of decentralised microbiology results within the clinical work flow, the feasibility of maximising time gains using the FAPP, the safety and effectiveness of antibiotic rationalisation based on results and the willingness of clinicians to deviate from traditional paradigms of empirical management.

Risks and benefits

In usual care, thoracic CT scans of various types are performed at some point during the care pathway for approximately 12% of patients managed for nv-HAP. Here we will trial the systematic use of low dose, non-contrast, thoracic CT scans (CT) as the first test in those suspected of nv-HAP because there is evidence this may lead to improved patient outcomes.[11] The CT scan used in HAP-FAST carries a radiation exposure of, on average, 1.5mSv, which is greater than a CXR (0.05 mSv) but lower than annual UK background radiation exposure of 2.7mSv.[13] A recognised consequence of performing a thoracic CT scan at any point in a patient's acute care is the detection of unexpected abnormalities such as anatomical variants, alternative diagnoses for the presenting symptoms and incidental findings such as pulmonary nodules. Given the frequency of detection of pulmonary nodules in routine care, there are well established pathways for their investigation and follow-up supported by national guidelines.[21,22]

Patients who can self-expectorate sputum will be randomised to either a standard microbiological diagnostic pathway (No FAPP) with initial empirical antibiotic selection as per their local policy – or to analyse sputum using the FAPP. Clinicians are provided with an antibiotic guide with pathogen targeted treatment options for those randomised to use the FAPP. It is possible that based on either empirical antibiotic prescribing or FAPP guided treatment, a participant may receive antibiotics that are not effective against an undetected pathogen. This risk is always present due to the imperfect nature of microbiological tests and so it is standard clinical practice for patients to be closely monitored for response to treatment during the early stages of pneumonia and this study protocol allows for the clinicians treating the participant to escalate or change their therapy as clinically indicated.

AIMS AND OBJECTIVES

The study aim is to determine the feasibility of a full-scale randomised controlled trial (RCT) comparing different diagnostic pathways in adult patients suspected of nv-HAP.

The following HAP-FAST objectives will assess feasibility parameters:

1. For each intervention, estimate effect size and dispersion for a range of possible outcomes to inform the sample size of a definitive study.
2. Evaluate the practicality and fidelity of a range of possible outcome measures using completion rates, missing data, effect size and dispersion.
3. To estimate eligibility, recruitment, and consent rates.
4. Estimate rates of successful follow up.

5. Assess the web-based randomisation process and incorporate clinical and researcher feedback.
6. Perform a costing analysis of nv-HAP to inform the cost-effectiveness analysis for any definitive study.
7. Assess human factors involved in delivery of the study and how the different diagnostic tests influence clinical decision making by conducting qualitative interviews and focus groups with healthcare workers and researchers.
8. Evaluate willingness of clinicians to recruit to the study.
9. Evaluate willingness of potential participants or their consultees to be recruited.
10. Evaluate adherence to antibiotic guidelines as outlined in the study protocol.
11. Assess the study participant and carer experience of participating in the study via qualitative interviews.

METHODS AND ANALYSIS

Study Setting

Participants are identified and recruited from 4 acute hospitals in the Northwest of the UK: Aintree University Hospital, Royal Liverpool University Hospital, Royal Preston Hospital and Wythenshawe Hospital. Sites were selected to capture ethnic and socioeconomic diversity. Preliminary data from a longitudinal HAP improvement programme demonstrated a sufficiently large caseload potential participants in these settings within the study's timeframe.[23]

Study Design

HAP-FAST is a feasibility study consisting of a pilot study, two qualitative studies, and a costing analysis. The study participants will also provide clinical samples to support exploratory analyses of the immune-pathophysiology of nv-HAP.

Pilot Study

Participants and Sample Size

Since the aim is to assess feasibility, a sample size justification is given rather than a calculation. We aim to recruit 220 adult participants, based on prospective audits of HAP in the UK Northwest revealing between 600 and 1000 cases per year across our recruiting sites and assuming 30% of cases are eligible of whom 40% are recruited to the trial. Recruitment targets will likely be affected by the seasonality of HAP, with a greater burden in winter and seasonal variation in pathogens and thus we aim to recruit across the majority of a calendar year.

Pilot Study Consent & Assent

HAP is potentially severe as evidenced by the in-patient mortality of 24%. NICE recommend treatment is commenced within 4 hours. Clinicians therefore face a narrow timeframe during which patients must be clinically assessed and diagnostic tests must be ordered, completed, reported, interpreted and acted upon. Patients with nv-HAP frequently have impaired mental capacity due to underlying cognitive impairment or acute delirium. Therefore, due to the emergency nature of HAP, in common with research in other emergency settings such as trauma and intensive care, HAP-FAST uses a Research Without Prior Consent (RWPC) model.[24-26] The use of RWPC for nv-HAP trials has been studied previously and deemed acceptable by patients and the public.[26]

At the point of suspecting nv-HAP, treating clinicians at the recruiting sites can randomise, carry out the interventions and obtain the initial sample set. Randomisation leads to an automatic email alerting the site research team who then obtain written informed consent from the patient or for those lacking capacity from a personal or professional proxy before discharge. Every effort will be made to obtain written informed consent after discharge if a patient is discharged before consent is obtained. Patients who decline to provide consent or no longer wish to continue in the study will be withdrawn.

Pilot Study Eligibility Criteria

Eligibility criteria for Stage 1 randomisation to CXR vs CT and Stage 2 randomisation to FAPP or no FAPP can be seen in **Table 1**. Patients who are ineligible for randomisation to Stage 2 will still be able to participate in the trial.

Table 1: Inclusion and Exclusion Criteria for Stage 1 and 2 Randomisation

	Stage 1 CXR vs CT	**Stage 2 FAPP vs No FAPP (standard laboratory sputum analysis)**
Inclusion Criteria	Age ≥18 years	The clinician intends to treat the patient for HAP, or a hospital acquired respiratory tract infection (RTI)
	Suspected HAP (For the purposes of this study, HAP is defined as per the BTS and FDA definitions i.e. pneumonia which develops 48 hours after an admission to hospital for an alternative diagnosis; or a new presentation to hospital with pneumonia in a patient who has been discharged from an overnight stay in hospital within the last 10 days)	A sputum sample has been obtained before 2nd dose of antibiotic
Exclusion Criteria	Already received a chest X-ray to confirm suspected HAP diagnosis	Following the CXR or CT the clinician decides not to treat with antibiotics for either HAP or a hospital acquired RTI
	Diagnosis or suspected diagnosis of ventilator acquired pneumonia	
	Intention to palliate rather than cure	
	Interventions cannot be completed before administration of second antibiotic dose *	
	Cannot be randomised to low-dose, non-contrast CT scan on clinical grounds e.g. strong suspicion of PE (A non-contrast, low-dose thoracic CT scan is an inappropriate test for a PE and if that is high in the differential diagnosis then tick yes here)	
	Pregnancy (A urine pregnancy test is required as part of routine care prior to a chest X-ray or CT scan. If the test reveals the patient is pregnant, they will not be eligible for the study)	
	Previous study participation (patients with second of third episodes of HAP will not be re-recruited)	

* In the circumstance where a patient is diagnosed with HAP whist receiving antibiotics for a non-respiratory infection (e.g. UTI) if the HAP diagnosis leads to a change in the antibiotic prescription to cover the HAP, then that patient will be eligible for recruitment. However, if the diagnosis of HAP does not result in a change in antibiotic, then the patient **is not eligible**.

Interventions and Treatments

Participants are initially randomised between a standard-care chest X-ray (CXR) and low-dose, non-contrast, thoracic CT scan (CT). If the clinician decides to give antibiotics to treat nv-HAP and the participant can produce a sputum sample prior to the administration of the second dose of antibiotics, they are further randomised between sputum testing by FAPP alongside local, standard of care microbiological processing or standard processing alone - no FAPP. A study specific antibiotic guideline has been produced and approved by all recruiting sites for use with the results of the FAPP. It is anticipated that patients randomised to standard microbiological testing will receive an empirical antibiotic prescription supported by usual microbiological tests. Additional advice regarding antibiotic treatment is available from microbiology specialists in line with local policies. Participants who cannot provide sputum and who are not randomised at Stage 2 will be managed as per usual care. These interventions are summarised in **Table 2** and **Figure 1**.

Table 2: Treatment Pathways in Pilot study

Result of Stage 1 Randomisation	Result of Imaging	Sputum Available?	Result of Stage 2 Randomisation	Treatment	Group
CXR	Clinician decides to treat for HAP / hospital acquired RTI	YES	FAPP	• Use an aliquot of respiratory specimen in the FAPP • Send remainder of specimen to microbiology for standard tests • Prescribe antibiotics with reference to the FAPP antibiotic guideline	1
		YES	No FAPP	• Prescribe empirical antibiotics based on local guidelines	2
		NO	N/A	• Prescribe empirical antibiotics based on local guidelines	3
	Clinical diagnosis is **not** HAP / RTI	N/A	N/A	• Patient receives usual care and is followed up as per the study schedule	4
CT Scan*	Clinician decides to treat for HAP/ hospital acquired RTI	YES	FAPP	• Use an aliquot of respiratory specimen in the FAPP • Send remainder of specimen to microbiology for standard tests • Prescribe antibiotics with reference to the FAPP antibiotic guideline	5
		YES	No FAPP	• Prescribe empirical antibiotics based on local guidelines	6
		NO	N/A	• Prescribe empirical antibiotics based on local guidelines	7
	Clinical diagnosis is **not** HAP / RTI	N/A	N/A	• Patient receives usual care and is followed up as per the study schedule	8

* Low-dose, non-contrast, CT scan of the thorax "hot reported".

Outcome measures

A key objective of HAP-FAST is to gather data to inform the choice of outcome measure for a fully powered RCT. We searched the COMET database for core outcome sets in HAP trials.[27] Some groups advocate all-cause mortality assessed on a non-inferiority basis.[28] However, others argue discerning the mortality attributable to HAP, as opposed to underlying comorbidity, is difficult without unfeasibly large trials.[29] One group proposed a hierarchical, composite, primary outcome of survival at day 28 and 'clinical cure' between days 7-10 but unfortunately did not provide a pragmatic definition of clinical cure.[30] A group convened by the FDA suggested using mortality plus resolution of symptoms.[31] HAP-FAST will therefore evaluate a range of outcomes including mortality, antibiotic usage and clinical cure incorporating a pneumonia specific Patient Reported Outcome Measure (PROM) called the CAP-SYM score.

Pilot Study Randomisation

The pilot study has been designed as a sequential, multiple assignment, randomised trial (SMART) with a 1:1 allocation ratio, with the purpose to address study objectives 1-5.[32] The randomisation list has been created by an independent statistician and participant allocations are generated by completion of the web-based randomization platform. The SMART study design is presented schematically in **Figure 1**.

Pilot Study Blinding

The study is open-label and treating clinicians, researchers and participants will know which intervention is being administered via the web-based randomisation process.

Pilot Study Outcome Measures & Participant Timeline

Baseline, and outcome data are collected at distinct time points according to the schedule in **Tables 3 and 4.** Participants will be assessed by the study team daily until day 10 to track symptomatic recovery, changes in Quality of Life (QOL) and determine time to clinical cure. Participants will have symptoms and QOL assessed on day 28 as an in or out-patient. Follow up will be conducted as a phone call 90 days (+/- 14 days) following entry into the study to assess symptoms, QOL and to remind them to return a survey booklet on health and social care use up to day 90.

Pilot Study Data Analysis

All analyses will be carried out on an intention to treat basis, retaining all participants in their initially randomised groups irrespective of any protocol deviations. The focus of analysis will be to assess feasibility and recruitment for each participating site and overall pilot study as well as assessments of efficacy for each outcome for treatment arm comparisons of CXR vs CT (**Figure 1**- group 1-4 vs group 5-8) and FAPP vs No FAPP (**Figure 1**- group 1+ 5 vs group 2 and 6). No inference will be drawn – all results will be treated as hypothesis generating.

Continuous data will be presented using median (interquartile range) and mean (standard deviation) as appropriate, with boxplots summarising measurements at each time-point by treatment group. Categorical data will be presented as frequencies and percentages. Time-to-event data will be presented with Kaplan-Meier curves and summarised by median (95% confidence interval) if possible.

As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis. Such methods will be fully described in the full statistical analysis plan, which will be written prior to the conduct of any comparative analysis of the treatment arms, including methods employed for missing data.

Qualitative Sub-Studies

Clinicians

This qualitative sub-study will address objectives 5,7,8 and 10 to evaluate the human factors involved in the delivery of the study, clinician willingness to recruit participants and adherence to antibiotic guidelines as per study protocol (**Table 3**).[26,33] A range of clinical, allied health professional and research staff will be invited to participate in focus groups of approximately 8 participants. Focus groups will be topic guided, yet conversational and exploratory and conducted in a comfortable private environment.

Patients and Carers

This qualitative sub-study will address objectives 9 and 11 to evaluate patient willingness to participate in the study and their experience from recruitment to study-follow-up (**Table 3**).[34] Approximately 15 participants (5 from each of the three recruiting Trusts) will be purposively recruited for in-depth semi-structured interviews based on age, gender, and underlying comorbidity class (medical admission, surgical admission, acute admission). Relatives and carers of some study participants will also be interviewed.

Table 3: Schedule for Recording of Data Outcomes

Objective		
Primary Objective		
The primary objective is to determine the feasibility of a full-scale Randomised Controlled Trial (RCT) comparing different diagnostic dynamic treatment regimens (DTRs) in adult patients suspected of HAP.		
Secondary Objective		
Objective	Outcome	Time-point
Inform the sample size of a definitive study	Time to clinical cure*	Day 90
	Antibiotic usage for the HAP episode	Day 90
	EQ-5D-5L	Baseline, day 10, 28 and 90
	Length of hospital stay post HAP diagnosis	Day 90
	Mortality	Day 14, 28 and 90
To measure key outcome measures (completion rates, missing data, estimates and dispersion)	Estimate rates of completion of questionnaires - EQ5D5L, CAP-sym, economic evaluation Summary statistics and proportion of missing data for time to clinical care, antibiotic usage for HAP diagnosis, EQ-5D-5L, length of hospital stay post HAP diagnosis, mortality	Screening Randomisation Follow up End of Treatment End of Study
To estimate eligibility, recruitment and consent rates	Rate of recruitment; Proportion screened that meet eligibility criteria; ** Proportion eligible that consent and where they present; ** Proportion consented and randomised that complete study pathway as per protocol; Proportion consented and randomised that withdraw from study intervention or follow up; **	Screening Randomisation Follow up End of Treatment End of Study
Estimate rates of successful follow up	Proportion consented and randomised that complete study pathway as per protocol; Proportion consented and randomised that withdraw from study intervention or follow up; **	End of Study
Assess the web-based randomisation process and incorporate clinical and researcher feedback	Qualitative conclusions based on staff focus groups	Qualitative analysis

Perform a costing analysis of HAP to inform the cost-effectiveness analysis for any definitive study	Summary statistics for numbers and types of costs with comparison between DTRs	End of Study
Assess human factors involved in delivery of the study and how the different diagnostic tests influence clinical decision making by conducting qualitative interviews and focus groups with healthcare workers and researchers	Qualitative conclusions based on staff focus groups	Qualitative analysis
Evaluate willingness of clinicians to recruit to the study	Qualitative conclusions based on staff focus groups	Qualitative analysis
Evaluate willingness of potential participants or their consultees to be recruited	Qualitative conclusions based on participant and carer interviews	Qualitative analysis
Evaluate adherence to antibiotic guidelines and study protocol	Summary statistics relating to antibiotic use in the pilot study with a comparison between the DTRs	End of Study
Assess the study participant and carer experience of participating in the study	Qualitative interviews	Qualitative analysis

Exploratory Sub-Study

Clinical samples are taken at enrolment to the pilot RCT, on day 3 and at day 28 and comprise venous blood, sputum and a nose swab and participants will be asked for additional consent for this sub-study. These samples will be used to explore the role immune cells and inflammatory mediators play in the pathophysiology of nv-HAP and how these vary with pathogen. The samples from the HAP-FAST pilot study cohort (patients suspected of HAP) will be compared with equivalent samples from patients who chronically produce sputum, are not exacerbating, and are being managed as out-patients in respiratory clinics.

Health Economic Evaluation

This costing analysis will address objective 6 by capturing the direct costs in hospital associated with HAP as well as the post-discharge indirect costs with a bespoke questionnaire (up to 90 days following diagnosis). We will evaluate the performance of this questionnaire which we have developed with reference to a range of similar studies.[35-38] We will capture item completion rates, and discuss participant and carer's views of the questionnaire to refine it for the future full-scale RCT.

DATA COLLECTION & MANAGEMENT

Data Management

For the HAP-FAST study the responsibilities for Data Management and monitoring are delegated to the Liverpool Clinical Trial Centre (LCTC). Data collection will be directly entered on to a secure database as the source document and this includes validation features to alert the user of inconsistent or missing data. Data of written informed consent processes and participation in the clinical trial will be added to the patient's medical record chronologically.

Baseline assessment data will be obtained from patient medical notes, followed by use of the CAP-SYM questionnaire,[39] EQ-5D-5L questionnaire, research sample collection (for exploratory sub-study), monitoring of blood test results, and a post-discharge indirect cost survey as shown in **Table 4**. Separate Data Management and Trial Monitoring Plans will detail the internal processes that will be conducted at the LCTC throughout the study in line with regulatory, ethical, and legal obligations.

Table 4: Schedule for Assessments and Follow-Up

Specific Activity	Stage 1 randomisation Day 0	Stage 2 Randomisation	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 28 (+/- 7 days)	Day 90 (+/- 14 days)
Assessment of eligibility	X	X												
Concomitant medication check	X													
Randomisation	X	X												
Urine pregnancy test as required pre Chest X-ray/CT scan	X													
Chest X-ray	X													
CT scan	X													
Sputum sample		X			[3]X								[3]X	
FAPP		X												
Informed consent		[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X
Past Medical history	X													
Admission related data (date, time, symptoms, co-morbidities, ward type, reason for admission, clinical frailty score)	X													

Patient demographics (age, sex, postcode, height, weight, calculated BMI)	X													
Details of antibiotic use	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (temperature, blood pressure pulse rate, oxygen saturation rate, respiratory rate, NEWS2 score)	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Record clinician's description of symptoms	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Record clinician's respiratory exam findings	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Blood test results (haemoglobin, platelets, white blood count, neutrophils, lymphocytes, creatinine, c-reactive protein and urea)	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
CAP-sym score	[4]X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	X	X
Record survival status	X		X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L	[4]X											[1]X	X	X
Nasal swab	[3 5]X				[3]X								[3]X	

Research blood sample	[3][5]X				[3]X								[3]X	
Post-discharge Indirect Cost Survey														X
Record microbial results from admission														X
Record any further imaging and findings														X

[1] collected until day 10 or discharge
[2] collected as soon as possible up until discharge
[3] collected for the exploratory sub-study only
[4] not to be collected until written informed consent is obtained.
[5] must be collected within 24 hours of stage 1 randomisation

Confidentiality

This study will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used, and stored if necessary for the study (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

MONITORING

Trial Monitoring

Given this study is designed to evaluate feasibility rather that safety or efficacy there is no on-site monitoring planned. LCTC will however be monitoring CRF completion and making consent checks. The Trial Management Group (TMG), including investigators, Patient and Public Involvement (PPI) representatives and LCTC members, will meet regularly to monitor all aspects of day-today conduct, management and progression of the study. The Trial Steering Committee (TSC) consists of an independent lay chairperson, 2 independent experts in the field, an independent biostatistician, the chief investigator, and a second PPI representative to provide overall supervision of the study.

Patient and Public involvement (PPI)

Patient and Public representatives will be consulted throughout the duration of the study by acting as members of the TMG and TSC.

ETHICS & DISSEMINATION

Research Ethics Approval

The study will be conducted in accordance with Good Clinical Practice (GCP) and will abide by the principles of the World Medical Association Declaration of Helsinki. The protocol, patient information sheet and all proposed public-facing material was prepared along with our PPI team members and has undergone combined review by the UK NHS Research Ethics Committee (REC) and Health Research Authority (22/WA/0315). The committee was specifically configured to assess studies recruiting patients who lack capacity and reviewed Medical Physics Expert and Clinical Radiation Expert reports conducted in compliance with Ionising Radiation (Medical Exposure) Regulations (IRMER) legislation.

Protocol Amendments

This publication has been based on version 3.0 of the protocol. Version 1.0 was submitted to the REC, resulting in amendments and use of Version 2.0 from the start of the trial. Further amendments, to improve clarity, were approved in October 2023 to: the eligibility criteria (clarifying 'the development of Pneumonia within 10 days of discharge' as a component of the definition of HAP and removing a fixed time-period requirement for stage 2 randomisation) patient information sheets (including format and hypostatical changes, additional consent statements for use of clinical samples, provision of a letter to deceased participant's next of kin), consent processes (allowing verbal consent for the qualitative study, allowing postal consent for patients discharged before written informed consent obtained), study processes (removal of requirement for the statistical team to be blinded to participant allocation, adding a 7-day window for day 28 follow-up and reducing frequency of collection of concomitant medication in the schedule of activities).

Protocol Deviations

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions, or principles of GCP and REC requirements are handled based on their nature and severity by LCTC and reported to the trial oversight committees with serious breaches being reported to Sponsor and REC within 7 days.

Dissemination

The findings of HAP-FAST will be published and disseminated within scientific and lay communities regardless of the magnitude or direction of effect.

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AUTHOR'S CONTRIBUTIONS

DW wrote the grant and obtained the funding and is the Chief Investigator of the HAP-FAST trial and associated sub-studies. SA, LT, SJA, BY, FS, AA, SW, AJ and DW wrote and amended this trial protocol. LT, SA and DW led the writing of the mechanistic sub-study components, BY, FS and DW led the writing of the qualitative sub-study components. AA contributed a patient and public involvement perspective throughout the protocol drafting and approval process and chairs the HAP-FAST steering committee. SW and AJ are, respectively, trial manager and lead statistician for Liverpool Clinical Trial Centre (LCTC) and contributed to the protocol development and ongoing trial processes. SJA is site Principal Investigator at one of the recruiting sites. NS is NIHR Associated Principal Investigator at one of the sites and drafted this protocol submission and all other authors reviewed and edited this manuscript.

FUNDING STATEMENT

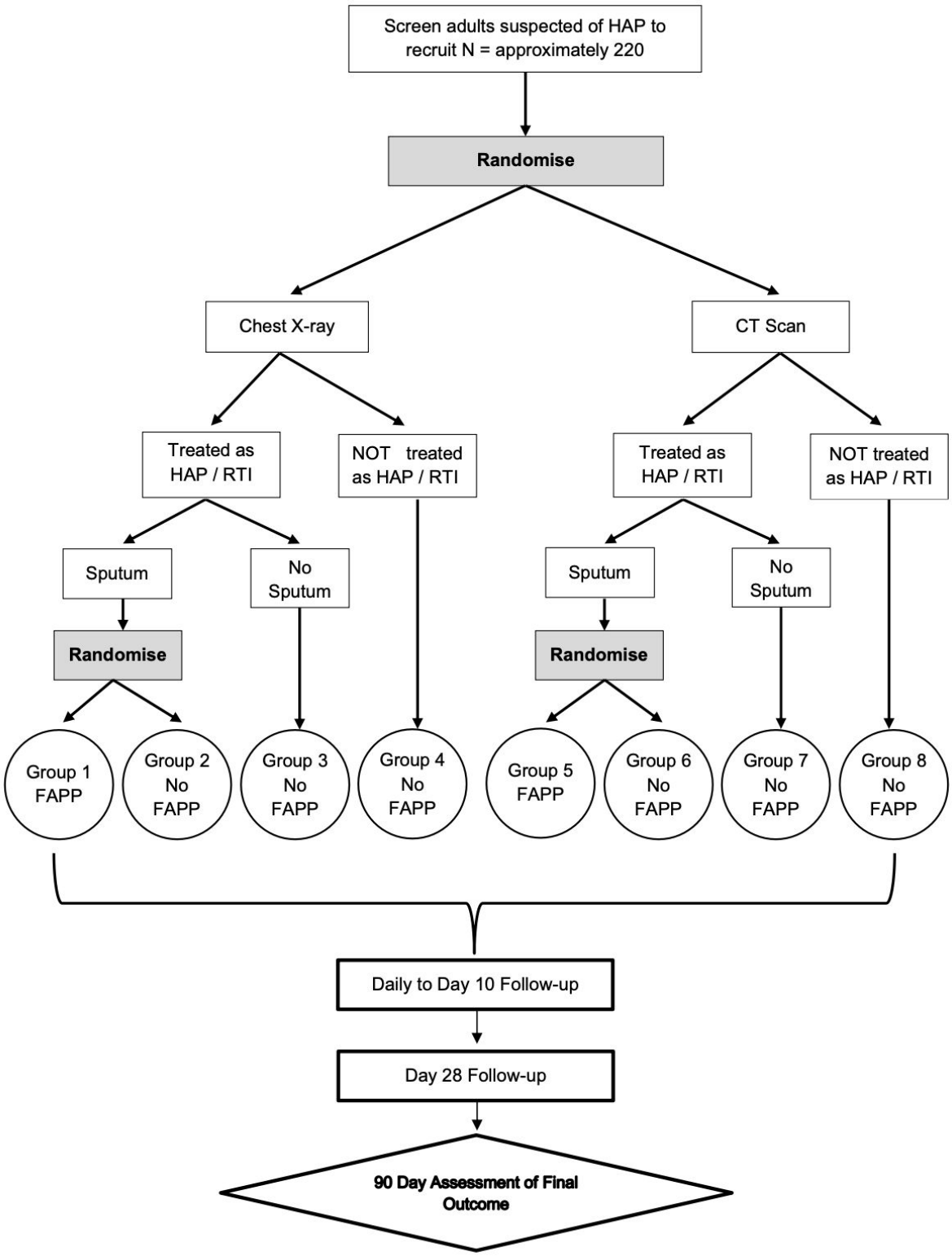
This work was supported by the National Institute of Health Research (NIHR300669)

COMPETING INTERESTS STATEMENT

The BIOFIRE® FILM ARRAY® machines for each study site were loaned, free of charge by bioMérieux. FAPP test kits for running on those machines were also provided by bioMérieux. bioMérieux had no role in the content of the funding application, protocol, ethics application for this work nor will they have a role in handling or interpretation of the data or its dissemination.

LT has received consulting fees from MHRA; and from Astrazeneca and Synairgen, paid to the University of Liverpool; speakers' fees from Eisai Ltd, and support for conference attendance from AstraZeneca.

Figure 1: Pilot sequential multiple assignment randomised trial (SMART) design



Feasibility study of the clinical and cost-effectiveness of contemporary diagnostics for patients with suspected Hospital-Acquired Pneumonia (HAP).

HAP-FAST Protocol
V3.0, 14/11/2023

Study Sponsor(s):
The University of Liverpool, Clinical Directorate
Thompson Yates Building
The Quadrangle, Brownlow Hill, Liverpool
L3 5RB

Research Ethics Ref: 22/WA/0315

Sponsor Ref: UoL001676

Funder Ref: NIHR300669

ClinicalTrials.gov: NCT05483309

Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: _____ **Date:** _____

Dr Daniel Wootton
Senior Clinical Lecturer

HAP-FAST Protocol V3.0, 14/11/2023
Based on protocol template v1.0 20/02/2020

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of Sponsor:

Signature: _____ **Date:** _____

HAP-FAST Protocol V3.0, 14/11/2023
Based on protocol template v1.0 20/02/2020

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of the Lead Statistician:

Signature: _____ **Date:** _____

Dr Ashley Jones
Head of Statistics, Liverpool Clinical Trials Centre

General Information

This document describes the HAP-FAST study including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the study, but sites entering participants for the first time are advised to contact the coordinating centre, Liverpool Clinical Trials Centre, to confirm they have the most up to date version. Clinical problems relating to this study should be referred to the relevant Chief Investigator, Dr Daniel Wootton, via the LCTC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 15.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

Contact Details: Institutions

Sponsor:	**Trial Management, Monitoring and Analysis:**	**Statistics:**
The University of Liverpool, Clinical Directorate, Thompson Yates Building The Quadrangle, Brownlow Hill, Liverpool, L3 5RB Tel: 00 44 (0) 7717 863747 Email: sponsor@liverpool.ac.uk	Liverpool Clinical Trials Centre, 1st Floor, Block C, Waterhouse Building, 1-3 Brownlow Street, University of Liverpool, L69 3GL Telephone Number: 0151 794 9766 E-mail: hapfast@liverpool.ac.uk	Liverpool Clinical Trials Centre, 1st Floor Block C, Waterhouse Building, 1-3 Brownlow Street, University of Liverpool, L69 3GL E-mail: hapfast@liverpool.ac.uk
Dr Daniel Wootton, MRCP, DTM+H, PhD, Clinical Immunology, Microbiology and Immunology, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, 8 West Derby Street, Liverpool, L69 7BE Telephone: 0151 529 3796 E-mail: dwootton@liverpool.ac.uk		

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	
Karen Wilding, Senior Clinical Research Governance Manager, The University of Liverpool, Clinical Directorate, Thompson Yates Building, The Quadrangle, Brownlow Hill, Liverpool, L3 5RB Tel: 00 44 (0) 7717 863747 Email: sponsor@liverpool.ac.uk	Dr Daniel Wootton, MRCP, DTM+H, PhD, Clinical Immunology Microbiology and Immunology, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, 8 West Derby Street, Liverpool, L69 7BE Telephone: 0151 529 3796 E-mail: dwootton@liverpool.ac.uk	

In cases where the CI is unavailable to respond to urgent queries the following individual/s will act as cover:

Medical Expert who will Advise on Protocol Related Clinical Queries:		
Dr Stephen Aston, MBChB, PhD, Senior Clinical Lecturer, University of Liverpool and Honorary Consultant in Infectious Diseases, Liverpool University Hospitals NHS Foundation Trust Email: Saston@liverpool.ac.uk		

Additional Contacts:

The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File.

1 Table of Contents

2 Glossary

AE	Adverse Event
CI	Chief Investigator
CXR	Chest X-Ray
eCRF	Electronic Case Report Form
DTR	Dynamic Treatment Regimens
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
FAPP	FILMARRAY® Pneumonia Panel
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Health Care Professional
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive Web Response System
LCTC	Liverpool Clinical Trials Centre
MA	Marketing Authorisation
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
NIMP	Non-Investigational Medicinal Product
NRES	National Research Ethics Service
PI	Principal Investigator
PSF	Pharmacy Site File
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSI	Reference Safety Information
RSO	Research Support Office
SAE	Serious Adverse Event
SDV	Source Data Verification
SMART	Sequential Multiple Assignment Randomised Trial
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

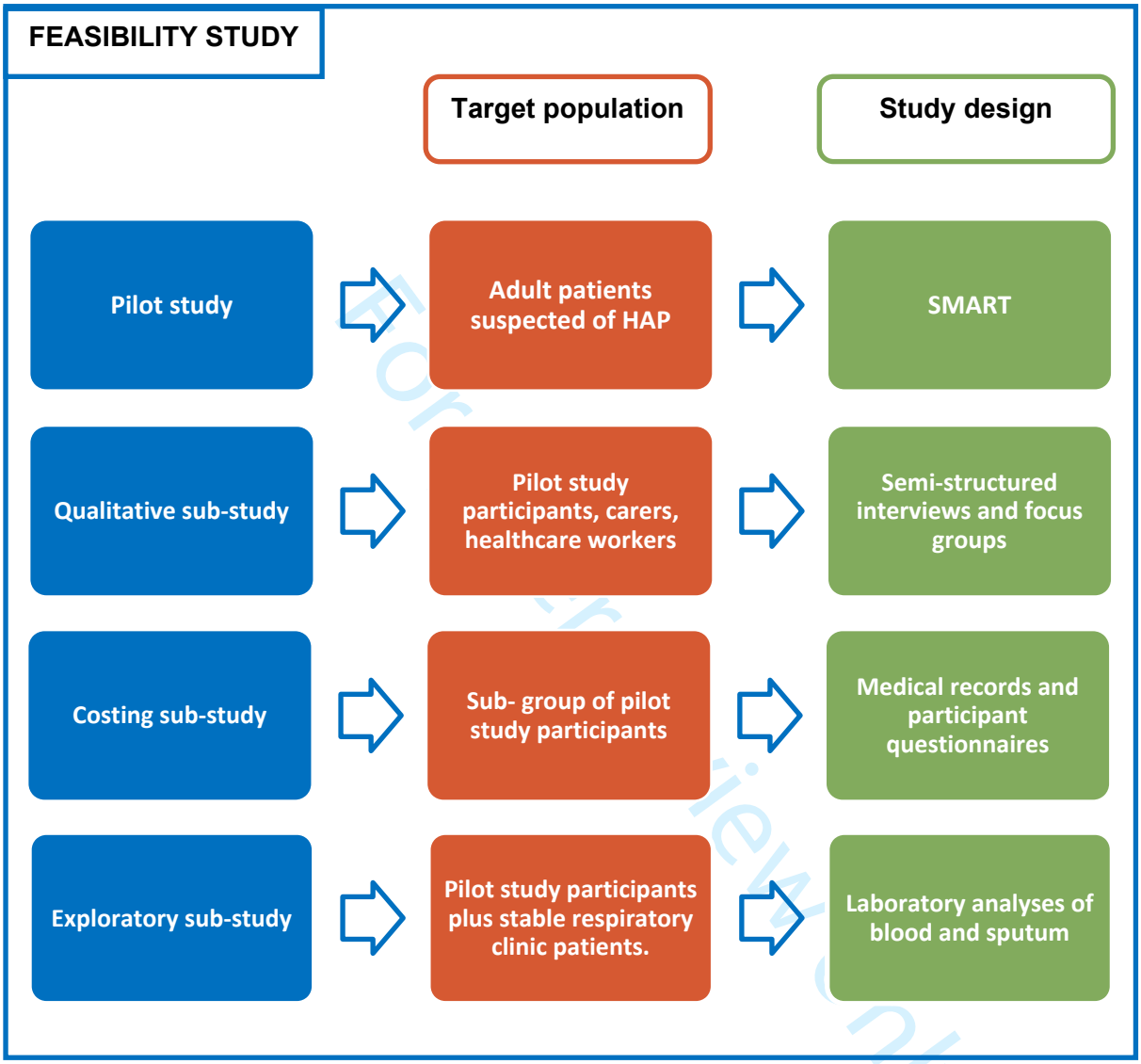
3 Protocol Overview

Full Title:	Feasibility study of the clinical and cost-effectiveness of contemporary diagnostics for patients with suspected Hospital-Acquired Pneumonia (HAP).
Acronym:	HAP-FAST
Phase:	Pilot Study
Target Population:	Adults suspected of HAP
Sample size:	• Pilot Sequential Multiple Assignment Randomised Trial (SMART) = approximately 220 participants from 3 Trusts • Qualitative sub-study = 30 (= 15 pilot participants, 6 carers of participants, plus 9 patients who decline participation). Approximately 30 members of staff for focus groups • Exploratory sub-study = participants from the pilot study and up to 50 participants from respiratory clinics in Liverpool
Inclusion Criteria:	For Pilot Study: Stage 1: • ≥ 18 years • Patients with suspected HAP Stage 2: • The clinician intends to treat the patient for HAP or a hospital acquired respiratory tract infection (RTI) • Sputum has been obtained before 2nd dose of antibiotic
Exclusion Criteria:	For Pilot Study: Stage 1: • Already received a chest X-ray (CXR) to confirm suspected HAP diagnosis • Diagnosis or suspected diagnosis of ventilator acquired pneumonia • Intention to palliate rather than cure • Interventions cannot be completed before administration of second antibiotic dose • Cannot have low-dose, non-contrast CT scan on clinical grounds e.g. strong suspicion of PE • Pregnancy • Previous study participation (patients with second or third episodes of HAP will not be re-recruited) Stage 2: • Following the CXR or CT the clinician decides not to treat with antibiotics for either HAP or a hospital acquired RTI
Study Centres and Distribution:	• Liverpool University Hospitals NHS Foundation Trust • Lancashire Teaching Hospitals NHS Foundation Trust • Manchester University NHS Foundation Trust
Participant Study Duration:	• 12 months of recruitment or until 220 participants are recruited, and 3 months of follow-up

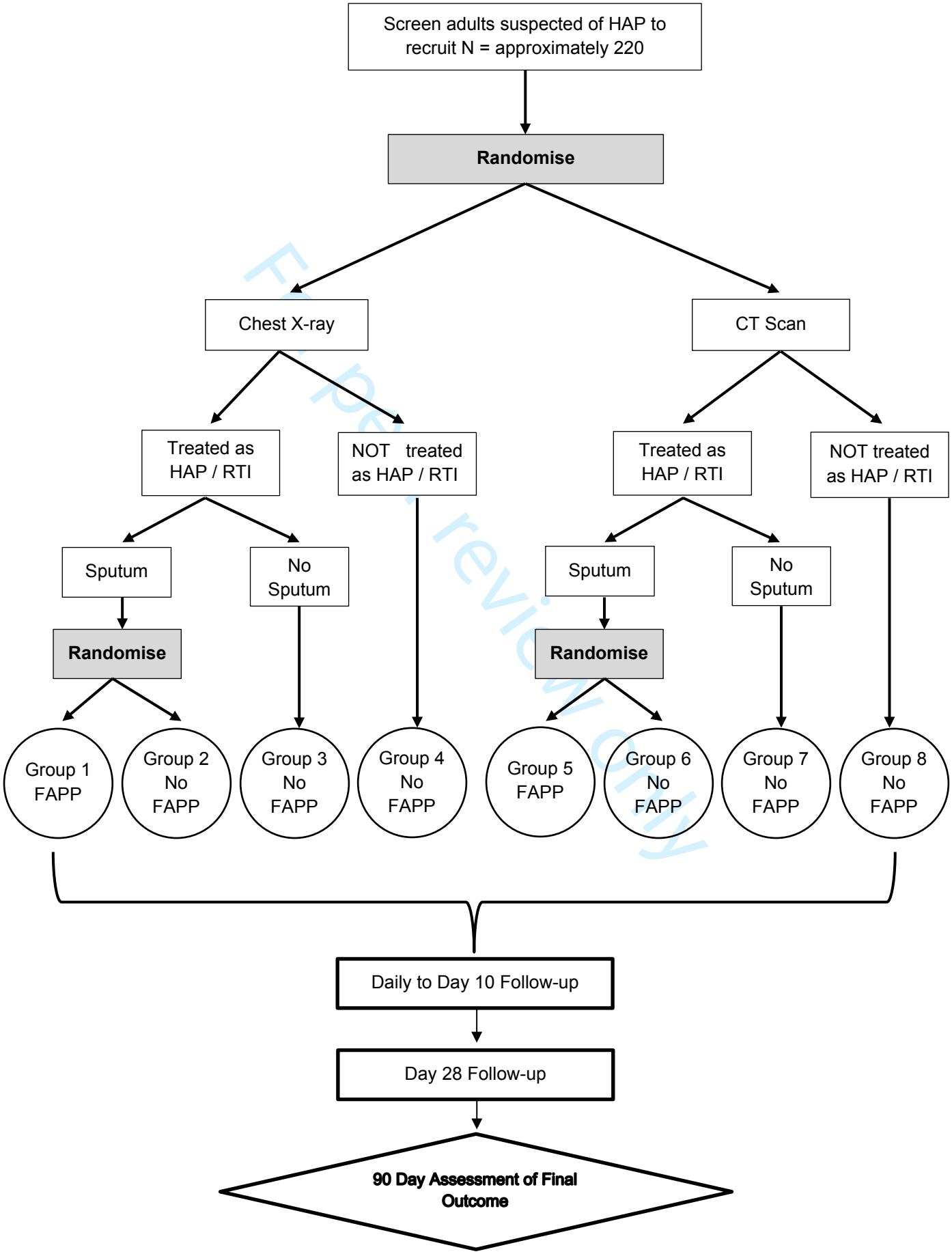
	• Duration of follow-up: 90 Days including 10 days of treatment
Study Duration	Start date: 07/06/2023 End of recruitment: 23/06/2024 End of Follow up: 21/09/2024
HAP Description of Interventions:	Stage 1: Radiographic Diagnosis using chest X-ray vs CT Scan Stage 2: 'FILMARRAY® Pneumonia Panel' (FAPP) vs No FAPP Treatments received by participants will be determined by the diagnostic information obtained during Stages 1 and 2 of the pilot study.
Objectives	
Primary:	The primary objective is to determine the feasibility of a full-scale Randomised Controlled Trial (RCT) comparing different diagnostic dynamic treatment regimens (DTRs) in adult patients suspected of HAP. See section 9 for further details on endpoint/outcome measures.
Secondary:	The secondary objective is the efficacy outcomes that will be investigated in a large scale RCT. These will be determined on the basis of the following outcomes: 1. Inform the sample size of a definitive study 2. To measure key outcome measures (completion rates, missing data, estimates and dispersion) 3. To estimate eligibility, recruitment and consent rates 4. Estimate rates of successful follow up 5. Assess the web-based randomisation process and incorporate clinical and researcher feedback 6. Perform a costing analysis of HAP to inform the cost-effectiveness analysis for any definitive study 7. Assess human factors involved in delivery of the study and how the different diagnostic tests influence clinical decision making by conducting qualitative interviews and focus groups with healthcare workers and researchers 8. Evaluate willingness of clinicians to recruit to the study 9. Evaluate willingness of potential participants or their consultees to be recruited 10. Evaluate adherence to antibiotic guidelines as outlined in the study protocol 11. Assess the study participant and carer experience of participating in the study via qualitative interviews
Exploratory/ Translational:	Describe the dynamics and characteristics of immune cells and inflammatory responses and their associations with severity and outcome among our HAP cohort during HAP.

3.1 Schematic of Study Design

3.1.1 Overall Study



3.1.2 Pilot sequential multiple assignment randomised trial (SMART) design



4 Roles and Responsibilities

4.1 Sponsor

The Sponsor's name is the University of Liverpool and is legally responsible for the study. They will formally delegate specific Sponsoring roles to the Chief Investigator and Clinical Trials Unit.

4.2 Funder

This study is funded by an Advanced Fellowship awarded by the National Institute of Health Research (NIHR) to Dr Wootton.

Funder(s)	Financial and Non-financial Support Given	Role
NIHR Advanced Fellowship (Dr D Wootton)	£1,111,228.00	This funding source had no role in the design of this study and will not have any role in the analyses or interpretation of the data, or decision to submit results.
BioMerieux	Loan of FILMARRAY machines and covering the cost of 50% of the pneumonia kits used.	This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.
University of Liverpool	Fully funded UK PhD	The Institute of Infection, Veterinary and Ecological Sciences within the University of Liverpool has provided tuition, bench, consumable and stipend funds for a UK student to conduct PhD studies relating to immune cell and inflammatory mediators in HAP.

Chief Investigator: Dr Daniel Wootton is the Chief Investigator for the trial and is responsible for overall design and conduct of the study in collaboration with other members of the study team.

Principal Investigators: In each participating centre a principal investigator will be identified to be responsible for identification, recruitment, data collection and completion of eCRFs, along with follow up of study participants and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit: LCTC at the University of Liverpool in collaboration with the Chief Investigator, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, Trial Master File management, data management, randomisation, statistical analysis and participating site coordination.

4.3 Oversight Committees

HAP-FAST is subject to oversight from the following committees:

Trial Management Group (TMG)
A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical), sponsor representatives, PPI representatives and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the study and will be responsible for the day-to-day running and management of the study. The TMG will meet at least monthly at setup stage and then reduce to quarterly throughout the year unless more frequent meetings are required.

Trial Steering Committee (TSC)
The Trial Steering Committee will consist of an independent chairperson, 2 independent experts in the field of pneumonia diagnostics, biostatistician, the CI and PPI representatives. The role of the TSC is to provide overall supervision for the study and provide advice through its independent Chairperson. The decision for the continuation of the study lies with the TSC, with funder input. The TSC will meet prior to onset of recruitment and discuss the future schedule of meetings – but we anticipate this will be at least once during recruitment and once to discuss the final results.

4.4 Protocol Contributors

Name	Affiliations	Contribution to protocol
Dr Daniel Wootton (DW)	University of Liverpool	Lead Author, CI
Stephanie Willshaw	University of Liverpool	Trial Manager
Anica Alvarez Nishio	PPI representative	Patient and public perspective
Dr Ashley Jones	University of Liverpool	Statistical lead
Prof Bridget Young (BY)	University of Liverpool	Oversight of qualitative study
Dr Lance Turtle (LT)	University of Liverpool	Collaborator – exploratory sub-study
Dr Simon Abrams (SA)	University of Liverpool	Collaborator – exploratory sub-study
Liverpool Clinical Trials Centre	University of Liverpool	Protocol development

5 INTRODUCTION

5.1 Background

Hospital-Acquired Pneumonia (HAP) refers to a type of severe lung infection that develops while a patient is in hospital or has been recently discharged. HAP is common, frequently fatal and there is sparse evidence to support its management. Recent guidelines have called for studies focussed on diagnostics.[1]

There are problems diagnosing the condition; HAP diagnosis relies on a chest X-ray (CXR) but misinterpretation leads to over-diagnosis.[2] There are also problems diagnosing the cause of HAP; sputum culture takes too long to meaningfully impact upon antibiotic decisions. Together, these diagnostic inadequacies contribute to poor clinical outcomes and inappropriate antibiotic usage.[3]

CT scans are more accurate than chest X-rays at diagnosing pneumonia but there are no studies to demonstrate impact on outcome in HAP. The close to patient test, 'FILMARRAY® Pneumonia Panel' (FAPP)

can identify 28 pneumonia pathogens from a respiratory sample in 75 minutes – but clinical and cost-effectiveness in an NHS setting has not been evaluated in the context of non-ventilator acquired HAP.

The HAP-FAST study will therefore investigate whether using CT scans or the FAPP, or both together, helps improve antibiotic use and patient recovery while being cost effective.

5.2 **Rationale**

CT scans in pneumonia

Our current method of diagnosing pneumonia, by using a chest X-ray, is inaccurate.[4,5] Using a CT scan as the gold standard, CXR had a positive predictive value of 27% in 3423 US patients with possible Community acquired Pneumonia (CAP).[6] Claessens demonstrated that performing a CT after a CXR in suspected CAP might avoid antibiotics in 14%.[7]

CT scans are particularly useful when a patient is unable to stand for a CXR, as is often the case in suspected HAP. In bedridden patients with suspected pneumonia, a CT scan changed 48% of CXR-based management plans.[8]

Comorbidities, such as chronic obstructive pulmonary disease or congestive cardiac failure are more common in the elderly and can be misdiagnosed as HAP using CXR. Prendki et al. found that using CT scans avoided antibiotic use in 8.5% of elderly Swiss patients with suspected pneumonia.[9]

These studies demonstrate the diagnostic superiority of CT scans in the context of pneumonia. However, the effectiveness of a CT scan compared to CXR has not been investigated.

Rapid microbiological testing in HAP

Current use of antibiotics in HAP is imprecise and hampered by low-quality, often conflicting evidence. A Spanish study demonstrated 60% of bacterial detections were Gram-positive and a retrospective Scottish study found 71% were Gram-negative.[10,11] Neither study tested for viruses but subsequent studies have detected viruses in up to 22% of patients with HAP.[12,13] It is clear there is a wide range of potential pathogens but since HAP trial evidence is lacking, clinical guidelines extrapolate recommendations from the more comprehensive ventilator associated pneumonia (VAP) literature. However, the most comprehensive, comparative study of the aetiology of HAP and VAP indicates the comparison may be invalid.[14] Most recently, the INHALE group compared two rapid molecular diagnostic tests to conventional NHS microbiological testing of respiratory samples from patients with pneumonia on critical care. They reported higher pathogen detection sensitivity of the new rapid tests when compared to conventional methods – and demonstrated once again that viruses are identified in a significant proportion.[15]

In this context, the 2014 pneumonia management guidelines NICE made one research recommendation relating to HAP,

"Can rapid microbiological diagnosis of Hospital-Acquired Pneumonia reduce the use of extended-spectrum antibiotic therapy, without adversely affecting outcomes?"[1]

To clarify 'rapid' in this context, NICE reviewed the evidence for the timing of antibiotics in HAP and found no evidence, however, they recommend antibiotics are commenced within 4 hours of diagnosis in line with strong evidence in CAP. The only commercially available platform to comprehensively test for pneumonia specific pathogens and provide results within 4 hours is the BIOFIRE® FILMARRAY® Pneumonia Panel Plus. https://www.biomerieux-diagnostics.com/biofire-filmarray-pneumonia-panel. This CE marked, United States

Food and Drug Administration (FDA) approved near patient test can simultaneously detect 18 bacterial and 10 viral causes of HAP and the presence of 7 antimicrobial resistance genes.[15] Sample preparation takes 2 minutes, requires no expertise and results are available in 75 minutes. A recent comparison of the FilmArray Pneumonia Panel (FAPP) demonstrated that, when applied to respiratory sample from patients with pneumonia in critical care, it detected more pathogens more rapidly than conventional techniques.[15] This test could dramatically change the way we manage HAP but before it is widely implemented, questions relating to the interpretation of results and cost-effectiveness within the NHS setting need to be addressed.[16]

Outcome measures in HAP trials

We have searched the COMET data-base for core outcome sets in HAP trials.[17] Some groups advocate all-cause mortality assessed on a non-inferiority basis.[18] However, others have made a compelling statistical argument as to why discerning the mortality attributable to HAP, as opposed to underlying comorbidity, is difficult without unfeasibly large trials.[19] Several groups have recently advocated combining mortality with a physiological or patient-based outcome measure. A Delphi exercise to determine HAP trial endpoints suggested a hierarchical, composite, primary outcome of survival at day 28 and 'clinical cure' between days 7-10.[20] Unfortunately, this report did not provide a pragmatic definition of clinical cure. A group convened by the FDA suggested using mortality plus resolution of symptoms.[21]

The evidence summarised above demonstrates that CT scans improve the accuracy of pneumonia diagnosis, and that the new FAPP test could facilitate targeted rather than empirical prescribing. However, what is lacking is any trial evidence that these interventions actually achieve the outcome NICE has asked for which is to improve antibiotic use in a safe and cost effective way. The HAP-FAST study aims to address this evidence gap.

5.3 Risk and Benefits

5.3.1 Potential Risks

Standard of care for this patient population is to diagnose HAP through a chest X-ray. Patients entered into this study will be randomised to either standard chest X-ray or low-dose, non-contrast, thoracic CT scan. CT scans are frequently used as part of the diagnostic work up for patients with pneumonia but here we will trial their systematic use as the first test in those suspected of HAP.

A low dose, non-contrast, thoracic CT scan carries a radiation exposure of 1.5mSv, which is greater than a CXR (0.05 mSv) but lower than annual UK background radiation exposure of 2.7mSv.[9] Thus, the study scans carry very low risk compared to the in-hospital mortality of 27% for HAP. Furthermore, CT scans are more accurate than chest X-rays at diagnosing HAP, which will in turn lead to more accurate treatment of suspected HAP.

A recognised consequence of performing a thoracic CT scan at any point in a patient's acute care is the detection of unexpected abnormalities. These range from rare things such as anatomical variants, to alternative diagnoses for the presenting symptoms such as pulmonary emboli or heart failure. Commonly, thoracic CT scans will detect a pulmonary nodule. Pulmonary nodules are discreet abnormalities which range in size and density and are of unknown aetiology. Their significance derives from the fact that some will turn out to be early stage malignancies. The detection of pulmonary nodules is so common that hospitals have well established pathways for their investigation and follow-up which are supported by national guidelines.[22] The number of scans in the CXR v CT groups will be compared and reported.

Standard of care for the microbiological diagnosis of the cause of HAP is the culture of a respiratory specimen – most commonly a self-expectorated sputum specimen.[23] Culture of sputum is designed to detect the bacterial pathogens which are thought to commonly cause HAP. In the event that a bacterial pathogen is detected, culture provides an opportunity for antibiotic susceptibility testing which provides the clinician with useful information about which antibiotics might and might not help treat the patient.

The FAPP test is a molecular test and it is possible there will be discrepancies between the detections made using the FAPP and those made using culture.[15] However, our study design suggests all samples used in the FAPP should also be sent for culture, and therefore if a pathogen is missed by the FAPP there is an opportunity for it to be detected, as usual, by culture.

It is theoretically possible that, based on a FAPP result, a participant could receive an antibiotic which is not effective against an undetected pathogen. This is always the case with imperfect microbiological tests and is the reason why all patients are closely monitored for response to treatment during the early stages of pneumonia. If a participant were to deteriorate following FAPP guided treatment, the protocol allows for the clinicians treating the participant to escalate or change their therapy as clinically indicated.

More detail regarding management of risks associated with this study are detailed in a separate Risk Assessment maintained in the Trial Master File.

5.3.2 **Potential Benefits**

There is evidence that the use of a CT scan instead of a CXR as the initial radiological test for patients suspected of pneumonia leads to improved management decisions by clinicians.[7] In some instances this might be the confirmation of pneumonia which would not have been apparent on a CXR. In other cases it might be the detection of an alternative explanation for symptoms such as a pulmonary embolus, malignancy or radiological features of heart failure.

Sputum culture takes on average 3 days to produce a result. During this time patients treated for HAP would currently receive empirical antibiotics based on assumptions of the likely pathogen. The FAPP offers the possibility of detecting the causative pathogen and the potential for resistance before antibiotics are started so that the correct choice can be made at the beginning of treatment. Evidence suggests FAPP is considerably more sensitive in detecting respiratory pathogens than conventional culture.[15] Moreover, sputum culture does not detect viruses which are implicated in many cases of HAP – whereas the FAPP test will detect common respiratory viruses.[15] As a consequence, participants in the FAPP arm of this study may incur several benefits such as avoiding unnecessary antibiotics, reduced risk of receiving inadequate antibiotics and avoiding the unnecessary receipt of antibiotics with a high propensity to cause harm.

5.4 **Objectives**

5.4.1 **Primary Objective**

The primary objective is to determine the feasibility of a full-scale Randomised Controlled Trial (RCT) comparing different diagnostic dynamic treatment regimens (DTRs) in adult patients suspected of HAP.

5.4.2 **Secondary Objective(s)**

The primary objective will be determined on the basis of the following objectives:

1. Inform the sample size of a definitive study

2. To measure key outcome measures (completion rates, missing data, estimates and dispersion)
3. To estimate eligibility, recruitment and consent rates
4. Estimate rates of successful follow up
5. Assess the web-based randomisation process and incorporate clinical and researcher feedback
6. Perform a costing analysis of HAP to inform the cost-effectiveness analysis for any definitive study
7. Assess human factors involved in delivery of the study and how the different diagnostic tests influence clinical decision making by conducting qualitative interviews and focus groups with healthcare workers and researchers
8. Evaluate willingness of clinicians to recruit to the study
9. Evaluate willingness of potential participants or their consultees to be recruited
10. Evaluate adherence to antibiotic guidelines as outlined in the study protocol
11. Assess the study participant and carer experience of participating in the study via qualitative interviews

6 STUDY DESIGN

HAP-FAST is a feasibility study consisting of a pilot study, two qualitative studies, and a costing analysis. The study participants will also provide clinical samples to support exploratory analyses of the immune-pathophysiology of HAP.

6.1 Pilot Study

The pilot study is designed as a sequential, multiple assignment, randomized trial (SMART) with a 1:1 allocation ratio.[24] Its purpose is to address the main feasibility objectives – specifically secondary objectives 1-5. The flow-diagram in section 3.1 above shows how participants will flow through the study.

Participants are initially randomised between a chest X-ray (CXR) and low-dose thoracic CT scan (CT). Following the imaging, participants whose clinician decides to manage them as either hospital acquired pneumonia (HAP) or hospital acquired respiratory tract infection (RTI), and who are able to produce a sputum sample, are further randomised to 'FILMARRAY® Pneumonia Panel' (FAPP) or no FAPP. All other participants will be managed as per usual care.

The randomisation results in 4 dynamic treatment regimens (DTRs).

Table 1: Definition of DTRs

Dynamic treatment regimen (DTR)	**Phase 1 intervention**	**Phase 2 intervention**	
		Phase 1 indicates HAP/RTI and patient has sputum	**Phase 1 indicates no HAP/RTI and/or patient has no sputum**
DTR 1	CXR	FAPP	No FAPP
DTR 2	CXR	No FAPP	
DTR 3	CT	FAPP	No FAPP
DTR 4	CT	No FAPP	

Screening, baseline and outcome data are collected at distinct time-points according to the schedule detailed in Section 10.9 below.

6.1.1 **Blinding**

The study is open-label and treating clinicians, researchers and participants will know which treatment / intervention is being administered.

6.1.2 **Study Setting**

Participants will be identified and recruited from 3 NHS hospital Trusts in the UK. Participants will be assessed by the study team daily until day 10 to track symptomatic recovery, changes in QOL and determine time to clinical cure. Participants will have symptoms and QOL assessed face to face on day 28 (+/- 7 days) as an in or out-patient. Follow up will be conducted as a phone call 90 days (+/- 14 days) following entry into the study to assess symptoms, QOL and to remind them to return a survey booklet on health and social care use up to day 90.

6.1.2.1 **Selection of Participating Sites**

Participating sites will be opened to recruitment upon successful completion of all global (e.g. REC and HRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

As this is a pilot study, four sites, over three NHS Trusts have already been selected for involvement in the study; Aintree University Hospital and Royal Liverpool University Hospital (Liverpool University Hospitals NHS Foundation Trust), Royal Preston Hospital (Lancashire Teaching Hospitals NHS Foundation Trust) and Wythenshawe Hospital (Manchester University NHS Foundation Trust). Preliminary data demonstrates sufficient number of potential participants within the study's timeframe.

6.1.2.2 **Selection of Principal Investigators**

Principal Investigators will be required to demonstrate equipoise, relevant experience and commitment during early stage feasibility assessment. All investigators will have the particular medical expertise necessary to conduct the study in accordance to the protocol and all regulatory and ethical requirements. Written agreement to conduct research as such will be obtained prior to site initiation.
A suitable co-investigator should be identified at each site to deputise in case of PI absence.

6.2 **Costing Analysis Sub-Study**

The purpose of this study is to address secondary objective 6. A sub-group of pilot study participants' clinical pathways from baseline to 90 days will be analysed to investigate the costs associated with patients suspected of HAP. Itemised hospital costs for participants within each intervention group will be obtained using (i) NHS Schedule of costs; (ii) British National Formulary, and (iii) NHS drug prices and local hospital finance department data. Clinical judgement will be used to determine whether individual costs are related to HAP or underlying health conditions or the condition which provoked the original admission to hospital. Where there is ambiguity in attributing a cost, we will clarify with the treating clinical team. Post-hospitalisation costs will be captured up to 90 days following baseline. A bespoke questionnaire will be provided to each participant on discharge – see appendix C. The questionnaire will capture items such as absence from work, domiciliary care costs, visits to the GP and out of hospital prescribing.

Further details are given in section 11.1.

6.3 Qualitative Sub-Study

6.3.1 Patients and Carers

The purpose of this study is to address secondary objectives 9 and 11. Approximately 15 participants (5 from each of the three recruiting Trusts) will be purposively recruited for in-depth semi-structured interviews based on age, gender and underlying comorbidity class (medical admission, surgical admission, acute admission). Carers of 6 study participants (2 per hospital) who lack capacity will also be recruited to be interviewed. The participant and carer interviews will focus on:

- Perceptions of the interventions
- Recruitment and consent – in particular the deferred consent model
- Study documentation and communication
- Care and treatment following randomisation
- Study follow-up

We will also aim to interview approximately 9 participants (3 from each Trust) who decline to participate in the feasibility study. We will attempt to achieve a representative sample of such participants based on the same purposive sampling approach described above but as reasons for declining emerge into themes we may refine this purposive sampling strategy. An open approach to the topics for these interviews will be taken and directed by the core reason for declining but where no obvious reason is offered the above interview focus areas will be explored.

6.3.2 Clinicians

The purpose of this study is to address secondary objectives 7, 8 and 10. We will hold two rounds of focus groups and/or interviews at each hospital – the first after 3 months of recruitment and the next after 9 months of recruitment. We will invite a range of clinical, allied health professional and research staff to participate. We anticipate there being approximately 8 participants in each focus group. Focus groups and interviews will be topic guided, yet conversational and exploratory and conducted in a comfortable private environment.

Further details are given in section 11.2.

6.4 Exploratory Sub-Study

Clinical samples of venous blood, sputum and a nose swab will be taken from participants in the pilot RCT. These samples will be used to explore the role immune cells and inflammatory mediators play in the pathophysiology of HAP and how these vary with pathogen. The samples from the pilot study – which recruits patients suspected of HAP – will be compared with equivalent samples from patients who chronically produce sputum, are not exacerbating, and are being managed as out-patients in respiratory clinics.

Further details are given in section 11.3

7 ELIGIBILITY CRITERIA

The HAP-FAST study aims to recruit approximately 220 participants based on sample size calculations described in Section 13.2.1. Patients will be enrolled into the study under a deferred consent model allowing them to be randomised and provide research samples prior to written informed consent or assent being obtained. This ensures study processes do not delay investigation and management (see Section 10.5 for more information regarding informed consent processes).
As soon as possible after stage one randomisation, written informed consent (or assent in the context of patients lacking capacity) will be sought.

Patients who decline to provide written informed consent after randomisation and no longer wish to continue in the study will be withdrawn (see section 10.7 for more information).

7.1 Stage 1 Randomisation

7.1.1 Inclusion Criteria

For Stage 1, patients must comply with all of the following at randomisation to be eligible for the trial:

- Age ≥ 18 years
- Suspected HAP*

* For the purposes of this study, HAP is defined as per the BTS and FDA definitions i.e. pneumonia which develops 48 hours after an admission to hospital for an alternative diagnosis; or a new presentation to hospital with pneumonia in a patient who has been discharged from an overnight stay in hospital within the last 10 days.[25,26]

7.1.2 Exclusion Criteria

Any patient meeting any of the criteria listed below at randomisation will be excluded from study participation:

- Already received a chest X-ray to confirm suspected HAP diagnosis
- Diagnosis or suspected diagnosis of ventilator acquired pneumonia
- Intention to palliate rather than cure
- Interventions cannot be completed before administration of second antibiotic dose*
- Cannot be randomised to low-dose, non-contrast CT scan on clinical grounds e.g. strong suspicion of PE**
- Pregnancy***
- Previous study participation (patients with second of third episodes of HAP will not be re-recruited)

* In the circumstance where a patient is diagnosed with HAP whist receiving antibiotics for a non-respiratory infection e.g. cellulitis or UTI, if the HAP diagnosis leads to a change in the antibiotic prescription to cover the HAP then that patient will be eligible for recruitment. However, if the diagnosis of HAP does not result in a change in antibiotic then the patient **is not eligible**.

**A non-contrast, low-dose thoracic CT scan is an inappropriate test for a PE and if that is high in the differential diagnosis then tick yes here.

***A urine pregnancy test is required as part of routine care prior to a chest X-ray or CT scan. If the test reveals the patient is pregnant, they will **not be eligible** for the study as they will be unable to receive a CT scan as part of this study. Pregnancy tests are not required at future time points.

7.2 Stage 2 Randomisation

7.2.1 Inclusion Criteria

A patient is eligible to be entered into the 2nd randomisation if:

- The clinician intends to treat the patient for HAP or a hospital acquired respiratory tract infection (RTI)
- A sputum sample has been obtained before 2nd dose of antibiotic

7.2.2 Exclusion Criteria

A patient is not eligible to be entered into the 2nd randomisation if:

- Following the CXR or CT the clinician decides not to treat with antibiotics for either HAP or a hospital acquired RTI

Patients ineligible for randomisation at stage 2 will still be able to participate in the trial.

7.3 **Co-enrolment Guidelines**

To avoid potentially confounding issues, ideally participants should not be recruited into other intervention trials during their participation in HAP-FAST. However, where recruitment into another study is considered to be appropriate this must first be discussed with the LCTC who will contact the Chief Investigator, Dr Daniel Wootton, for consideration on a case by case basis.

8 TRIAL TREATMENT/INTERVENTIONS

8.1 **Introduction**

The pilot study has a SMART design, where the randomisation pertains to diagnostic strategies which may or may not affect treatments received. In general, choice of treatment will be determined by the diagnostic information available to clinicians.

8.2 **Treatment Definitions**

Treatment is determined by the diagnostic information available to clinicians. There are 8 distinct possible routes through the study. These are labelled 1-8 on the pilot study schematic in 3.1.2. Each determines a different approach to treatment.

Participants' treatment will ultimately be at the discretion of the treating clinician. However, for those participants diagnosed with HAP or a hospital acquired respiratory tract infection (RTI) antibiotics should be prescribed with reference to the local treatment policy unless the participant has a sputum sample and is randomised to use the FAPP. If the FAPP is used then antimicrobial treatment can be guided by a study specific, pre-defined treatment algorithm. Where a patient is deemed to have met sepsis criteria, administration of the first dose of antibiotic will be as per sepsis guidelines, with revision of subsequent antibiotics based on the FAPP results. The guideline will indicate that for those who do not meet sepsis criteria, there should be no longer than 4 hours from the time of radiological confirmation of HAP/RTI to the administration of the first dose of antibiotic.

A summary of which approach to take dependent on the participant's flow through the study is given in the table below. See also 8.4 for greater detail regarding diagnostic interventions.

Table 2: Interventions and Treatments

Result of Stage 1 Randomisation	**Result of Imaging**	**Sputum Available?**	**Result of Stage 2 Randomisation**	**Treatment**	**Group**
CXR	Clinician decides to treat for HAP / hospital acquired RTI	YES	FAPP	• Use an aliquot of respiratory specimen in the FAPP • Send remainder of specimen to microbiology for standard tests • Prescribe antibiotics with reference to the FAPP antibiotic guideline	1
		YES	No FAPP	• Prescribe empirical antibiotics based on local guidelines	2
		NO	N/A	• Prescribe empirical antibiotics based on local guidelines	3
	Clinical diagnosis is **not** HAP / RTI	N/A	N/A	• Patient receives usual care and is followed up as per the study schedule	4
CT Scan*	Clinician decides to treat for HAP/ hospital acquired RTI	YES	FAPP	• Use an aliquot of respiratory specimen in the FAPP • Send remainder of specimen to microbiology for standard tests • Prescribe antibiotics with reference to the FAPP antibiotic guideline	5
		YES	No FAPP	• Prescribe empirical antibiotics based on local guidelines	6
		NO	N/A	• Prescribe empirical antibiotics based on local guidelines	7
	Clinical diagnosis is **not** HAP / RTI	N/A	N/A	• Patient receives usual care and is followed up as per the study schedule	8

* Low-dose, non-contrast, CT scan of the thorax “hot reported”.

8.3 Manufacturing and Distribution

The BIOFIRE® FILMARRAY® system and the Pneumonia Panels are manufactured and distributed by BioMerieux. Both the system and panels are CE marked and Food and Drug administration (FDA) approved.

BioMerieux will loan a BIOFIRE® FILMARRAY® system to sites free of charge for use in the study. Pneumonia Panels will be procured centrally by the University of Liverpool and distributed to sites as needed.

At site set up, an initial supply of Pneumonia Panels will be issued. Resupply will be as and when required, totalling one Pneumonia Panel per participant randomised to FAPP.

Requests for re-supply should be made to hapfast@liverpool.ac.uk.

8.4 Administration of Diagnostic Assessments

8.4.1 Standard Chest X-ray (CXR)

This chest X-ray will be carried out by a trained radiographer as per standard NHS practices.

8.4.2 Intervention - CT Scan

This low dose thoracic CT-Scan will be carried out as per standard local protocols and by a trained radiographer as per standard NHS practices.

8.4.3 Standard microbiological testing

Participants will cough into a standard, labelled, sputum pot to provide the sample. Participants will provide this sample as standard of care. A member of the clinical team (e.g. doctor, nurse, HCA, porter) will then take the sample to be processed in the laboratory as per standard NHS practices.

8.4.4 Intervention - FAPP

The BIOFIRE® FILMARRAY® Pneumonia Panel (FAPP) will be used to identify the cause of HAP quickly. It is carried out through the collection of sputum samples from participants directly. Participants will cough into a standard, labelled, sputum pot to provide the sample. Participants will provide this sample as standard of care. A member of the clinical team (e.g. doctor, nurse, HCA, porter) will then take the sample to the FilmArray machine location (site specific) and will either run the sample themselves (if trained and delegated to do so) or find a trained person to run the sample. The FAPP test uses only a small fraction of the sputum sample (500microLitres) and the remaining sample is sent for standard microbiological testing as above.

The procedure for performing a pneumonia panel test using the BIOFIRE® FILMARRAY® is explained in the manual provided in appendix D. In addition to this reference, all relevant staff at sites will have initial training on the machine and tests and will have access to an online video tutorial via the study website (www.hap-fast.org.uk).

BIOFIRE® FILMARRAY® Pneumonia Panel test kits must be stored in a relatively temperature stable environment. In particular they should not be exposed to direct sunlight or subjected to temperatures above 28°C.

8.5 Investigation Modifications

After the patient has entered the study, the clinician is free to give alternative treatment / intervention to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the study for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from the protocol treatment and study follow-up without giving reasons and without prejudicing further treatment, see section 10.7.1.

8.6 Accountability Procedures

Accountability logs will be maintained at site to record the receipt and return of the BIOFIRE® FILMARRAY® system (when provided for use in the study).

Accountability logs will also be maintained for the Pneumonia Panels to record receipt, use and destruction/return.

The LCTC will maintain a master accountability log and perform reconciliation between panels provided to sites, administered and destroyed/returned.

8.7 Concomitant Medications

8.7.1 Data on Concomitant Medication

Concomitant medication information should be collected on a specific electronic case report form and will be used for assessment of cost-effectiveness and as part of the secondary and exploratory analyses of factors affecting outcome in HAP and factors associated with specific pathogens or combinations of pathogens.

9 OUTCOMES

The key objective is determining the feasibility of a future definitive RCT. The secondary objectives of the study will help make a final decision as to whether a definitive study is feasible:

Objective		
Primary Objective		
The primary objective is to determine the feasibility of a full-scale Randomised Controlled Trial (RCT) comparing different diagnostic dynamic treatment regimens (DTRs) in adult patients suspected of HAP.		
Secondary Objective		
Objective	Outcome	Time-point
Inform the sample size of a definitive study	Time to clinical cure*	Day 90
	Antibiotic usage for the HAP episode	Day 90
	EQ-5D-5L	Baseline, day 10, 28 and 90
	Length of hospital stay post HAP diagnosis	Day 90
	Mortality	Day 14, 28 and 90
To measure key outcome measures (completion rates, missing data, estimates and dispersion)	Estimate rates of completion of questionnaires - EQ5D5L, CAP-sym, economic evaluation	Screening Randomisation Follow up End of Treatment End of Study

	Summary statistics and proportion of missing data for time to clinical care, antibiotic usage for HAP diagnosis, EQ-5D-5L, length of hospital stay post HAP diagnosis, mortality	
To estimate eligibility, recruitment and consent rates	Rate of recruitment; Proportion screened that meet eligibility criteria; ** Proportion eligible that consent and where they present; ** Proportion consented and randomised that complete study pathway as per protocol; Proportion consented and randomised that withdraw from study intervention or follow up; **	Screening Randomisation Follow up End of Treatment End of Study
Estimate rates of successful follow up	Proportion consented and randomised that complete study pathway as per protocol; Proportion consented and randomised that withdraw from study intervention or follow up; **	End of Study
Assess the web-based randomisation process and incorporate clinical and researcher feedback	Qualitative conclusions based on staff focus groups	Qualitative analysis
Perform a costing analysis of HAP to inform the cost-effectiveness analysis for any definitive study	Summary statistics for numbers and types of costs with comparison between DTRs	End of Study
Assess human factors involved in delivery of the study and how the different diagnostic tests influence clinical decision making by conducting qualitative interviews and focus groups with healthcare workers and researchers	Qualitative conclusions based on staff focus groups	Qualitative analysis
Evaluate willingness of clinicians to recruit to the study	Qualitative conclusions based on staff focus groups	Qualitative analysis
Evaluate willingness of potential participants or their consultees to be recruited	Qualitative conclusions based on participant and carer interviews	Qualitative analysis
Evaluate adherence to antibiotic guidelines and study protocol	Summary statistics relating to antibiotic use in the pilot study with a comparison between the DTRs	End of Study
Assess the study participant and carer experience of participating in the study	Qualitative interviews	Qualitative analysis

* defined as the number of days from baseline when there is a combination of resolution of signs and symptoms present at enrolment and improvement or lack of progression of radiological signs

** reasons why, and stage will be collected to inform future trial design

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification and Screening

Standard screening logs will not be maintained due to the nature of the study and the urgent need to treat. As soon as a patient is identified as having suspected HAP, they will be assessed for eligibility and included in the study. For participants who are assessed for eligibility but not randomised at stage one, ineligibility reason will be recorded by the online randomisation system as this will provide important information for monitoring purposes.

10.2 Eligibility Assessment and Confirmation

Eligibility for randomisation can only be confirmed by an appropriately qualified medical professional. Eligibility criteria are described in detail in Section 7.

Eligibility confirmation will be performed by the study team and recorded via the randomisation system and must be documented in the participant's medical notes. Details must include at a minimum who confirmed full eligibility and when this was confirmed.

It is not required to obtain written informed consent to complete eligibility assessments. This study is using a deferred consent model for recruiting participants.

10.3 Randomisation / Registration

Participants will be assigned a unique study number via an online platform accessible from networked hospital computers on relevant wards. The Liverpool Clinical Trials Centre (LCTC) will coordinate and supervise the online randomisation process and hold the randomisation sequence. Randomisation will be two stage – first to CXR or CT – then to FAPP or not FAPP.

Please note, participants may be randomised (at stage 1 and stage 2) prior to obtaining written informed consent. This study is using a deferred consent model for recruiting participants.

10.3.1 Randomisation Process

There are 2 stages of randomisation in the pilot study. Both will use a secure (24-hour) web-based randomisation systems controlled centrally by the LCTC.

Randomisation 1: Choice of imaging
Participants will be randomised to undergo either CT scan or chest X-ray (in a ratio of 1:1).

Randomisation 2: FAPP or No FAPP
Once imaging has been completed, and a clinical judgement is made, participants who:

- Are to be treated as HAP or a hospital acquired RTI and
- Are able to produce a sputum sample will be randomised to FAPP or No FAPP (in a ratio of 1:1).

Clinical staff with a .NHS email address prefixed with one of the recruitment site prefixes (e.g. joe.bloggs@luhft.nhs.uk) will be able to access to the randomisation system(s). When the system requirements (i.e. eligibility) are confirmed at the stage 1 randomisation, the participant DTR allocation and a unique study number (randomisation number) will be displayed on a secure webpage. When a randomisation has occurred two emails will automatically be sent.

The first email is a “HAP-FAST randomisation confirmation” and will go to three addresses: the member of staff who performed the randomisation, the LCTC trial co-ordinator and the site research team. The aim of this email is primarily to alert the site research team to the randomisation and enable them to locate the participant in order to complete the baseline eCRF, provide study information and seek written informed consent (or assent).

The second email will be sent to the site research team and the LCTC trial coordinator and will include the email address of the staff member who performed the randomisation process. The aim of this mail is to enable the site to keep an auditable log of who is performing randomisations.

In the event that informed consent is declined after stage 1 randomisation but before stage 2 randomisation, a system barrier will prevent stage 2 randomisation from occurring. See section 10.5.4 for details on declined consent.

10.3.2 **Randomisation System Failure**

In the event of a randomisation system failure, the centre should contact the coordinating team at the LCTC (Monday to Friday between 9:00 to 17:00 excluding bank holidays) to try to resolve the problem. If the problem cannot be resolved the LCTC will perform central randomisation and randomise the participant using the back-up randomisation system. The back-up randomisation system is an exact replica of the live system but is based on a standalone PC at LCTC.

10.4 **Sampling**

10.4.1 **Sample Collection**

Sputum samples will be requested and collected using standard clinical materials and techniques from all participants as is standard clinical practice in patients suspected of HAP. Each sputum request will be flagged to the local laboratory as being part of the HAP-FAST study. Residual sputum from the clinical sample will be retained for use in the exploratory sub-study. Two additional research specific sputum samples will be taken using standard clinical materials and techniques.
Research specific blood samples will be taken using standard procedures e.g. vacutainer tubes. Where possible, these research-specific samples will be coordinated with clinical samples.
Research specific nasal swabs will be taken using the standard clinical method (as is done for e.g. COVID-19 lateral flow or PCR tests).

10.4.2 **Sample Storage and Handling**

Sputum: participants randomised to the FAPP arms will have their sputum samples sub-sampled (= approx. 500microL) for the FAPP machine and then the remainder will be passed to the local Microbiology department for standard testing. The method for sub-sampling a sputum sample and running it on the FAPP will be made clear in the laboratory manual and the procedure will be summarised on laminated posters above each machine and is also explained in detail in the video which will appear on the study website (www.hap-fast.org.uk) which will be accessible from all networked computers in participating Trusts.

Participants randomised to the non-FAPP arms will have their samples passed to the local hospital’s microbiology department. After the NHS microbiology laboratory has performed their tests, any remaining

sputum belonging to a HAP-FAST participant will be stored for subsequent use in the exploratory sub-study; see section 11.3 for further details on this sub-study.

Blood: some of the research specific samples will be sent to NHS laboratories and some will have initial processing prior to storage on site as specified in the laboratory handbook. Stored samples at each site will then be sent to University of Liverpool laboratories.

Nasal swabs: these will be stored on site prior to dispatch in batches to University of Liverpool laboratories.

10.4.3 **Custodianship**

Stored samples will be subject to standard practices at each hospital site.

10.5 Informed Consent

10.5.1 **Deferred Informed Consent Process**

Due to the potential severity of HAP there is a short timeframe of eligibility between HAP being suspected and diagnostic tests being carried out. Moreover, eligible patients, as a consequence of their acute illness and or underlying comorbidities may have impaired capacity to provide written informed consent and consequently require a consultee for assent.

Because of these factors, it is not reasonably practicable to obtain written informed consent from the patient or a legal representative prior to randomisation to study interventions and procedures. The HAP-FAST study consent process for the study will therefore incorporate a deferred consent model as has been used in other emergency situations.[27-29] The use of deferred consent model for HAP trials has been studied previously and deemed acceptable by patients and the public.[29]

10.5.2 **Obtaining Written Informed Consent/Assent**

Patients who are randomised to the study interventions by the clinical team will be approached by a member of the local research team to obtain written informed consent as soon as possible before they are discharged. A written information sheet that forms part of the ethically approved Patient Information Sheet (PIS) and Consent form will be provided. This will include a detailed explanation of the HAP-FAST study (and associated sub-studies) and will make clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The research staff will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise. In the rare circumstance where a participant is discharged to home having been randomised to the study under deferred consent, all data captured will be analysed and processed using task in the public interest as the legal basis for processing. However, every effort should be made by the research team to obtain written informed consent even after discharge. To facilitate informed consent being obtained after a patient has been discharged, informed consent may be obtained via post. The researcher will discuss the trial by telephone or video conferencing and details of the discussion will be recorded in the patient notes. The ethically approved Patient Information Sheet and Consent form should be signed by the patient at home and then returned to the research site. The researcher who carried out the informed consent discussions should sign the consent form upon receipt. A copy of the fully signed consent form must be posted back to the patient for their records, the original filed in the ISF and a final copy must be sent to the LCTC.

10.5.3 **Patients who lack capacity**

Patients with underlying cognitive impairment are at risk of HAP and patients with HAP can have delirium as part of their pneumonia syndrome. As a consequence, it is not uncommon for patients who have HAP to lack the capacity to consent to clinical trials such as HAP-FAST. In order to be representative of the HAP population as a whole – and in order to allow patients who lack capacity the chance to gain the potential benefits of joining the HAP-FAST study, we will recruit patients who lack capacity to provide written informed consent. In this instance, a personal consultee will be sought. The personal consultee will be someone who knows the person who lacks capacity in a personal capacity and is able to advise the researcher about the person who lacks capacity's wishes and feelings in relation to the project and whether they should continue to participate in the research. After taking reasonable steps to identify a personal consultee, if the research team discover the person who lacks capacity has no close relatives in regular contact, it would be more appropriate to identify a nominated consultee. The researcher will nominate a third party unconnected with the research who is willing to act as a nominated consultee such as a member of the clinical team.

In the event that a patient dies before informed consent has been obtained, the participant's next of kin will be contacted to notify them of participation in the trial. An appropriate and sensitive interval, such as six weeks after the patient's death, will be left before contacting the grieving family to inform them of their relative's participation. It is important to recognise that relatives and friends are not able to consent on behalf of the deceased participant. The data captured whilst the deceased participant was alive will remain in the study unless the relatives express recollection of the participant having very strong negative views about research in which retention of data will be considered on a case by case basis.

10.5.4 **Consent Form Completion**

After verbal and written information has been provided, the individual seeking consent will ensure that the patient/consultee has fully understood all the information and will ask if they are happy to consent to continue in the study. If required, potential participants will be given up to 24 hours to decide if they would like to sign the consent form.

Where this is the case, written informed consent will be obtained by means of a dated signature on the consent form. This should be countersigned and dated by the person who obtained informed consent i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

All efforts must be made to obtain written informed consent / assent before the participant is discharged. Written informed consent must be obtained before patient questionnaires (EQ-5D-5L and CAP Sym) are completed. Biological samples (sputum, blood and nasal) must not be analysed until written informed consent has been obtained (see section 11.3 for sample processing). Samples will be sent to the University of Liverpool Biobank where informed consent will be confirmed before the samples are released for analysis. Samples are to be destroyed if consent is not in place (see lab manual).

The original signed document will be retained in the trial site's Investigator Site File (ISF) and copies will be made:

- One copy provided to the patients/consultees for their information
- One copy transferred securely to the LCTC
- One copy filed in the participant's medical records

N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.
Each participant's GP will be notified via letter of their patient's involvement in the research study.

10.5.5 **Participants who decline to consent**

Patients who are randomised but decline consent to continue with the study will have the reason for declining recorded on a withdrawal eCRFs.

All data captured up until this point will still be included in the analysis and processed using task in the public interest as the legal basis for processing. Refer to section 10.7.1 for more details.

10.5.6 **Loss of Capacity.**

If the participant that has consented then becomes unable to give informed consent, the previously obtained consent remains valid. They will be monitored for any signs of objection or distress during research visits. Any signs that would prompt a reconsideration of their continued participation will be communicated to the research nurse at these visits. This would also be the case if their nominated relative raised concerns regarding their continued participation.

10.5.7 **Adults who Gain Capacity during the Course of their Participation**

When a patient's participation has been consented for by a legal representative and the participant then regains capacity, the research team will provide the Patient Information Sheet and request consent from the participant. Participants will be advised that consent is voluntary and they may withdraw without any detriment to their care. If a participant regains capacity once discharged from hospital they will be approached to ask whether they would like to continue participating at their next scheduled research assessment. If they choose to continue to participate in the study they will be requested to sign the consent form.

10.6 **Baseline Assessments**

Baseline assessments should be completed as per the Schedule of Assessments (Section 10.99) in order to accurately complete the Baseline eCRF and collect the necessary information for the study analyses. This includes the following assessments:

- Concomitant medications
- Past medical history
- Admission related data
- Patient demographics
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate, oxygen saturation, NEWS2 score)
- Details of antibiotic use
- Clinical symptom assessment
- Clinical respiratory exam
- Routine blood tests results (haemoglobin, platelets, white blood count, neutrophils, lymphocytes, creatinine, c-reactive protein and urea)
- EQ-5D-5L
- Nasal swab*
- Research blood sample*
- CAP-Sym
- Survival status

*optional sub-study assessments

These assessments will be transcribed from the patient's medical notes into the Baseline eCRF as close to stage 1 randomisation as possible.

Baseline research blood samples MUST be collected within 24 hours of stage 1 randomisation or be classed as a missed visit.

The baseline EQ-5D-5L MUST only be completed once written informed consent (or assent) has been obtained, and within 4 days of stage 1 randomisation.
The CAP-Sym MUST only be completed once written informed consent (or assent) has been obtained.

10.7 Intervention Discontinuation and Participant Discontinuation/Withdrawal

Participants will undergo trial activities such as follow-up assessments, data collection, and sample collection and retention. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

10.7.1 Participant Withdrawal from Follow Up

Participants/consultees are free to withdraw from follow up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The LCTC should be informed via email and via completion of a Withdrawal eCRF to be returned to the LCTC within 7 days.

If participants/consultees express a wish to withdraw from follow up, the research team at site should ascertain if this is for all elements of study follow-up, or if for example, data from routine assessments can still be collected for the study. In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the participant's condition becomes stable.

10.7.2 Participant Transfer

If a participant moves from the area, every effort should be made for the participant to be followed-up at another participating study centre and for this study centre to take over responsibility for the participant or for follow-up via GP.
A copy of the participant eCRFs should be provided to the new site. The participants/consultees remain the responsibility of the original site until the new site PI has signed the Transfer eCRF. However, data collected up until the point of transfer remains the responsibility of the original site's PI who will be required to manage data queries relating to that data.

10.7.3 Loss to Follow-up

A participant will be considered lost to follow up if they fail to return for the scheduled visit and are not contactable by the site research team.

If a participant fails to attend/facilitate a required study visit the following actions must be taken:

- Site will attempt to contact the participant and reschedule the missed visit within 7 days and advise the participant on the importance of maintaining the assigned visit schedule

- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the participant (i.e. 3 telephone calls and, if necessary, a headed letter to last known address). These efforts should be recorded in the patient medical notes
- If the participant continues to be unreachable they should be considered withdrawn from the study with a primary reason of lost to follow up and this should be recorded on the appropriate eCRF

10.8 End of Trial

The end of the study is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the study database. The study may be closed prematurely by the Trial Steering Committee (TSC).

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the study closes as planned or prematurely. This includes activities such as:

1) End of Trial notification to REC
2) Trial-related materials reconciled and returned/disposed of as appropriate
3) All site data entered onto the study database, discrepancies raised and satisfactory responses received
4) Quality Control checks of the Investigator Site Files and Trial Master File as appropriate

10.8.1 Study Discontinuation

In the event that the study is discontinued, participants will continue to be treated as per standard of care at each NHS institution. The design of the study should mean that study discontinuation would not have an impact on treatment received.

10.9 Schedule for Assessments and Follow-up

All assessments and follow up are to be conducted in line with the Schedule of Assessments below:

Specific Activity	Stage 1 randomisation Day 0	Stage 2 Randomisation	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 28 (+/- 7 days)	Day 90 (+/- 14 days)
Assessment of eligibility	X	X												
Concomitant medication check	X													
Randomisation	X	X												
Urine pregnancy test as required pre Chest X-ray/CT scan	X													
Chest X-ray	X													
CT scan	X													

HAP-FAST Protocol V3.0, 14/11/2023
Based on protocol template v1.0 20/02/2020

Sputum sample		X			[3]X								[3]X	
FAPP		X												
Informed consent		[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X
Past Medical history	X													
Admission related data (date, time, symptoms, co-morbidities, ward type, reason for admission, clinical frailty score)	X													
Patient demographics (age, sex, postcode, height, weight, calculated BMI)	X													
Details of antibiotic use	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (temperature, blood pressure pulse rate, oxygen saturation rate, respiratory rate, NEWS2 score)	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Record clinician's description of symptoms	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Record clinician's respiratory exam findings	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Blood test results (haemoglobin, platelets, white blood count, neutrophils, lymphocytes, creatinine, c-reactive protein and urea)	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		

CAP-sym score	[4]X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	X	X
Record survival status	X		X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L	[4]X											[1]X	X	X
Nasal swab	[3][5]X				[3]X								[3]X	
Research blood sample	[3][5]X				[3]X								[3]X	
Post-discharge Indirect Cost Survey														X
Record microbial results from admission														X
Record any further imaging and findings														X

[1] collected until day 10 or discharge

[2] collected as soon as possible up until discharge

[3] collected for the exploratory sub-study only

[4] not to be collected until written informed consent is obtained

[5] must be collected within 24 hours of stage 1 randomisation

11 SUB-STUDIES

11.1 Costing analysis

11.1.1 Background

This feasibility study will test a number of diagnostic pathways, referred to here as dynamic treatment regimens (DTRs), for managing patients suspected of Hospital Acquired Pneumonia (HAP). Following this feasibility study, we will design a definitive RCT to determine which DTR is most effective. However, for that future study to generate a complete assessment of the effectiveness of each different DTR, the relative cost of each DTR must be known. This will enable a cost effectiveness analysis of clinical efficacy versus cost to conclude which DTR should become NHS standard of care in the future.

At present, the cost of HAP within an NHS setting is not known nor are the individual components which contribute to that overall cost. Moreover, it is likely that a small number of costs have a disproportionate impact on the overall cost of HAP, for example length of stay, but we do not know the extent to which these will vary across DTRs. To address these evidence gaps, a costing analysis of HAP will be embedded within the feasibility study. This costing analysis will seek to capture in detail the direct costs incurred in hospital. However, we will also capture post-discharge indirect costs with a bespoke questionnaire. We will evaluate the performance of this questionnaire which we have developed with reference to a range of similar studies.[30-33] We will capture item completion rates, and discuss participant and carer's views of the questionnaire in order to refine it for the future full scale RCT.

11.1.2 **Aim**

The aim will be to determine the design and analysis plan for a cost effectiveness analysis of the different DTRs to be embedded into the future definitive RCT.

11.1.3 **Objectives**

1. Itemise costs associated with the different DTRs in the feasibility study
2. Determine which costs are directly attributable to HAP – and generate an estimate and standard deviation for the cost of HAP within the NHS
3. Determine which are the largest and most influential costs in HAP and how they vary across DTRs
4. Determine the effect of recruitment site on the above costs
5. Use a patient questionnaire to estimate the post hospitalisation indirect costs in HAP and how these are affected by the DTRs
6. Evaluate the performance and participant experience of the post discharge questionnaire in order to refine it for use in a future RCT

11.1.4 **Methods**

1. Itemise hospital costs for participants within each DTR. The time point for beginning each subject's costing analysis will be the date and time of diagnosis of HAP. Prospective, micro-costing of healthcare materials and processes will be obtained from the following databases:
    i. NHS Schedule of costs
    ii. British National Formulary
    iii. NHS drug prices and local hospital finance department data
2. By consulting the patients record, clinical judgement will be used to determine whether individual costs are related to HAP or underlying health conditions or the condition which provoked the original admission to hospital. Where there is ambiguity in attributing a cost, we will clarify with the treating clinical team.
3. Micro-costing data will undergo sensitivity analysis to determine the key drivers of costs to take forward into a future definitive RCT. As part of this, we will generate a summary of key cost driver statistics, the variability between DTRs and the effects size of each DTR on cost and the scope of hospital activity which represents the biggest contributor to overall cost of a HAP episode.
4. We will evaluate any differences in DTR costs between the 3 recruiting hospital Trusts. This will allow us to generalise HAP costs within the NHS and determine the extent to which any large costs are site specific.
5. In accordance with the NICE guide to methods of technology appraisal (Section 2.2.9), we will capture personal social services costs and describe how these differ between DTRs.
https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781
6. Indirect costs will be captured up to 90 days following the diagnosis of HAP. A bespoke questionnaire will be provided to each subject on discharge – see appendix C. The questionnaire will capture items such as absence from work, domiciliary care costs, visits to the GP and out of hospital prescribing.
7. Validate and refine the content and format of the post-hospitalisation indirect costing questionnaire in order to improve it for use in the future full-scale RCT.

11.2 Qualitative sub-study

11.2.1 Background

We will conduct a qualitative study nested within the above pilot RCT study to systematically gather the views of a range of study stakeholders and use the findings to inform the design and methodology of a future fully powered RCT. Qualitative studies have previously been used to enhance trial design from participants' perspectives and improve future participants' experiences within trials. In particular we are keen to understand potential barriers to recruitment – from both the patient, carer, healthcare worker and researcher perspectives. Moreover, we want to analyse the perceptions of these same stakeholders with respect to our consent model. As explained above, written consent will be deferred until after randomisation. This is due to the inability to predict the onset of HAP and the urgency of performing diagnostic tests and administering treatment.[28]

11.2.2 Aim

To inform and refine the protocol to ensure optimal recruitment and retention to a future fully powered randomised control trial.

Research questions to be addressed in interviews and focus groups

- Among research practitioners
  What are the perceived barriers to recruitment and retention within the pilot study protocol and how might these be overcome?
  What was their experience of the deferred consent model?[29,34]
- Among participants, their carers and eligible patients who declined to participate
  What was their experience of participation and follow-up within the pilot study protocol and how might this experience be improved? In particular, how do they feel about the deferred consent model and what are the perceived benefits and downsides of the two interventions?
  What were the perceived barriers to participation and follow-up within the pilot study protocol and how might these be overcome?[35]
- Among healthcare workers involved in the management of hospital acquired pneumonia
  What were doctors' experience of randomisation within the pilot study protocol and what are their suggestions for refining the process?
  How do doctors describe the decision-making process around the prescription of antibiotics for study participants with HAP/RTI and how this was influenced (or not) by the FAPP and the CT scan?
  Among radiographers, nurses, physios – what are their experiences of the pilot study, perceived barriers to its delivery and how might the study be improved to enhance recruitment, efficiency, and retention?
  How do healthcare workers talk about participation conduct and the perceived 'worth' of research and their role in it – and how might that influence the successful conduct of a trial? https://academic.oup.com/fampra/article/24/3/269/484626?view=extract

Objectives to address the aim and answer the research questions

1. Conduct and analyse semi structured interviews with a purposive sample of participants and their carers and use the findings to refine trial design.
2. Conduct and analyse semi structured interviews with a sample of eligible patients who declined to participate.
3. Conduct and analyse a series of focus groups and interviews with a purposive sample of healthcare workers and researchers to learn from their experience of conducting the study and improve the design for a future RCT.

11.2.3 **Methods**

Recruitment and sampling

Assessment of study participant and carer experience of participating in the study

Sampling

To maximise variation in terms of age, gender and underlying comorbidity (medical admission, surgical admission, acute admission), 5 participants from each of the 3 recruiting Trusts (i.e. an initial sample of 15 participants) will be purposively sampled for these in-depth semi-structured interviews. More participants may need to be interviewed as required to reach data saturation. We will similarly interview the carers of 6 participants (2 per hospital) who lack capacity.

Recruitment and consent

Written informed consent for participation in qualitative interviews will be requested from all patients who are approached about the pilot study. Due to the nature of qualitative research, remote (e.g. telephone, MS Teams/Zoom) interviews may be required - in which case we will seek verbal recorded consent.

Participants will be made aware that not everyone will be selected for an interview and participants will have the option on the consent form to opt in or out of the qualitative interview irrespective of their participation in the pilot study. Those who volunteer will have their contact details shared with an experienced post-doctoral qualitative study researcher. The researcher will then liaise with recruiters to establish when the participant will be discharged from hospital. 14 days after hospital discharge, the researcher will contact the participant to offer more information as required and arrange an initial interview date and time.

Interview design and conduct

Given the high proportion of frail and elderly participants who develop HAP our preference is that most interviews will be face-to-face in their homes, residential care settings, rehab units, or other preferred place, as permitted by social distancing restrictions at the time. If restrictions are still in place, or if participants prefer, they will be interviewed by telephone or video-call.

Interviews will be topic guided, yet conversational and exploratory and conducted in a comfortable private environment. Interviews will be conducted by the qualitative researcher under the supervision of the qualitative lead (BY). Patient and carer topic guides will be periodically revised in light of the ongoing analysis to ensure exploration of unanticipated but important issues. However, the starting point for topic guides will be developed collaboratively with public contributors and we anticipate that interviews would explore the following areas:

- Perceptions of the interventions;
    - in particular the process of having a CT scan
    - perceptions around the increased radiation exposure associated with CT scans
    - perceptions around the identification of unexpected findings by CT scans
    - perceived value – or not – of the FAPP test and its influence on pathogen identification and antibiotic prescribing
- Recruitment and consent – in particular the deferred consent model
- Study documentation and communication
- Care and treatment following randomisation
- Study follow-up

Eligible patients who decline to participate in the feasibility study

We will interview a sample of 9 patients (3 from each Trust) who decline to participate in the feasibility study, aiming for a diverse sample of such patients based on the same purposive sampling approach described

above, but as interviewing progresses and our analysis of the views and experiences of those who decline develops, we may refine this purposive sampling strategy. A flexible and sensitive approach will be taken interviewing patients who decline the feasibility study. For example, if the patient prefers, an interview could take place during the admission – so long as the patient is stable enough to take part and an appropriately private environment can be found. In this case, it may be that a member of the wider research team, with the relevant interviewing experience and where delegated by the PI, conducts the interview. In some instances, it may be possible for a qualitative researcher to conduct in-patient interviews on site in the hospital – for example on a non-acute rehabilitation ward – or via a phone interview where a suitable environment permits. Where in-patient interviews are neither preferred nor possible – out-patient interviews as described above will be offered.

Exploration of clinical and research teams' views of the study and its implementation

Focus groups as well as interviews have been chosen to capture not only a range of views but the interaction of different cadres of staff – which will be informative given the possible power dynamics and differing points of view within clinical environments.

Sampling

We will hold 2 rounds of focus groups at each Trust– the first after 3 months of recruitment and the next after 9 months of recruitment (i.e., a total of 6 focus groups). We will invite a range of clinical, allied health professional and research staff to participate. We anticipate there being approximately 8 participants in each focus group. Interviews will also be conducted if required.

Recruitment and consent

The site PI will identify a representative range of healthcare workers and research practitioners who have had experience of the pilot RCT. Information leaflets will be offered and those who are interested will agree to have their contact details shared with a qualitative post-doctoral researcher who will coordinate the focus group or interview. Our aim will be for consent to be written and the focus group or interview to be in person. However, due to the ongoing pandemic and associated restrictions we may need to perform remote, video assisted (e.g., MS Teams/Zoom) focus groups/interviews - in which case we will seek verbal recorded consent.

Focus group and interview design and conduct

Focus groups and interviews will be topic guided, yet conversational and exploratory and conducted in a comfortable environment. They will be conducted by an experienced qualitative researcher, under the supervision of the qualitative lead (BY). We anticipate key area to explore will be:

- Recruitment and consent process
  A particular focus will be on the deferred consent model and the process of randomisation and the degree to which these were practical and acceptable.
  What, if any, are the perceived barriers to recruitment and how might these be addressed and the process improved.
- Interventions
  Implementation of early CT scans and their reporting
  Implementation of the FAPP
  We will focus on an exploration of attitudes to obtaining sputum samples – their perceived benefit in the usual care Dynamic Treatment Regimens (DTRs) versus the FAPP containing DTRs.
  What are the perceived barriers or obstacles to obtaining sputum samples and how can they be overcome?
- Antibiotic prescribing

How clinical decision making has been influenced by the CT scans and the FAPP?
What are the factors that affect adherence to antibiotic guidelines?

11.2.4 **Analysis**

Data analysis

We will draw on recommendations regarding the design, conduct, analysis and reporting of qualitative research, including those on qualitative studies embedded in feasibility trials, to ensure the methodological integrity and utility of the qualitative work.[36,37]

Interviews and focus groups will be audio-recorded, checked and anonymised by the research team before being transcribed by a professional agency. Once transcripts have been checked, all audio-recordings will be deleted. All audio recordings, transcripts and associated spreadsheets with participant data will be encrypted, securely stored and appropriately access restricted.

Professional qualitative data analysis computer software will be used to assist with coding the transcripts. The qualitative researcher will lead the analysis in collaboration with DW and they will meet regularly with BY to review a proportion of transcripts and compare coding and interpretations.

The interviews and focus groups will initially be analysed as separate sets to avoid, for example, interpretations of the staff interviews overshadowing those of the patients and relatives or vice-versa. Analysis of transcripts will be interpretative and draw on thematic approaches suited to the pragmatic aim of this qualitative research which is to inform a future study. Analysis will primarily be inductive but may incorporate deductive elements to assess the resonance of the findings to other studies. Rather than take the expressed views at face value we will compare and interpret across interviews to understand the psychological factors behind the way in which colleagues and participants speak about this research. As the analysis progresses, we will seek to develop categories and themes that integrate across the patient, relative and staff datasets by comparing across these, whilst also highlighting divergence in their perspectives.

11.3 **Exploratory sub-studies**

Laboratory based exploratory sub-studies will be performed on research blood, sputum and nasal swab samples obtained from the pilot study participants (see schedule of events) and compared to a sample of up to 50 stable, sputum producing participants without pneumonia. The work will be carried out by University of Liverpool PhD students supervised by DW, SA and LT.

Aim

Explore associations between immune cells, causative pathogens, inflammatory responses, severity and outcome among our HAP cohort.[38-46]

Objectives

1: Characterisation of immune cells and inflammatory responses in whole blood, sputum and nasal swabs from up to 50, non-exacerbating, sputum producing volunteers from clinic.

2: Measure immune cells and inflammatory responses in samples from the cohort of HAP patients and explore associations with clinical outcome.

3: Use regression analysis to explore associations between immune cell numbers and characteristics, inflammatory responses, markers of coagulation and different pathogens identified using the FAPP from the pilot study cohort.

4: Collaborate with NHS immunology laboratory to translate research assays above into the NHS laboratory to support future clinical and clinical research work.

11.3.1 Inclusion criteria for stable, sputum producing patients identified from NHS clinics and sampled for the exploratory study

Inclusion

- ≥18 years
- Ongoing follow up in a respiratory clinic
- Chronic sputum production
- Fit either of the two categories:
    - no colonising organisms found in sputum during stable state on at least 2 consecutive occasions at least 3 months apart
    - same organism identified in sputum while clinically stable on at least 2 occasions at least 3 months apart

Exclusion

- Not willing or able to provide 3 paired blood, sputum and nasal swab samples each ≥ 2 weeks apart
- Patients taking the following drugs:
    - Long term oral steroid use (any dose)
    - Methotrexate
    - Cyclophosphamide
    - Anti-TNF drugs, Rituximab or other biological therapies
- Exacerbation or infection requiring acute antibiotics and or oral steroids within the last 4 weeks*

*If a patient exacerbates in between the three planned samples – e.g. between the first and second – then 4 weeks should elapse following completion of any treatments before any subsequent samples are taken i.e. patient should be at a self-reported baseline level of symptoms.

11.3.1.1 Screening stable sputum producing patients for exploratory work

Research teams within the participating NHS Trusts will screen clinics for patients meeting the above criteria.

11.3.1.2 Recruitment and consent of stable sputum producing patients for exploratory work

Patients identified by the research teams as potential recruits will be flagged to clinicians during planned clinic visits. Clinicians carrying out clinic appointments will ask patients if they would mind talking to the research team before or after their appointment.
The research team will provide a Patient Information Sheet and explain the research and what is involved. If the patient agrees to provide samples they will sign a consent form.

11.3.1.3 Samples for stable sputum producing patients for exploratory work

Blood samples taken to support these exploratory sub-studies will be identical to those described in the main pilot study of patients with HAP i.e. 32.5 ml Research blood sample comprising:

2 x 9 ml EDTA
2 x 2.5 ml PAX-gene
1 x 5 ml serum gel
1 x 4.5 ml citrate (clotting)

Sample collection

Sample timing is flexible and should be arranged to suit both the participant and the available research and laboratory staff, however samples should not be taken less than 14 days apart. If the participant is willing, then the first paired blood, sputum and nasal swab samples could be obtained during the same visit as the consent is obtained. Blood samples will be taken by the research team or phlebotomy service present in clinic. If the participant would prefer to come back on another occasion for sampling then the time and date can be arranged with the research team.

Sample storage and handling

See also the laboratory manual

Some samples will be sent to the NHS clinical laboratories. Other samples will have an initial stage of processing within the research laboratory at Liverpool University Hospitals NHS Foundation Trust or the laboratory at Ronald Ross building of the University of Liverpool. Some assays will occur immediately within the above research laboratories – others will occur later, on stored, frozen aliquots of these samples.

12 SAFETY REPORTING

As this study only incorporates well-established and non-invasive diagnostic investigations that would normally be carried out as standard of care, safety events will not be recorded as part of this study.

12.1 Contact Details and Out-of-hours Medical Cover

Emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for HAP-FAST participants. All participants will be provided with a contact card and copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

13 STATISTICAL CONSIDERATIONS

13.1 Introduction

This section relates primarily to the pilot study aspects of the feasibility study. Questions of sample size and analysis regarding the sub-studies are outlined in section 11.

13.2 Sample Size

13.2.1 Sample Size Calculation

Since this is a feasibility/pilot study, a sample size justification is given rather than a calculation. Prospective audits of HAP at Liverpool University Hospitals NHS Foundation Trust and Lancashire Teaching Hospitals NHS Foundation Trust reveal 1200 and 706 cases per year respectively. Assuming 30% of cases are eligible of whom 40% are recruited we estimate 220 participants. This is at the top end of pilot study size described in the audit of UK CLRN database but we feel it is justified by the above objectives, in particular to establish a signal of efficacy and to inform decisions regarding outcome selection.

13.2.2 **Sample Size considerations**

Two factors further affect recruitment targets:-

- Seasonality: our hospital audits demonstrate that HAP incidence is greater in the winter than the summer. To account for seasonal variation in pathogens it is important that we recruit across a full calendar year.
- Differences between hospitals: we do not know whether recruitment will be similar in each hospital. We will recruit from more than one hospital since the definitive study will need to be multi-centre, and one of our aims is to demonstrate feasibility in 2 hospitals with different characteristics.

13.3 **Method of Randomisation**

13.3.1 **Allocation Sequence Generation**

For each randomisation system, a randomisation list will be created by an independent statistician.

13.3.2 **Allocation Sequence**

Participant allocations will be irrevocably generated upon completion of the web-based randomisation form.

Interim Analyses
There are no planned interim analyses for this study.

Analyses of the accumulating data will be performed at regular intervals (at least annually) for review by the review committees (TMG/TSC). These analyses will be performed at the LCTC. The committees will be asked to give advice on whether the accumulated data from the study, together with results from other relevant trials, justifies continuing recruitment of further participants or further follow-up. A decision to discontinue recruitment, in all participants or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the study and the general clinical community.

13.4 **Analysis Plan**

13.4.1 **Pilot Study**

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the SAP are summarised below:

Feasibility and overall recruitment rate will be assessed for each participating site and overall by calculating the total number of participants randomised per month and the ratio of successful recruitment to eligible patients approached.

Much of the analysis will be performed using summary statistics and graphical representations of outcomes at each time-point and by DTR. Formal assessments of efficacy, will be made for each outcome, for the following treatment arms comparisons: FAPP vs no FAPP (groups 1 and 5 vs groups 2 and 6); and CXR vs CT (groups 1-4 vs groups 5-8). No inference will be drawn – all results will be treated as hypothesis generating.

Continuous data will be presented using median (interquartile range) and mean (standard deviation) as appropriate, with boxplots summarising measurements at each time-point by treatment group. Categorical

data will be presented as frequencies and percentages. Time-to-event data will be presented with Kaplan-Meier curves, and summarised by median (95% confidence interval) if possible.

All analyses shall be carried out on an intention to treat basis, retaining all participants in their initially randomised groups irrespective of any protocol deviations.

As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis. Such methods will be fully described in the SAP.

14 DATA MANAGEMENT AND TRIAL MONITORING

For the HAP-FAST study the responsibilities for Data Management and monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans will detail regarding the internal processes that will be conducted at the LCTC throughout the study. Justification for the level of monitoring is provided within those documents and the study-specific risk assessment. All data will be managed as per local LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

14.1 Source Documents

Data will be entered directly on to the database without the use of a paper case report form. As such, for data items where no prior record exists the eCRF on the database will be considered the source document. A HAP-FAST source document list will be produced for each site to be kept in the ISF and provide detail of what constitutes HAP-FAST-specific source data.

Date of written informed consent processes (including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (and possible treatment arms) should be added to the patient's medical record chronologically.

14.2 Data Collection Methods

Data are to be entered into the study database by members of the research team at site. The database includes validation features which will alert the user to certain inconsistent or missing data on data entry. If any problems are identified via automated validation or central monitoring, a query will be raised within the database and the site will be notified. A complete log of discrepancies and data amendments is automatically maintained including the date of each change, the reason for the change and the person who made the change, thus providing a complete audit trail. Automated email reminders can be generated by the database if follow up data from a scheduled participant visit is overdue.
Training will be provided as necessary prior to data entry.

14.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the study and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with Sponsor.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of monitoring will be conducted.

This will be dependent on the documented risk assessment of the study which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to study interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the study are detailed in Roles and Responsibilities see section 0.

14.3.1 **Central Monitoring**

There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the study data, to be detailed in the Trial Monitoring Plan. Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to participant rights and safety will also be regularly performed as per LCTC processes. Where discrepancies are found, data queries will be raised by the LCTC and sent to site staff to resolve or explain discrepancies, with appropriate corrections made on the database.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

14.3.2 **Clinical Site Monitoring**

In order to perform their role effectively, the trial coordinator and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the PISC. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

1) assessing compliance with the study protocol
2) discussing any emerging problems that may have been identified prior to the visit
3) checking eCRF and query completion practices

14.4 **Risk Assessment**

(ICH GCP 5.18.3) "The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the study. In general there is a need for on-site monitoring, before, during and after the study; however …central monitoring in conjunction with procedures such as investigators' training and meetings and extensive written guidance can assure appropriate conduct of the study in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified."

A bespoke trial risk assessment will be conducted for HAP-FAST, which will inform the level of monitoring to be implemented.

14.5 **Confidentiality**

This study will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the study

(e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

eCRFs will be labelled with a unique trial randomisation number. Verification that appropriate written informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the LCTC by recruiting sites. This transfer of identifiable data is disclosed in the PISC.
N.B. Consent forms must be transferred separately to any other study documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by the LCTC will be notified promptly to the study Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

Research sites will be responsible for administering questionnaires to study participants 3 months following completion of assessments and therefore will be required to receive contact details including name, address, email and telephone details. Access to these contact details will be restricted.

14.6 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of study-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the study specific training. A greenlight checklist will verify all approvals are in place prior to study initiation at LCTC and the individual centre.
- The study will be conducted in accordance with procedures identified in the protocol.
- The independent members of the TSC will provide independent oversight of the study.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the study Data Management Plan.

14.7 Records Retention

The retention period for the HAP-FAST data and information is 10 years from the official End of Trial date.

The PI at each investigational site must make arrangements to store the essential study documents (as defined by ICH GCP guidelines) including the Investigator Site File and the applicable participant medical records, for the full length of the study's retention period and will arrange for confidential destruction at the end of this period as instructed by the Liverpool Clinical Trials Centre.

The PI is also responsible for archiving all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the study will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g. laboratories, third-party vendors, etc.).

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All eCRFs and study data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

15 REGULATORY AND ETHICAL CONSIDERATIONS

15.1 Statement of Compliance

The procedures detailed within this protocol are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken.

15.2 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone ethical review by an independent Research Ethics Committee and has received a favourable opinion.

15.3 Approvals

The protocol, PISC and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA) and host institution(s) for written approval.
Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

15.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and MHRA and REC requirements are handled based on their nature and severity.

15.4.1 Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

15.4.2 **Serious breaches**

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the study become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committee (TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.
The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the study. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to the REC.

Breaches confirmed as 'serious' will be reported to the REC within 7 days by the LCTC on behalf of the University of Liverpool and notified to the TMG and TSC at their next meeting.
Any requests for additional information from the Sponsor, TMG, TSC, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.
Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

16 **INDEMNITY**

The University of Liverpool holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

17 **PUBLICATION AND DISSEMINATION**

17.1 **Publication Policy**

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the study's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this study will be attached to any publications resulting from this study and members of the TSC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

17.1.1 **Authorship**

Contributors to all 4 of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the HAP-FAST Consortium which will also be named at the manuscript head.

17.2 **Dissemination to Key Stakeholders**

On completion of the research, a Final Trial Report will be prepared and submitted to the REC. The results of HAP-FAST will be published regardless of the magnitude or direction of effect.

17.3 **Data Sharing**

At the end of the study, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank eCRF) will be prepared in order to be shared with external researchers. All requests for access to the IPD will be reviewed by the Sponsor.

18 **CHRONOLOGY OF PROTOCOL AMENDMENTS**

18.1 **Version 3.0 (15/Sept/2023)**

Summary of Amendment from Protocol v2.0 to Protocol v3.0		
Protocol Section Number	Protocol Section Title	Summary of Changes
6.1.2	Study Setting	Addition of a +/- 7 day window for the day 28 follow-up visit.
6.3.2	Clinicians	Option for interviews to be conducted with health care professionals as well as focus groups.
7.1.1	Inclusion Criteria	Definition for Hospital Acquired Pneumonia added.
7.2.1	Inclusion Critiera	Requirement that sputum has been obtained prior to the 2nd dose of antibiotic.
7.2.2	Exclusion Crtieria	Removal of “A sputum sample cannot be obtained before 2nd dose of antibiotic" as an exclusion criteria as this is covered in the inclusion criteria.
10.4.1	Sample Collection	Clarification of where sputum samples will be obtained from.

10.5.2	Obtaining Written Informed Consent/Assent	Postal consent added.
10.5.4	Consent Form Completion	Clarification that samples cannot be analysed until informed consent has been obtained.
10.9	Schedule for Assessments and Follow-up	Removal of requirement for stage 2 randomisation to be done within 8 hours of stage 1 randomisation. Removal of requirement for concomitant medications checks to be done every day for 10 days and at day 28.
11.2.3	Methods	Verbal consented added for patients taking part in the qualitative sub-study.

18.2 **Version 2.0 (30/Nov/2022)**

Summary of Amendment from Protocol v1.0 to Protocol v2.0		
Protocol Section Number	Protocol Section Title	Summary of Changes
1.1.2	Exclusion Criteria	Ventilator acquired pneumonia has been added to the exclusion criteria for stage one randomisation.
10.5.2	Obtaining Written Informed Consent/Assent	Clarification that data captured up until discharge will be kept for analysis if informed consent has not been obtained.
10.5.3	Patients who lack capacity	A personal consultee or a nominated consultee will be appointed to provide informed consent is a patient lacks capacity. Patient's next of kin will be informed of their participation in the trial if they pass away before informed consent is obtained.

18.3 **Version 1.0 (12/09/2022)**

Original Approved version.

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20 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

20.1 Appendix A: CAP-sym questionnaire

Participant Identification Number: _____

Date: _____

In the past 24 hours, how much have you been bothered by:	Patient did not have the symptom/problem	Patient had the symptom/problem and it bothered him/her...				
		Not at all	A little	Moderately	Quite a bit	Extremely
*1. Coughing?	0	1	2	3	4	5
*2. Chest pains?	0	1	2	3	4	5
*3. Shortness of breath?	0	1	2	3	4	5
4. Coughing up phlegm/sputum (secretion from the chest)?	0	1	2	3	4	5
5. Coughing up blood?	0	1	2	3	4	5
*6. Sweating?	0	1	2	3	4	5
*7. Chills?	0	1	2	3	4	5
*8. Headache?	0	1	2	3	4	5
*9. Nausea?	0	1	2	3	4	5
10. Vomiting?	0	1	2	3	4	5
11. Diarrhea?	0	1	2	3	4	5
12. Stomach pain?	0	1	2	3	4	5
*13. Muscle pain?	0	1	2	3	4	5
*14. Lack of appetite?	0	1	2	3	4	5
*15. Trouble concentrating?	0	1	2	3	4	5
16. Trouble thinking?	0	1	2	3	4	5
*17. Trouble sleeping?	0	1	2	3	4	5
*18. Fatigue?	0	1	2	3	4	5

* Indicates items that are included in the CAP-Sym 12.

20.2 Appendix B: EQ-5D-5L Quality of Life Questionnaire

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

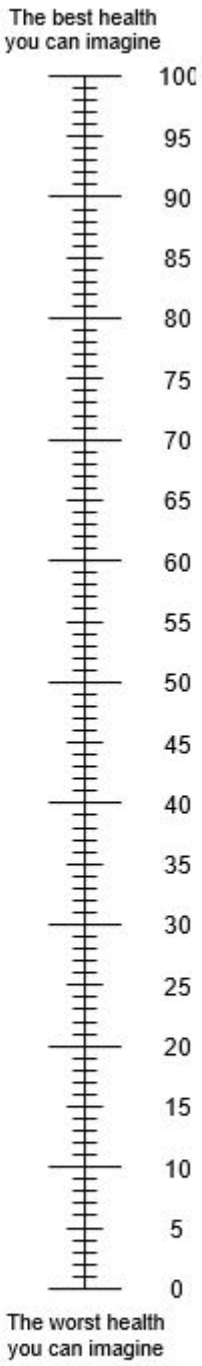
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

20.3 Appendix C: POST-DISCHARGE INDIRECT COST SURVEY

Thank you for completing this survey. The idea of this survey is to get an idea of how events in hospital influence what happens once a patient goes home. We are interested in the period up to 90 days (three months) from the date you joined the study

We would recommend you add notes to this questionnaire every week as it is easy to forget the details about what has happened.

We have provided you with an addressed envelope to return the questionnaire. In case it gets lost in the post we will give you a call at around 90 days to go through it with you.

1.

Since your discharge from hospital, have you had a GP appointment?	Yes ☐	No ☐
If yes, how many appointments?	_____ appointments	
What were the reasons for these appointments?		

2.

Since your discharge, have you had to go back to hospital?	Yes ☐	No ☐
What were your symptoms that prompted you to go back to hospital?		
How long were you in hospital for?	_____ days	

3.

Since your discharge from hospital, have you had any further investigations (for example blood tests, scans, breathing tests or camera tests)?	Yes ☐	No ☐
Do you know why the doctor ordered these tests?		

4.

After you left hospital did you go to a respite or rehabilitation bed?	Yes ☐	No ☐
If yes, what kind of facility did you go to?	Care home ☐ Nursing home ☐ Rehabilitation bed ☐ Other:_____	
How many days were you there?	_____days	

5.

Since your discharge, have you gone to a hospital clinic appointment?	Yes ☐	No ☐
If yes, what was the reason for the clinic appointment		

6.

Have you had *NEW* any help from the following community services?	How long do their visits last?	How many times a week do they come to help?	What is the reason you need this help?
Home carer □	_____ hours	_____ per week	
District nurse □	_____ hours	_____ per week	
Cleaner □	_____ hours	_____ per week	
Social worker □	_____ hours	_____ per week	
Health visitor □	_____ hours	_____ per week	
Physiotherapist □	_____ hours	_____ per week	
Occupational therapist □	_____ hours	_____ per week	
Other:_____	_____ hours	_____ per week	
Other:_____	_____ hours	_____ per week	

7.

Since your discharge from hospital, have you started taking any new medications prescribed by your GP?	Yes ☐	No ☐
If yes, what were these medications?	Course length (if long term, please leave blank)	
Medication name:	_____ days	
Medication name:	_____ days	
Medication name:	_____ days	
Medication name:	_____ days	
Other:		

8.

Have you missed work due to being ill since your discharge from hospital?	Yes ☐	No ☐
If yes, how many days have you missed?	_____ days	
How much do you earn an hour? Approximately	£_____	
How many hours do you work in a normal working day?	_____ hours	
What is the reason you had had time off work?		

9.

Since your discharge from hospital, have friends or family had to take time off work to help you?	Yes ☐	No ☐
If yes, how many days have they missed	_____ days	
How much do they earn an hour? Approximately	£_____	
How many hours do you work in a normal working day	_____ hours	
What is the reason you need their help?		

20.4 Appendix D: BioFire® FilmArray® Pneumonia Panel Testing

BioFire® FilmArray® Pneumonia Panel Testing

Purpose

This procedure provides instructions for testing sputum-like specimens (induced or expectorated sputum, or endotracheal aspirates) or bronchoalveolar lavage (BAL)-like specimens (BAL or mini-BAL) using the BioFire Pneumonia Panel kit.

Background

The BioFire Pneumonia Panel is a multiplexed nucleic acid test intended for use with BioFire® FilmArray® 1.5, BioFire® FilmArray® 2.0, or BioFire® FilmArray® Torch systems for the simultaneous detection and identification of multiple respiratory viral and bacterial nucleic acids, as well as select antimicrobial resistance genes, in sputum-like specimens (induced or expectorated sputum, or endotracheal aspirates) or bronchoalveolar lavage (BAL)-like specimens (BAL or mini-BAL) obtained from individuals suspected of lower respiratory tract infection.

The following bacteria are reported semi-quantitatively with bins representing approximately 10^4, 10^5, 10^6, or ≥10^7 genomic copies of bacterial nucleic acid per milliliter (copies/mL) of specimen, to aid in estimating relative abundance of nucleic acid from these common bacteria within a specimen:

Bacteria reported with bins of 10^4, 10^5, 10^6, or ≥10^7 copies/mL		
Acinetobacter calcoaceticus-baumannii complex	Klebsiella oxytoca	Serratia marcescens
Enterobacter cloacae complex	Klebsiella pneumoniae group	Staphylococcus aureus
Escherichia coli	Moraxella catarrhalis	Streptococcus agalactiae
Haemophilus influenzae	Proteus spp.	Streptococcus pneumoniae
Klebsiella aerogenes	Pseudomonas aeruginosa	Streptococcus pyogenes

The following atypical bacteria, viruses, and antimicrobial resistance genes are reported qualitatively:

Atypical Bacteria		
Chlamydia pneumoniae	Legionella pneumophila	Mycoplasma pneumoniae
Viruses		
Adenovirus	Human Rhinovirus/Enterovirus	Parainfluenza Virus
Coronavirus	Influenza A	Respiratory Syncytial Virus
Human Metapneumovirus	Influenza B	
Antimicrobial Resistance Genes		
CTX-M	NDM	*mecA/C* and MREJ
IMP	OXA-48-like	
KPC	VIM	

Principle of the Procedure

The BioFire® FilmArray® Pneumonia Panel pouch is a closed-system disposable that stores all the necessary reagents for sample preparation, reverse transcription, polymerase chain reaction (PCR), and detection in order to isolate, amplify, and detect nucleic acid from multiple lower respiratory pathogens within a single bronchoalveolar lavage (BAL)-like (BAL or mini-BAL) or sputum-like (sputum or ETA) specimen. After sample collection, the user injects hydration solution and sample combined with sample buffer into the pouch, places the pouch into a BioFire® FilmArray® Instrument, and starts a run. The entire run process takes about one hour. Additional detail can be found in the appropriate FilmArray Operator's Manual.

Overview

The following is an overview of the operations and processes that occur during a pouch run. During a run, the BioFire® FilmArray® System:

- Lyses the sample by agitation (bead beading).
- Extracts and purifies all nucleic acid from the sample using magnetic bead technology.

- Performs nested multiplex PCR by:
  - First performing reverse transcription and a single, large-volume, massively multiplexed reaction (PCR1).
  - Then performing multiple singleplex, second-stage PCR reactions (PCR2) to amplify sequences within the PCR1 products.
- Uses endpoint melting curve data to detect and generate a result for each target on the BioFire Pneumonia Panel array.
- For the BioFire Pneumonia Panel, the system also uses real-time amplification data from the assays relative to a Quantified Standard Material (QSM) included in the pouch to provide an estimated value in genomic copies per milliliter (copies/mL) for bacterial analytes.

Specimen

Specimen Type	Bronchoalveolar lavage (BAL)-like specimens • Including BAL and mini-BAL collected according to standard technique Sputum-like specimens • Including induced and expectorated sputum, as well as endotracheal aspirate (ETA) collected according to standard technique
Minimum Sample Volume	Approximately 0.2 mL (200 µL) of specimen material will be captured by the Sample Swab for transfer into the test
Transport and Storage	Specimens should be tested with the BioFire® FilmArray® Pneumonia Panel as soon as possible If storage is required, specimens can be held: • Refrigerated for up to 1 day (2–8 °C)

NOTE: BAL-like or sputum-like specimens should not be centrifuged, pre-processed, treated with any mucolytic or decontaminating agents (e.g. MycoPrep, Sputasol, Snap n' Digest, DTT, sodium hydroxide, oxalic acid, trypsin, etc.), or placed into transport media before testing.

Note: In accordance with good laboratory practice recommendations, institutions should follow their own established rules for acceptance/rejection of sputum specimens (e.g. using Gram stain/Q-score) and therefore apply appropriate guidelines locally for acceptance/rejection of a sample for testing.

NOTE: Bleach can damage organisms/nucleic acid within the specimen, potentially causing false negative results. Contact between bleach and specimens during collection, disinfection, and testing procedures should be avoided.

Materials

Materials Provided	Materials Required But Not Provided
Each kit contains sufficient reagents to test 30 samples (30-test kit; RFIT-ASY-0144) or 6 samples (6-test kit; RFIT-ASY-0145): • Individually-packaged BioFire® FilmArray® Pneumonia Panel pouches • Single-use (1.0 mL) Sample Buffer ampoules • Single-use, pre-filled (1.5 mL) Hydration Injection Vials (blue) • Single-use Sample Injection Vials (red) • Individually-packaged Sample Swabs	• BioFire® FilmArray® System including: BioFire® FilmArray® 1.5, BioFire® FilmArray® 2.0, or BioFire® FilmArray® Torch and accompanying software • Pouch Loading Station • 10% bleach solution or a similar disinfectant

Procedure

Refer to the BioFire Pneumonia Panel Quick Guide, the FilmArray Training Video, or the FilmArray Operator's Manual for more detail and pictorial representations of these instructions.

Use clean gloves and other Personal Protective Equipment (PPE) when handling pouches and samples. Only prepare one BioFire Pneumonia Panel pouch at a time and change gloves between samples and pouches. Once sample is

added to the pouch, promptly transfer to the instrument to start the run. After the run is complete, discard the pouch in a biohazard container.

Prepare Pouch

1. Thoroughly clean the work area and the Pouch Loading Station with freshly prepared 10% bleach (or suitable disinfectant) followed by a water rinse.
2. Remove the pouch from its vacuum-sealed package by tearing or cutting the notched outer packaging and opening the protective aluminum canister.

NOTE: The pouch may still be used even if the vacuum seal of the pouch is not intact. Attempt to hydrate the pouch using the steps in the Hydrate Pouch section. If hydration is successful, continue with the run. If hydration fails, discard the pouch and use a new pouch to test the sample.

Check the expiration date on the pouch. Do not use expired pouches.

Insert the pouch into the Pouch Loading Station, aligning the red and blue labels on the pouch with the red and blue arrows on the Pouch Loading Station.

Place a red-capped Sample Injection Vial into the red well of the Pouch Loading Station.

3. Place a blue-capped Hydration Injection Vial into the blue well of the Pouch Loading Station.

Hydrate Pouch

1. Unscrew the Hydration Injection Vial from the blue cap.

Remove the Hydration Injection Vial, leaving the blue cap in the Pouch Loading Station.

Insert the Hydration Injection Vial's cannula tip into the pouch hydration port located directly below the blue arrow of the Pouch Loading Station.

Forcefully push down in a firm and quick motion to puncture seal until a faint "pop" is heard and there is an ease in resistance. Wait as the correct volume of Hydration Solution is pulled into the pouch by vacuum.

- If the Hydration Solution is not automatically drawn into the pouch, repeat Step 2 to verify that the seal of the pouch hydration port was broken. If Hydration Solution is again not drawn into the pouch, discard the current pouch, retrieve a new pouch, and repeat from Step 1: Prepare Pouch.

Verify that the pouch has been hydrated.

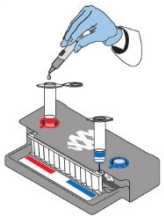
- Flip the barcode label down and check to see that fluid has entered the reagent wells (located at the base of the rigid plastic part of the pouch). Small air bubbles may be seen.
- If the pouch fails to hydrate (dry reagents appear as white pellets), repeat Step 2 to verify that the seal of the pouch hydration port was broken. If hydration solution is still not drawn into the pouch, discard the current pouch, retrieve a new pouch, and repeat from Step 1: Prepare Pouch.

Prepare Sample Mix

1. Add Sample Buffer to the Sample Injection Vial.
   - Hold the Sample Buffer ampoule with the tip facing up.

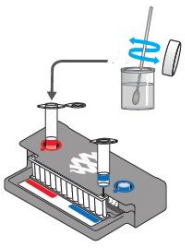
NOTE: Avoid touching the ampoule tip during handling, as this may introduce contamination.

- Firmly pinch at textured plastic tab on the side of the ampoule until the seal snaps.
- Invert the ampoule over the red-capped Sample Injection Vial and dispense Sample Buffer using a slow, forceful squeeze followed by a second squeeze.

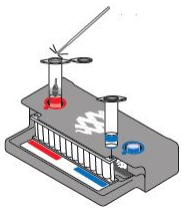


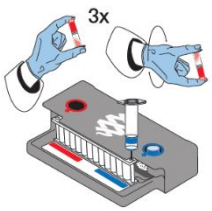
NOTE: Avoid squeezing the ampoule additional times. This will generate foaming, which should be avoided.

Using the Sample Swab provided in the test kit, thoroughly stir the BAL-like or sputum-like specimen for about 10 seconds.



2. Place the swab end of the Sample Swab into the Sample Injection Vial, then break off the swab handle.
3. Tightly close the lid of the Sample Injection Vial and discard the swab handle into the appropriate waste container.
4. Remove the Sample Injection Vial from the Pouch Loading Station and invert the vial at least 3 times to mix.

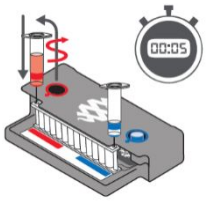




5. Return the Sample Injection Vial to the red well of the Pouch Loading Station.

Load Sample Mix

1. Slowly twist to unscrew the Sample Injection Vial from the red cap and wait for 5 seconds with the vial resting in the cap.



NOTE: Waiting 5 seconds decreases the risk of dripping and contamination from the sample.

2. Lift the Sample Injection Vial, leaving red cap in the well of the Pouch Loading Station, and insert the Sample Injection Vial cannula tip into the pouch sample port located directly below the red arrow of the Pouch Loading Station.
3. Forcefully push down in a firm and quick motion to puncture seal (a faint "pop" is heard) and sample is pulled into the pouch by vacuum.
4. Verify that the sample has been loaded.
   - Flip the barcode label down and check to see that fluid has entered the reagent well next to the sample loading port.
   - If the pouch fails to pull sample from the Sample Injection Vial, the pouch should be discarded. Retrieve a new pouch and repeat from *Step 1: Prepare Pouch*.
5. Discard the Sample Injection Vial and the Hydration Injection Vial in appropriate biohazard sharps container.
6. Record the Sample ID in the provided area on the pouch label (or affix a barcoded Sample ID) and remove the pouch from the Pouch Loading Station.

Run Pouch

The BioFire® FilmArray® Software includes step-by-step on-screen instructions that guide the operator through performing a run.

BioFire® FilmArray® 1.5 and BioFire® FilmArray® 2.0

1. Ensure that the BioFire 1.5 or BioFire 2.0 system (instrument and computer) is powered on and the software is launched.
2. Follow on-screen instructions and procedures described in the Operator's Manual to place the pouch in an instrument. Enter pouch, sample, and operator information.
3. Pouch identification (Lot Number and Serial Number) and Pouch Type information will be automatically entered when the barcode is scanned. If it is not possible to scan the barcode, the pouch Lot Number, Serial Number, and Pouch Type can be manually entered from the information provided on the pouch label into the appropriate fields. To reduce data entry errors, it is strongly recommended that the pouch information be entered by scanning the barcode.

NOTE: When selecting a Pouch Type manually, ensure that the Pouch Type matches the label on the BioFire® FilmArray® Pneumonia Panel pouch.

4. Enter the Sample ID. The Sample ID can be entered manually or scanned in by using the barcode scanner when a barcoded Sample ID is used.
5. Select and confirm the appropriate protocol from the Select Protocol dialog box. The BioFire Pneumonia Panel uses two different protocols that should be selected according to the sample type (BAL or sputum) that is being tested.
6. Enter a user name and password in the Name and Password fields.

NOTE: The font color of the username is red until the user name is recognized by the software.

7. Review the entered run information on the screen. If correct, select Start Run.

Once the run has started, the screen displays a list of the steps being performed by the instrument and the number of minutes remaining in the run.

NOTE: The bead-beater apparatus can be heard as a high-pitched noise during the first minute of operation.

8. When the run is finished, follow the on-screen instructions to remove the pouch, then immediately discard it in a biohazard waste container.
9. The run file is automatically saved in the BioFire® FilmArray® Instrument database, and the test report can be viewed, printed, and/or saved as a PDF file.

BioFire® FilmArray® Torch

1. Ensure that the BioFire Torch system is powered on.

2. Select an available Module (instrument) on the touch screen or scan the barcode on the pouch using the barcode scanner.
3. Pouch identification (Lot Number and Serial Number) and Pouch Type information will be automatically entered when the barcode is scanned. If it is not possible to scan the barcode, the pouch Lot Number, Serial Number, and Pouch Type can be manually entered from the information provided on the pouch label into the appropriate fields. To reduce data entry errors, it is strongly recommended that the pouch information be entered by scanning the barcode.

NOTE: When selecting a Pouch Type manually, ensure that the Pouch Type matches the label on the BioFire Pneumonia Panel pouch.

4. Enter the Sample ID. The Sample ID can be entered manually or scanned in by using the barcode scanner when a barcoded Sample ID is used.
5. Insert the pouch into the available Module (instrument).
   - Ensure that the pouch fitment label is lying flat on top of pouch and not folded over. As the pouch is inserted, the Module (instrument) will grab onto the pouch and pull it into the chamber.
6. Select and confirm the appropriate protocol from the Select Protocol dialog box. The BioFire® FilmArray® Pneumonia Panel uses two different protocols that should be selected according to the sample type (BAL or sputum) that is being tested.
7. Enter operator user name and password, then select Next.

NOTE: The font color of the username is red until the user name is recognized by the software.

8. Review the entered run information on the screen. If correct, select Start Run.

Once the run has started, the screen displays a list of the steps being performed by the Module (instrument) and the number of minutes remaining in the run.

9. At the end of the run, remove the partially ejected pouch, then immediately discard it in a biohazard waste container.

NOTE: The bead-beater apparatus can be heard as a high-pitched noise during the first minute of operation.

10. The run file is automatically saved in the Biofire® FilmArray® Instrument database, and the test report can be viewed, printed, and/or saved as a PDF file.

Quality Control

Process Controls

Two process controls are included in each pouch:

1. RNA Process Control
   - The RNA Process Control assay targets an RNA transcript from the yeast *Schizosaccharomyces pombe*. The yeast is present in the pouch in a freeze-dried form and becomes rehydrated when sample is loaded. The control material is carried through all stages of the test process, including lysis, nucleic acid purification, reverse transcription, PCR1, dilution, PCR2, and DNA melting. A positive RNA Process Control result indicates that all steps carried out in the BioFire Pneumonia Panel pouch were successful.
2. Quantified Standard Material (QSM) Control
   - The QSM assay detects a quantified standard synthetic nucleic acid that is subject to all stages of the test process following sample lysis (bead beating). A positive QSM control result indicates that the expected level of QSM is present (approximately 10^6 copies/mL) for use in determining assay and bin results for bacterial analytes.

Monitoring Test System Performance

The BioFire® FilmArray® Software will automatically fail the run if the melting temperature (Tm) for either the RNA Process Control or the QSM is outside of an acceptable range (80.3–84.3°C for the RNA Process Control and 82.7–86.7°C for the QSM). If required by local, state, or accrediting organization quality control requirements, users can monitor the system by trending Tm values for the control assays and maintaining records according to standard laboratory quality control practices. Refer to the appropriate FilmArray Operator's Manual for instructions on obtaining control assay Tm values.

Interpretation

The BioFire Software automatically analyzes and interprets the assay results and displays the final results in a test report (see the BioFire® FilmArray® Pneumonia Panel Quick Guide to view an example of a test report). The analyses performed by the BioFire Software and details of the test report are described below.

Assay Interpretation

When PCR2 is complete, the BioFire® FilmArray® Instrument performs a DNA melting analysis on the PCR products and measures the fluorescence signal generated in each well (for more information see appropriate FilmArray Operator's Manual). The BioFire Software then performs several analyses and assigns a final assay result. The steps in the analyses are described below.

Analysis of melt curves. The BioFire Software evaluates the DNA melt curve for each well of the PCR2 array to determine if a PCR product was present in that well. If the melt profile indicates the presence of a PCR product, then the analysis software calculates the melting temperature (Tm) of the curve and compares it against the expected Tm range for the assay. If the software determines that the Tm of the curve is within the assay-specific Tm range, the melt curve is called positive. If the software determines that the Tm of the curve is not in the appropriate Tm range, the melt curve is called negative.

Analysis of replicates. Once positive melt curves have been identified, the software evaluates the replicates for each assay to determine the assay result. For an assay to be called positive, two associated melt curves must be called positive and both Tms must be similar. Assays that do not meet these criteria are called negative.

Analysis of assay results for bacteria. The assays in the BioFire Pneumonia Panel for detection of bacteria that are reported semi-quantitatively are designed to amplify genes that are present in single copies within the chromosome of the target bacterium and are used to estimate genomic copies of bacterial nucleic acid per milliliter (copies/mL) of specimen. The BioFire Software calculates an approximate value for each gene target based on real-time PCR amplification data relative to the QSM (internal reference of known quantity). Assays with no measurable amplification or a value below 10^3.5 copies/mL are called negative. Assays with a value equal to or greater than 10^3.5 copies/mL are called positive.

Organism and Antimicrobial Resistance Gene Interpretation

Each positive and negative assay result is interpreted by the BioFire Software to provide results for the identification of specific bacteria, atypical bacteria, viruses, and antimicrobial resistance (AMR) genes as shown in Table 3. For most analytes detected by the BioFire Pneumonia Panel, interpretations are based on the result of a single assay. However, results for *Staphylococcus aureus*, Adenovirus, and the AMR genes require interpretation based on more than one assay result, as discussed in the relevant sections below.

Table 3. Analytes Detected by the BioFire® FilmArray® Pneumonia Panel

Bacteria		
Acinetobacter calcoaceticus-baumannii complex	Klebsiella oxytoca	Serratia marcescens
Enterobacter cloacae complex	Klebsiella pneumoniae group	Staphylococcus aureus
Escherichia coli	Moraxella catarrhalis	Streptococcus agalactiae
Haemophilus influenzae	Proteus spp.	Streptococcus pneumoniae
Klebsiella aerogenes	Pseudomonas aeruginosa	Streptococcus pyogenes
Atypical Bacteria		
Chlamydia pneumoniae	Legionella pneumophila	Mycoplasma pneumoniae
Viruses		
Adenovirus	Human Rhinovirus/Enterovirus	Parainfluenza Virus
Coronavirus	Influenza A	Respiratory Syncytial Virus
Human Metapneumovirus	Influenza B	
Antimicrobial Resistance Genes		
CTX-M	NDM	*mecA*/*C* and MREJ
IMP	OXA-48-like	
KPC	VIM	

Interpretations and Semi-quantitative Bin Results for Bacteria

The BioFire Pneumonia Panel provides a Detected or Not Detected result as well as a semi-quantitative bin result (10^4 copies/mL, 10^5 copies/mL, 10^6 copies/mL, or ≥10^7 copies/mL) for most bacteria. The bin result represents the approximate number of specific bacterial genomes in the specimen and is intended to provide a simple assessment of relative abundance of nucleic acid from different bacteria in a lower respiratory specimen based on a molecular method. For bacteria, negative assays (no measurable amplification or value less than 10^3.5 copies/mL) are reported as Not Detected. Positive assays are reported as Detected and a bin result is assigned based on the assay value. Each bin is defined by discrete upper and lower limits spanning a 1-log range of values (see Table 4) such that the bin result reflects the assay value within the nearest ±0.5-log.

Table 4. BioFire Pneumonia Panel Bin Results for Bacteria

Assay Result		**Reported Result and Bin Result**	
Negative OR	<10^3.5 copies/mL	Not Detected	
Positive AND	≥10^3.5 – <10^4.5 copies/mL	Detected	10^4 copies/mL
Positive AND	≥10^4.5 – <10^5.5 copies/mL	Detected	10^5 copies/mL
Positive AND	≥10^5.5 – <10^6.5 copies/mL	Detected	10^6 copies/mL
Positive AND	≥10^6.5 copies/mL	Detected	≥10^7 copies/mL

1.0 Staphylococcus aureus

The BioFire Pneumonia Panel pouch contains two different assays (Saureus1 and Saureus2) for the detection of *Staphylococcus aureus*. The BioFire® FilmArray® Software interprets each of these assays independently (as described above), and if one or a combination of the assays is positive, the result will be *Staphylococcus aureus* Detected with the appropriate bin result. If both assays are negative, the result will be *Staphylococcus aureus* Not Detected.

NOTE: Detection of bacterial nucleic acid may be indicative of colonizing or normal respiratory flora and may not indicate the causative agent of pneumonia. Semi-quantitative Bin (copies/mL) results generated by the BioFire® FilmArray® Pneumonia Panel are not equivalent to CFU/mL and do not consistently correlate with the quantity of bacterial analytes compared to CFU/mL. For specimens with multiple bacteria detected, the relative abundance of nucleic acid (copies/mL) may not correlate with the relative abundance of bacteria as determined by culture (CFU/mL). Clinical correlation is advised to determine significance of semi-quantitative Bin (copies/mL) for clinical management.

Interpretations for Atypical Bacteria and Viruses

Results for most atypical bacteria and viruses are reported as Detected or Not Detected based on an individual corresponding assay result. If the assay is positive the result will be Detected, and if the assay is negative, the result will be Not Detected. However, Adenovirus detection is reported based on the results of multiple assays, as described below.

2.0 Adenovirus

The BioFire Pneumonia Panel pouch contains three different assays (Adenovirus2, Adenovirus3, and Adenovirus7) for the detection of all species and serotypes of Adenovirus. The BioFire® FilmArray® Software interprets each of these assays independently (as described above) and the results are combined as a final result for the virus. If one or any combination of assays is positive, the result will be Adenovirus Detected. If all assays are negative, the result will be Adenovirus Not Detected.

Interpretations for Antimicrobial Resistance (AMR) Genes

Results for AMR genes are also reported qualitatively (Detected/Not Detected) based on corresponding assays, but only if an applicable bacterium (i.e. potential carriers of the AMR gene;

Table 5) is also detected (≥10^3.5 copies/mL) in the sample.
The results for each of the antimicrobial resistance genes will be listed as either:
Detected—when an applicable bacterium is detected AND the antimicrobial resistance gene assay(s) are positive.
Not Detected—when an applicable bacterium is detected AND the antimicrobial resistance gene assay(s) are negative.
N/A—when all applicable bacteria are Not Detected, regardless of the result for the antimicrobial resistance gene assay(s).

Table 5. Antimicrobial Resistance (AMR) Genes and Applicable Organisms

AMR Gene Result	**Applicable Bacteria**
mecA/C and MREJ	Staphylococcus aureus
CTX-M IMP KPC NDM VIM	Acinetobacter calcoaceticus-baumannii complex Enterobacter cloacae complex Escherichia coli Klebsiella aerogenes Klebsiella oxytoca Klebsiella pneumoniae group Proteus spp. Pseudomonas aeruginosa Serratia marcescens
OXA-48-like	Enterobacter cloacae complex Escherichia coli Klebsiella aerogenes Klebsiella oxytoca Klebsiella pneumoniae group Proteus spp. Serratia marcescens

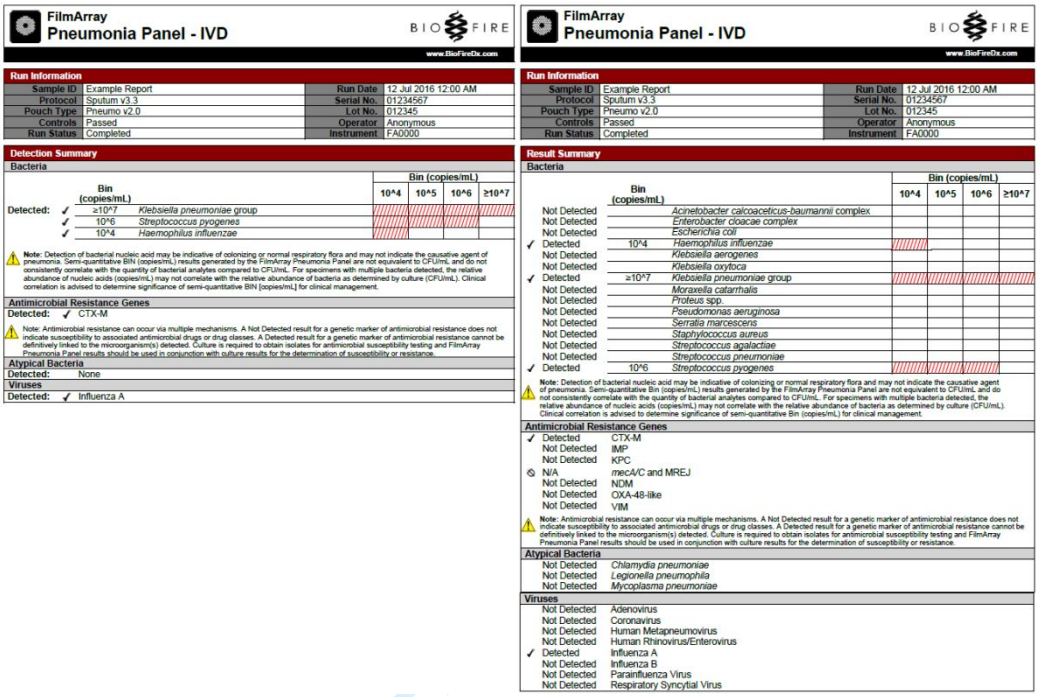
Each AMR gene result is associated with a single corresponding assay except for the *mecA/C* and MREJ result, which is dependent on both the *mecA/C* assay and the MREJ assay (see Table 6). Detection of both *Staphylococcus aureus* and the *mecA/C* and MREJ markers is indicative of methicillin resistant *Staphylococcus aureus* (MRSA).

Table 6. Possible Assay Results and Interpretation for mecA/C and MREJ

BioFire Pneumonia Panel Results		**Staphylococcus aureus**	***mecA/C* Assay**	**MREJ Assay**
Staphylococcus aureus *mecA/C* and MREJ	**Detected** **Detected**	Detected	Positive	Positive
Staphylococcus aureus *mecA/C* and MREJ	**Detected** **Not Detected**	Detected	Positive	Negative
Staphylococcus aureus *mecA/C* and MREJ	**Detected** **Not Detected**	Detected	Negative	Positive
Staphylococcus aureus *mecA/C* and MREJ	**Not Detected** **N/A**	Not Detected	Any Result	Any Result

NOTE: Antimicrobial resistance can occur via multiple mechanisms. A Not Detected result for a genetic marker of antimicrobial resistance does not indicate susceptibility to associated antimicrobial drugs or drug classes. A Detected result for a genetic marker of antimicrobial resistance cannot be definitively linked to the microorganism(s) detected. Culture is required to obtain isolates for antimicrobial susceptibility testing, and BioFire® FilmArray® Pneumonia Panel results should be used in conjunction with culture results for the determination of susceptibility or resistance.
BioFire Pneumonia Panel Test Report

The two-page BioFire® FilmArray® Pneumonia Panel report is displayed upon the completion of a run and contains three sections: Run Information, Detection Summary, and Result Summary. It can be saved as a PDF file and/or printed if desired.



FilmArray Pneumonia Panel - IVD — BIOFIRE — www.BioFireDx.com

Run Information

Sample ID	Example Report	Run Date	12 Jul 2016 12:00 AM
Protocol	Sputum v3.3	Serial No.	01234567
Pouch Type	Pneumo v2.0	Lot No.	012345
Controls	Passed	Operator	Anonymous
Run Status	Completed	Instrument	FA0000

Detection Summary

Bacteria

		Bin (copies/mL)	10^4	10^5	10^6	≥10^7
Detected:	✓	≥10^7 *Klebsiella pneumoniae* group				
	✓	10^6 *Streptococcus pyogenes*				
	✓	10^4 *Haemophilus influenzae*				

Note: Detection of bacterial nucleic acid may be indicative of colonizing or normal respiratory flora and may not indicate the causative agent of pneumonia. Semi-quantitative BIN (copies/mL) results generated by the FilmArray Pneumonia Panel are not equivalent to CFU/mL and do not consistently correlate with the quantity of bacterial analytes compared to CFU/mL. For specimens with multiple bacteria detected, the relative abundance of nucleic acids (copies/mL) may not correlate with the relative abundance of bacteria as determined by culture (CFU/mL). Clinical correlation is advised to determine significance of semi-quantitative BIN (copies/mL) for clinical management.

Antimicrobial Resistance Genes

Detected: ✓ CTX-M

Note: Antimicrobial resistance can occur via multiple mechanisms. A Not Detected result for a genetic marker of antimicrobial resistance does not indicate susceptibility to associated antimicrobial drugs or drug classes. A Detected result for a genetic marker of antimicrobial resistance cannot be definitively linked to the microorganism(s) detected. Culture is required to obtain isolates for antimicrobial susceptibility testing and FilmArray Pneumonia Panel results should be used in conjunction with culture results for the determination of susceptibility or resistance.

Atypical Bacteria

Detected: None

Viruses

Detected: ✓ Influenza A

Result Summary

Bacteria

		Bin (copies/mL)	10^4	10^5	10^6	≥10^7
Not Detected		*Acinetobacter calcoaceticus-baumannii* complex				
Not Detected		*Enterobacter cloacae complex*				
Not Detected		*Escherichia coli*				
✓ Detected		10^4 *Haemophilus influenzae*				
Not Detected		*Klebsiella aerogenes*				
Not Detected		*Klebsiella oxytoca*				
✓ Detected		≥10^7 *Klebsiella pneumoniae* group				
Not Detected		*Moraxella catarrhalis*				
Not Detected		*Proteus* spp.				
Not Detected		*Pseudomonas aeruginosa*				
Not Detected		*Serratia marcescens*				
Not Detected		*Staphylococcus aureus*				
Not Detected		*Streptococcus agalactiae*				
Not Detected		*Streptococcus pneumoniae*				
✓ Detected		10^6 *Streptococcus pyogenes*				

Note: Detection of bacterial nucleic acid may be indicative of colonizing or normal respiratory flora and may not indicate the causative agent of pneumonia. Semi-quantitative Bin (copies/mL) results generated by the FilmArray Pneumonia Panel are not equivalent to CFU/mL and do not consistently correlate with the quantity of bacterial analytes compared to CFU/mL. For specimens with multiple bacteria detected, the relative abundance of nucleic acids (copies/mL) may not correlate with the relative abundance of bacteria as determined by culture (CFU/mL). Clinical correlation is advised to determine significance of semi-quantitative Bin (copies/mL) for clinical management.

Antimicrobial Resistance Genes

✓ Detected	CTX-M
Not Detected	IMP
Not Detected	KPC
⊘ N/A	*mecA/C* and MREJ
Not Detected	NDM
Not Detected	OXA-48-like
Not Detected	VIM

Note: Antimicrobial resistance can occur via multiple mechanisms. A Not Detected result for a genetic marker of antimicrobial resistance does not indicate susceptibility to associated antimicrobial drugs or drug classes. A Detected result for a genetic marker of antimicrobial resistance cannot be definitively linked to the microorganism(s) detected. Culture is required to obtain isolates for antimicrobial susceptibility testing and FilmArray Pneumonia Panel results should be used in conjunction with culture results for the determination of susceptibility or resistance.

Atypical Bacteria

Not Detected	*Chlamydia pneumoniae*
Not Detected	*Legionella pneumophila*
Not Detected	*Mycoplasma pneumoniae*

Viruses

Not Detected	Adenovirus
Not Detected	Coronavirus
Not Detected	Human Metapneumovirus
Not Detected	Human Rhinovirus/Enterovirus
✓ Detected	Influenza A
Not Detected	Influenza B
Not Detected	Parainfluenza Virus
Not Detected	Respiratory Syncytial Virus

Run Information

The Run Information section is displayed at the top of both pages of the test report. It provides information about the sample and the run, including Sample ID, Protocol (sample type), pouch information (Pouch Type, Lot Number, and Serial number), run date, run status (completed, incomplete, aborted, instrument error, instrument communication error, or software error), the identity of the operator who performed the test, and the instrument used to perform the test. Control results are reported as Passed, Failed, or Invalid. Table 7 provides additional information for each of the possible control field results.

Table 7. Interpretation of Controls Field on the BioFire® FilmArray® Pneumonia Panel Test Report

3.0 Control Result	4.0 Explanation	5.0 Action
6.0 Passed	7.0 The run was successfully completed 8.0 AND 9.0 Both pouch controls were successful.	10.0 None. 11.0 Report the results provided on the test report.
12.0 Failed	13.0 The run was successfully completed 14.0 BUT 15.0 At least one of the pouch controls (RNA Process Control and/or QSM) failed.	16.0 Repeat the test using a new pouch. 17.0 If the error persists, contact Customer Technical Support for further instruction.

3.0	Control Result	4.0	Explanation	5.0	Action
18.0	Invalid	19.0	The controls are invalid because the run did not complete. (Typically, this indicates a software or hardware error).	20.0	Note any error codes displayed during the run and the Run Status field in the Run Information section of the report. Refer to the appropriate FilmArray Operator's Manual or contact Customer Technical Support for further instruction.
				21.0	Once the error is resolved, repeat the test or repeat the test using another instrument.

Detection Summary

The Detection Summary section is displayed on the first page of the report and lists the Detected results under each category (bacteria, antimicrobial resistance genes, atypical bacteria, and viruses), including the semi-quantitative "Bin (copies/mL)" results for bacteria. If there are no Detected results in a specific category, the result shown is Detected: None.

Results Summary

The Results Summary is displayed on the second page of the report and provides a full list of test results for each organism and antimicrobial resistance gene including the "Bin (copies/mL)" result for bacteria. Possible results for each organism are Detected, Not Detected, Invalid, and N/A.

Table 8 provides an explanation for each interpretation and any follow-up necessary to obtain a final result.

Table 8. Reporting of Results and Required Actions

Result	Explanation	Action
Detected	The run was successfully completed AND The pouch controls were successful (Passed) AND The assay(s) for the organism were POSITIVE.[a]	Report results.
Not Detected	The run was successfully completed AND The pouch controls were successful (Passed) AND The assay(s) for the organism were NEGATIVE.[b]	Report results.
Invalid	The pouch controls were not successful (Failed) OR The run was not successful. (Run Status displayed as: Aborted, Incomplete, Instrument Error, or Software Error.)	See Table 7 for instruction.
N/A (Antimicrobial Resistance Genes only)	The run was successfully completed AND The pouch controls were successful (Passed) AND The assay(s) for the organism(s) associated with the antimicrobial resistance gene were NEGATIVE so the results of the antimicrobial resistance gene are not applicable to the test results.	Report results.

[a] For bacteria, the organism calculated value must be greater than or equal to 10^3.5 copies/mL for the assay to be POSITIVE.

[b] For bacteria, a NEGATIVE assay result may indicate no amplification or amplification with an organism calculated value less than 10^3.5 copies/mL.

Change Summary

It is possible to edit the Sample ID once a run has completed. If this information has been changed, an additional section called **Change Summary** will be added to each page of the test report. This Change Summary section lists the field that was changed, the original entry, the revised entry, the operator that made the change, and the date that the change was made. Sample ID is the only field of the report that can be changed.

Change Summary				
Field	Changed To	Changed From	Operator	Date
[1]Sample ID	Positive_example_XYZ	Positive _example	Jane Doe (JD)	16 Sept 2017

References/Related Documents

BioFire® FilmArray® Pneumonia Panel Instruction Booklet (RFIT-PRT-0575), BioFire Diagnostics, LLC.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	PAGE 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	PAGE 1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	PAGE 2
	2b	Specific objectives or hypotheses	PAGE 3-4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	PAGE 4-6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	PAGE 8
Participants	4a	Eligibility criteria for participants	PAGE 5
	4b	Settings and locations where the data were collected	PAGE 4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	PAGE 4-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	PAGE 3 - 4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	PAGE 4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A PROTOCOL
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	PAGE 5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	PAGE 5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	PAGE 5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	PAGE 5

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	PAGE 6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	PAGE 6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	PAGE 6
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A PROTOCOL
Recruitment	14a	Dates defining the periods of recruitment and follow-up	PAGE 6-7
	14b	Why the trial ended or was stopped	N/A PROTOCOL
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A PROTOCOL
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A PROTOCOL
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A PROTOCOL
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A PROTOCOL
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A PROTCOL
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A PROTOCOL
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	PAGE 1-2
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	PROTOCOL
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	PROTOCOL
Other information			
Registration	23	Registration number and name of trial registry	PAGE 1
Protocol	24	Where the full trial protocol can be accessed, if available	THIS

			SUBMISSION
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	PAGE 1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

HAPFAST- A feasibility study incorporating qualitative, mechanistic and costing sub-studies alongside a randomised pilot trial comparing chest x-ray to low-dose CT scan and empirical antibiotics to antibiotics guided by the BIOFIRE® FILM ARRAY® pneumonia panel in adults with suspected non-ventilator acquired Hospital-acquired Pneumonia (nv-HAP)

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Primary Subject Heading:	Respiratory medicine

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Keywords:	Respiratory infections < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), Diagnostic microbiology < INFECTIOUS DISEASES, Diagnostic radiology < RADIOLOGY & IMAGING

Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scores as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

HAPFAST- A feasibility study incorporating qualitative, mechanistic and costing sub-studies alongside a randomised pilot trial comparing chest x-ray to low-dose CT scan and empirical antibiotics to antibiotics guided by the BIOFIRE® FILM ARRAY® pneumonia panel in adults with suspected non-ventilator acquired Hospital-acquired Pneumonia (nv-HAP)

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ABSTRACT

Introduction

Non-ventilator associated Hospital-acquired Pneumonia (nv-HAP) is the most common health care associated infection (HCAI), has high associated mortality and morbidity and places a major burden on healthcare systems. Diagnosis currently relies on chest x-rays to confirm pneumonia and sputum cultures to determine the microbiological cause. This approach leads to over-diagnosis of pneumonia, rarely identifies a causative pathogen and perpetuates unnecessary and imprecise antibiotic use. The HAP-FAST study aims to evaluate the feasibility of a randomised trial to evaluate the clinical impact of low dose, non-contrast enhanced thoracic CT scans (CT) and rapid molecular sputum analysis using the BIOFIRE® FILMARRAY® pneumonia panel plus (FAPP) for patients suspected of nv-HAP.

Methods & Analysis

The HAP-FAST feasibility study consists of a pilot randomised trial, a qualitative study, a costing analysis, and exploratory analyses of clinical samples to investigate the immune-pathophysiology of HAP. Participants are identified and recruited from 4 acute hospitals in the Northwest of the UK. Using a Research Without Prior Consent (RWPC) model, the pilot trial will recruit 220 adult participants, with or without mental capacity, and with suspected HAP. HAP-FAST is a non-blinded, sequential, multiple assignment, randomised trial (SMART) with two possible stages of randomisation: firstly, chest x-ray (CXR) or CT; secondly, if treated as nv-HAP, FAPP or standard microbiological processing alone (no FAPP). Pathogen-specific antibiotic guidance will be provided for FAPP results. Randomisation uses a web-based platform and follow-up is for 90 days. The feasibility of a future trial will be determined by assessing trial processes, outcome measures, and patient and staff experiences.

Ethics & Dissemination

This study has undergone combined review by the UK NHS Research Ethics Committee (REC) and Health Research Authority. Results will be disseminated via peer-reviewed journals, via the funders website and through a range of media to engage the public.

Trial registration number (Clinical Trials Gov): NCT05483309
Protocol date and version: V3.0 14/11/2023
Study Funding: UK National Institute for Health and Care Research NIHR300669
Study Sponsor: The University of Liverpool UoL001676
Trial Management, Monitoring & Analysis: Liverpool Clinical Trials Centre (LCTC)

ARTICLE SUMMARY:

Strengths & Limitations of the Study

- Decentralised, clinician-led randomisation facilitates continual recruitment on all wards of participating hospitals, improving the representativeness of the study population, and providing insights into recruitment patterns for future trial.
- Low rates of self-expectorated sputum sample submission may mean study will provide limited assessment of use of FAPP platform.
- Qualitative sub-studies into participant, carer and healthcare worked experiences of the trial will inform a future trial fully powered for clinical endpoints.

INTRODUCTION:

Non-ventilator associated Hospital-acquired Pneumonia (nv-HAP) is the most common healthcare associated infection (HCAI).[1] UK in-patient mortality following nv-HAP is 24% and it extends length of hospital stay by, on average, 9 days.[2,3] Among those who survive to discharge, compared to other HCAIs, nv-HAP has the highest level of disability adjusted life years (DALYs) (ref). Nv-HAP therefore represents a major risk for patients and places a huge burden on healthcare systems.

Diagnostic Uncertainty in nv-HAP

Pneumonia is a syndrome that is diagnosed based on a case definition with three components: signs and symptoms of a lower respiratory tract infection, evidence of a systemic inflammatory response and radiological change compatible with infection on chest imaging.[4] Defining the specific aetiological cause requires microbiological tests. Traditional diagnostic methods, relying on chest x-rays for syndromic diagnosis of nv-HAP and sputum cultures for microbiological diagnosis of cause, often lead to over-diagnosis, delayed treatment decisions and inappropriate antibiotic use.[5,6] Together these diagnostic inadequacies contribute to poor clinical outcomes, and the UK National Institute for Health and Care Excellence (NICE) have called for a research focus on diagnostics.[7]

Addressing this evidence gap, the HAP-FAST study aims to evaluate the use of low dose, non-contrast enhanced CT scans as an alternative to chest x-rays, and the BIOFIRE® FILMARRAY® Pneumonia Panel Plus (FAPP) as an alternative to standard microbiological testing, both individually and in combination in patients suspected of nv-HAP.

Rationale for Chosen Diagnostics in this Study

CT scans in nv-HAP

Chest x-rays (CXR) have limitations when diagnosing pneumonia.[8-13] Using a CT scan as the gold standard, CXR had a positive predictive value of 27% in 3423 US patients with possible Community acquired Pneumonia (CAP).[10] Claessens et al demonstrated that performing a CT after a CXR in suspected CAP might avoid antibiotics in 14%.[11] The diagnostic inaccuracy of CXR is further exacerbated in bedridden patients, as is often the case in nv-HAP, with CT scan reports changing management plans based on CXR diagnosis in nearly half of patients.[13] Prendki et al found that using a CT scan instead of a CXR avoided antibiotic use in 8.5% of elderly Swiss patients with suspected pneumonia.[9] These non-randomised, observational studies are prone to bias and we need a randomised controlled trial to demonstrate the impact of CT scans on clinical outcomes following nv-HAP.

Rapid Microbiological Testing in nv-HAP

Empirical antibiotic treatment of nv-HAP is imprecise and hampered by conflicting evidence about the potential pathogens. A Spanish study demonstrated 60% of bacterial detections were Gram-positive and a retrospective Scottish study found 71% were Gram-negative.[14,15] Neither study tested for viruses but subsequent studies have detected viruses in up to 22% of patients with HAP.[16,17] Clinical guidelines often extrapolate recommendations from literature about ventilator associated pneumonia (VAP), but a comparative study suggests this comparison is invalid.[18] Most recently, the INHALE research group compared two rapid molecular diagnostic tests to conventional microbiological testing of respiratory samples from patients with pneumonia on critical care. They reported superior sensitivity for pathogen detection for the new rapid tests when compared to conventional methods and viruses were implicated in a significant proportion of cases.[19]

The BIOFIRE® FILMARRAY® Pneumonia Panel (FAPP) is a CE marked, United States Food and Drug Administration (FDA) approved point-of-care test that can simultaneously detect 18 bacteria, 9

viruses and 7 antimicrobial resistance genes from a respiratory sample in 75 minutes.[19] Compared to the traditional culture based methods, the speed, sensitivity and specificity of this diagnostic test has the potential to dramatically change the way nv-HAP is managed. However, before it is widely implemented, questions relating to the interpretation of results and cost-effectiveness within the NHS setting need to be addressed.[20] There are also key questions relating to: the implementation of decentralised microbiology results within the clinical work flow, the feasibility of maximising time gains using the FAPP, the safety and effectiveness of antibiotic rationalisation based on results and the willingness of clinicians to deviate from traditional paradigms of empirical management.

Risks and benefits

In usual care, thoracic CT scans of various types are performed at some point during the care pathway for approximately 12% of patients managed for nv-HAP. Here we will trial the systematic use of low dose, non-contrast, thoracic CT scans (CT) as the first test in those suspected of nv-HAP because there is evidence this may lead to improved patient outcomes.[11] The CT scan used in HAP-FAST carries a radiation exposure of, on average, 1.5mSv, which is greater than a CXR (0.05 mSv) but lower than annual UK background radiation exposure of 2.7mSv.[13] A recognised consequence of performing a thoracic CT scan at any point in a patient's acute care is the detection of unexpected abnormalities such as anatomical variants, alternative diagnoses for the presenting symptoms and incidental findings such as pulmonary nodules. Given the frequency of detection of pulmonary nodules in routine care, there are well established pathways for their investigation and follow-up supported by national guidelines.[21,22]

Patients who can self-expectorate sputum will be randomised to either a standard microbiological diagnostic pathway (No FAPP) with initial empirical antibiotic selection as per their local policy – or to analyse sputum using the FAPP. Clinicians are provided with an antibiotic guide with pathogen targeted treatment options for those randomised to use the FAPP. It is possible that based on either empirical antibiotic prescribing or FAPP guided treatment, a participant may receive antibiotics that are not effective against an undetected pathogen. This risk is always present due to the imperfect nature of microbiological tests and so it is standard clinical practice for patients to be closely monitored for response to treatment during the early stages of pneumonia and this study protocol allows for the clinicians treating the participant to escalate or change their therapy as clinically indicated.

AIMS AND OBJECTIVES

The study aim is to determine the feasibility of a full-scale randomised controlled trial (RCT) comparing different diagnostic pathways in adult patients suspected of nv-HAP.

The following HAP-FAST objectives will assess feasibility parameters:

1. For each intervention, estimate effect size and dispersion for a range of possible outcomes to inform the sample size of a definitive study.
2. Evaluate the practicality and fidelity of a range of possible outcome measures using completion rates, missing data, effect size and dispersion.
3. To estimate eligibility, recruitment, and consent rates.
4. Estimate rates of successful follow up.
5. Assess the web-based randomisation process and incorporate clinical and researcher feedback.
6. Perform a costing analysis of nv-HAP to inform the cost-effectiveness analysis for any definitive study.
7. Assess human factors involved in delivery of the study and how the different diagnostic tests influence clinical decision making by conducting qualitative interviews and focus groups with healthcare workers and researchers.

8. Evaluate willingness of clinicians to recruit to the study.
9. Evaluate willingness of potential participants or their consultees to be recruited.
10. Evaluate adherence to antibiotic guidelines as outlined in the study protocol.
11. Assess the study participant and carer experience of participating in the study via qualitative interviews.

METHODS AND ANALYSIS

Study Setting

Participants are identified and recruited from 4 acute hospitals in the Northwest of the UK: Aintree University Hospital, Royal Liverpool University Hospital, Royal Preston Hospital and Wythenshawe Hospital. Sites were selected to capture ethnic and socioeconomic diversity. Preliminary data from a longitudinal HAP improvement programme demonstrated a sufficiently large caseload potential participants in these settings within the study's timeframe.[23]

Study Design

HAP-FAST is a feasibility study consisting of a pilot study, two qualitative studies, and a costing analysis. The study participants will also provide clinical samples to support exploratory analyses of the immune-pathophysiology of nv-HAP. The start date of the trial (1st site) was on 07/06/2023 and the final date of follow-up will be 10/06/2024.

Pilot Study

Participants and Sample Size

Since the aim is to assess feasibility, a sample size justification is given rather than a calculation. We aim to recruit 220 adult participants, based on prospective audits of HAP in the UK Northwest revealing between 600 and 1000 cases per year across our recruiting sites and assuming 30% of cases are eligible of whom 40% are recruited to the trial. Recruitment targets will likely be affected by the seasonality of HAP, with a greater burden in winter and seasonal variation in pathogens and thus we aim to recruit across the majority of a calendar year.

Pilot Study Consent & Assent

HAP is potentially severe as evidenced by the in-patient mortality of 24%. NICE recommend treatment is commenced within 4 hours. Clinicians therefore face a narrow timeframe during which patients must be clinically assessed and diagnostic tests must be ordered, completed, reported, interpreted and acted upon. Patients with nv-HAP frequently have impaired mental capacity due to underlying cognitive impairment or acute delirium. Therefore, due to the emergency nature of HAP, in common with research in other emergency settings such as trauma and intensive care, HAP-FAST uses a Research Without Prior Consent (RWPC) model.[24-26] The use of RWPC for nv-HAP trials has been studied previously and deemed acceptable by patients and the public.[26]
At the point of suspecting nv-HAP, treating clinicians at the recruiting sites can randomise, carry out the interventions and obtain the initial sample set. Randomisation leads to an automatic email alerting the site research team who then obtain written informed consent from the patient or for those lacking capacity from a personal or professional proxy before discharge. Every effort will be made to obtain written informed consent after discharge if a patient is discharged before consent is obtained. Patients who decline to provide consent or no longer wish to continue in the study will be withdrawn. Data collected up to the point of withdrawal will be included in the analysis and permission will be sought to collect data from routine assessments to complete some outcome data.

Pilot Study Eligibility Criteria

Eligibility criteria for Stage 1 randomisation to CXR vs CT and Stage 2 randomisation to FAPP or no FAPP can be seen in **Table 1**. Patients who are ineligible for randomisation to Stage 2 will still be able to participate in the trial.

Table 1: Inclusion and Exclusion Criteria for Stage 1 and 2 Randomisation

	Stage 1 CXR vs CT	Stage 2 FAPP vs No FAPP (standard laboratory sputum analysis)
Inclusion Criteria	Age ≥18 years	The clinician intends to treat the patient for HAP, or a hospital acquired respiratory tract infection (RTI)
	Suspected HAP (For the purposes of this study, HAP is defined as per the BTS and FDA definitions i.e. pneumonia which develops 48 hours after an admission to hospital for an alternative diagnosis; or a new presentation to hospital with pneumonia in a patient who has been discharged from an overnight stay in hospital within the last 10 days)	A sputum sample has been obtained before 2nd dose of antibiotic
Exclusion Criteria	Already received a chest X-ray to confirm suspected HAP diagnosis	Following the CXR or CT the clinician decides not to treat with antibiotics for either HAP or a hospital acquired RTI
	Diagnosis or suspected diagnosis of ventilator acquired pneumonia	
	Intention to palliate rather than cure	
	Interventions cannot be completed before administration of second antibiotic dose *	
	Cannot be randomised to low-dose, non-contrast CT scan on clinical grounds e.g. strong suspicion of PE (A non-contrast, low-dose thoracic CT scan is an inappropriate test for a PE and if that is high in the differential diagnosis then tick yes here)	
	Pregnancy (A urine pregnancy test is required as part of routine care prior to a chest X-ray or CT scan. If the test reveals the patient is pregnant, they will not be eligible for the study)	
	Previous study participation (patients with second of third episodes of HAP will not be re-recruited)	

* In the circumstance where a patient is diagnosed with HAP whist receiving antibiotics for a non-respiratory infection (e.g. UTI) if the HAP diagnosis leads to a change in the antibiotic prescription to cover the HAP, then that patient will be eligible for recruitment. However, if the diagnosis of HAP does not result in a change in antibiotic, then the patient **is not eligible**.

Interventions and Treatments

Participants are initially randomised between a standard-care chest X-ray (CXR) and low-dose, non-contrast, thoracic CT scan (CT). If the clinician decides to give antibiotics to treat nv-HAP and the participant can produce a sputum sample prior to the administration of the second dose of antibiotics, they are further randomised between sputum testing by FAPP alongside local, standard of care microbiological processing or standard processing alone - no FAPP. A study specific antibiotic guideline has been produced and approved by all recruiting sites for use with the results of the FAPP. It is anticipated that patients randomised to standard microbiological testing will receive an

empirical antibiotic prescription supported by usual microbiological tests. Additional advice regarding antibiotic treatment is available from microbiology specialists in line with local policies. Participants who cannot provide sputum and who are not randomised at Stage 2 will be managed as per usual care. These interventions are summarised in **Table 2** and **Figure 1**.

Table 2: Treatment Pathways in Pilot study

Result of Stage 1 Randomisation	Result of Imaging	Sputum Available?	Result of Stage 2 Randomisation	Treatment	Group
CXR	Clinician decides to treat for HAP / hospital acquired RTI	YES	FAPP	• Use an aliquot of respiratory specimen in the FAPP • Send remainder of specimen to microbiology for standard tests • Prescribe antibiotics with reference to the FAPP antibiotic guideline	1
		YES	No FAPP	• Prescribe empirical antibiotics based on local guidelines	2
		NO	N/A	• Prescribe empirical antibiotics based on local guidelines	3
	Clinical diagnosis is **not** HAP / RTI	N/A	N/A	• Patient receives usual care and is followed up as per the study schedule	4
CT Scan*	Clinician decides to treat for HAP/ hospital acquired RTI	YES	FAPP	• Use an aliquot of respiratory specimen in the FAPP • Send remainder of specimen to microbiology for standard tests • Prescribe antibiotics with reference to the FAPP antibiotic guideline	5
		YES	No FAPP	• Prescribe empirical antibiotics based on local guidelines	6
		NO	N/A	• Prescribe empirical antibiotics based on local guidelines	7
	Clinical diagnosis is **not** HAP / RTI	N/A	N/A	• Patient receives usual care and is followed up as per the study schedule	8

Outcome measures

A key objective of HAP-FAST is to gather data to inform the choice of outcome measure for a fully powered RCT. We searched the COMET database for core outcome sets in HAP trials.[27] Some groups advocate all-cause mortality assessed on a non-inferiority basis.[28] However, others argue discerning the mortality attributable to HAP, as opposed to underlying comorbidity, is difficult without

unfeasibly large trials.[29] One group proposed a hierarchical, composite, primary outcome of survival at day 28 and 'clinical cure' between days 7-10 but unfortunately did not provide a pragmatic definition of clinical cure.[30] A group convened by the FDA suggested using mortality plus resolution of symptoms.[31] HAP-FAST will therefore evaluate a range of outcomes including mortality, antibiotic usage and clinical cure incorporating a pneumonia specific Patient Reported Outcome Measure (PROM) called the CAP-SYM score.

Pilot Study Randomisation

The pilot study has been designed as a sequential, multiple assignment, randomised trial (SMART) with a 1:1 allocation ratio, with the purpose to address study objectives 1-5.[32] The randomisation list has been created by an independent statistician and participant allocations are generated by completion of the web-based randomization platform. The SMART study design is presented schematically in **Figure 1**.

Pilot Study Blinding

The study is open-label and treating clinicians, researchers and participants will know which intervention is being administered via the web-based randomisation process.

Pilot Study Outcome Measures & Participant Timeline

Baseline, and outcome data are collected at distinct time points according to the schedule in **Tables 3 and 4.** Participants will be assessed by the study team daily until day 10 to track symptomatic recovery, changes in Quality of Life (QOL) and determine time to clinical cure. Participants will have symptoms and QOL assessed on day 28 as an in or out-patient. Follow up will be conducted as a phone call 90 days (+/- 14 days) following entry into the study to assess symptoms, QOL and to remind them to return a survey booklet on health and social care use up to day 90.

Pilot Study Data Analysis

All analyses will be carried out on an intention to treat basis, retaining all participants in their initially randomised groups irrespective of any protocol deviations. The focus of analysis will be to assess feasibility and recruitment for each participating site and overall pilot study as well as assessments of efficacy for each outcome for treatment arm comparisons of CXR vs CT (**Figure 1**- group 1-4 vs group 5-8) and FAPP vs No FAPP (**Figure 1**- group 1+ 5 vs group 2 and 6). No inference will be drawn – all results will be treated as hypothesis generating.

Continuous data will be presented using median (interquartile range) and mean (standard deviation) as appropriate, with boxplots summarising measurements at each time-point by treatment group. Categorical data will be presented as frequencies and percentages. Time-to-event data will be presented with Kaplan-Meier curves and summarised by median (95% confidence interval) if possible.

As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis. Such methods will be fully described in the full statistical analysis plan, which will be written prior to the conduct of any comparative analysis of the treatment arms, including methods employed for missing data.

Qualitative Sub-Studies

Clinicians

This qualitative sub-study will address objectives 5,7,8 and 10 to evaluate the human factors involved in the delivery of the study, clinician willingness to recruit participants and adherence to antibiotic guidelines as per study protocol (**Table 3**).[26,33] A range of clinical, allied health professional and research staff will be invited to participate in focus groups of approximately 8 participants. Focus groups will be topic guided, yet conversational and exploratory and conducted in a comfortable private environment.

Patients and Carers

This qualitative sub-study will address objectives 9 and 11 to evaluate patient willingness to participate in the study and their experience from recruitment to study-follow-up (**Table 3**).[34] Approximately 15 participants (5 from each of the three recruiting Trusts) will be purposively recruited for in-depth semi-structured interviews based on age, gender, and underlying comorbidity class (medical admission, surgical admission, acute admission). Relatives and carers of some study participants will also be interviewed.

Table 3: Schedule for Recording of Data Outcomes

Objective		
Primary Objective		
The primary objective is to determine the feasibility of a full-scale Randomised Controlled Trial (RCT) comparing different diagnostic dynamic treatment regimens (DTRs) in adult patients suspected of HAP.		
Secondary Objective		
Objective	Outcome	Time-point
Inform the sample size of a definitive study	Time to clinical cure*	Day 90
	Antibiotic usage for the HAP episode	Day 90
	EQ-5D-5L	Baseline, day 10, 28 and 90
	Length of hospital stay post HAP diagnosis	Day 90
	Mortality	Day 14, 28 and 90
To measure key outcome measures (completion rates, missing data, estimates and dispersion)	Estimate rates of completion of questionnaires - EQ5D5L, CAP-sym, economic evaluation Summary statistics and proportion of missing data for time to clinical care, antibiotic usage for HAP diagnosis, EQ-5D-5L, length of hospital stay post HAP diagnosis, mortality	Screening Randomisation Follow up End of Treatment End of Study
To estimate eligibility, recruitment and consent rates	Rate of recruitment; Proportion screened that meet eligibility criteria; ** Proportion eligible that consent and where they present; ** Proportion consented and randomised that complete study pathway as per protocol; Proportion consented and randomised that withdraw from study intervention or follow up; **	Screening Randomisation Follow up End of Treatment End of Study
Estimate rates of successful follow up	Proportion consented and randomised that complete study pathway as per protocol; Proportion consented and randomised that withdraw from study intervention or follow up; **	End of Study
Assess the web-based randomisation process and incorporate clinical and researcher feedback	Qualitative conclusions based on staff focus groups	Qualitative analysis

Perform a costing analysis of HAP to inform the cost-effectiveness analysis for any definitive study	Summary statistics for numbers and types of costs with comparison between DTRs	End of Study
Assess human factors involved in delivery of the study and how the different diagnostic tests influence clinical decision making by conducting qualitative interviews and focus groups with healthcare workers and researchers	Qualitative conclusions based on staff focus groups	Qualitative analysis
Evaluate willingness of clinicians to recruit to the study	Qualitative conclusions based on staff focus groups	Qualitative analysis
Evaluate willingness of potential participants or their consultees to be recruited	Qualitative conclusions based on participant and carer interviews	Qualitative analysis
Evaluate adherence to antibiotic guidelines and study protocol	Summary statistics relating to antibiotic use in the pilot study with a comparison between the DTRs	End of Study
Assess the study participant and carer experience of participating in the study	Qualitative interviews	Qualitative analysis

Exploratory Sub-Study

Clinical samples are taken at enrolment to the pilot RCT, on day 3 and at day 28 and comprise venous blood, sputum and a nose swab and participants will be asked for additional consent for this sub-study. These samples will be used to explore the role immune cells and inflammatory mediators play in the pathophysiology of nv-HAP and how these vary with pathogen. The samples from the HAP-FAST pilot study cohort (patients suspected of HAP) will be compared with equivalent samples from patients who chronically produce sputum, are not exacerbating, and are being managed as out-patients in respiratory clinics. Specific consent questions will ask about retention of samples for future studies relating to pneumonia and for the sharing of samples with other non-commercial labs.

Health Economic Evaluation

This costing analysis will address objective 6 by capturing the direct costs in hospital associated with HAP as well as the post-discharge indirect costs with a bespoke questionnaire (up to 90 days following diagnosis). We will evaluate the performance of this questionnaire which we have developed with reference to a range of similar studies.[35-38] We will capture item completion rates, and discuss participant and carer's views of the questionnaire to refine it for the future full-scale RCT.

DATA COLLECTION & MANAGEMENT

Data Management

For the HAP-FAST study the responsibilities for Data Management, audit and monitoring are delegated to the Liverpool Clinical Trial Centre (LCTC). Data collection will be directly entered on to a secure, auditable, database as the source document and this includes validation features to alert the user of inconsistent or missing data. Data of written informed consent processes and participation in the clinical trial will be added to the patient's medical record chronologically.

Baseline assessment data will be obtained from patient medical notes, followed by use of the CAP-SYM questionnaire,[39] EQ-5D-5L questionnaire, research sample collection (for exploratory sub-study), monitoring of blood test results, and a post-discharge indirect cost survey as shown in **Table 4/supplementary file**. Separate Data Management and Trial Monitoring Plans will detail the internal processes that will be conducted at the LCTC throughout the study in line with regulatory, ethical, and legal obligations.

Confidentiality

This study will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used, and stored if necessary for the study (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

MONITORING

Trial Monitoring

Given this study is designed to evaluate feasibility rather that safety or efficacy there is no on-site monitoring planned. LCTC will however be monitoring CRF completion, making consent checks and monitoring adherence. The Trial Management Group (TMG), including investigators, Patient and Public Involvement (PPI) representatives and LCTC members, will meet regularly to discuss the day-to-day conduct, management and progression of the study and troubleshoot issues such as adherence. The Trial Steering Committee (TSC) consists of an independent lay chairperson, 2 independent experts in the field, an independent biostatistician, the chief investigator, and a second PPI representative to provide overall supervision of the study.

Patient and Public involvement (PPI)

Patient and Public representatives will be consulted throughout the duration of the study by acting as members of the TMG and TSC.

ETHICS & DISSEMINATION

Research Ethics Approval

The study will be conducted in accordance with Good Clinical Practice (GCP) and will abide by the principles of the World Medical Association Declaration of Helsinki. The protocol, patient information sheet and all proposed public-facing material was prepared along with our PPI team members and has undergone combined review by the UK NHS Research Ethics Committee (REC) and Health Research Authority (22/WA/0315). The committee was specifically configured to assess studies recruiting patients who lack capacity and reviewed Medical Physics Expert and Clinical Radiation Expert reports conducted in compliance with Ionising Radiation (Medical Exposure) Regulations (IRMER) legislation.

Protocol Amendments

This publication has been based on version 3.0 of the protocol (supplementary file). Version 1.0 was submitted to the REC, resulting in amendments and use of Version 2.0 from the start of the trial. Further amendments, to improve clarity, were approved in October 2023 to: the eligibility criteria (clarifying 'the development of Pneumonia within 10 days of discharge' as a component of the

definition of HAP and removing a fixed time-period requirement for stage 2 randomisation) patient information sheets (including format and hypostatical changes, additional consent statements for use of clinical samples, provision of a letter to deceased participant's next of kin), consent processes (allowing verbal consent for the qualitative study, allowing postal consent for patients discharged before written informed consent obtained), study processes (removal of requirement for the statistical team to be blinded to participant allocation, adding a 7-day window for day 28 follow-up and reducing frequency of collection of concomitant medication in the schedule of activities).

Protocol Deviations

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions, or principles of GCP and REC requirements are handled based on their nature and severity by LCTC and reported to the trial oversight committees with serious breaches being reported to Sponsor and REC within 7 days.

Dissemination

The findings of HAP-FAST will be published and disseminated within scientific and lay communities regardless of the magnitude or direction of effect.

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AUTHOR'S CONTRIBUTIONS

DW wrote the grant and obtained the funding and is the Chief Investigator of the HAP-FAST trial and associated sub-studies. SA, LT, SJA, BY, FS, AA, SW, AJ and DW wrote and amended this trial protocol. AH, SA, NS and DW wrote the trial antibiotic guideline. LT, SA and DW led the writing of the mechanistic sub-study components, BY, FS and DW led the writing of the qualitative sub-study components. AA contributed a patient and public involvement perspective throughout the protocol drafting and approval process and chairs the HAP-FAST steering committee. SW and AJ are, respectively, trial manager and lead statistician for Liverpool Clinical Trial Centre (LCTC) and contributed to the protocol development and ongoing trial processes. SJA is site Principal Investigator at one of the recruiting sites. NS is NIHR Associate Principal Investigator at one of the sites and drafted this protocol submission and all other authors reviewed and edited this manuscript.

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This work was supported by the National Institute of Health Research (NIHR300669)

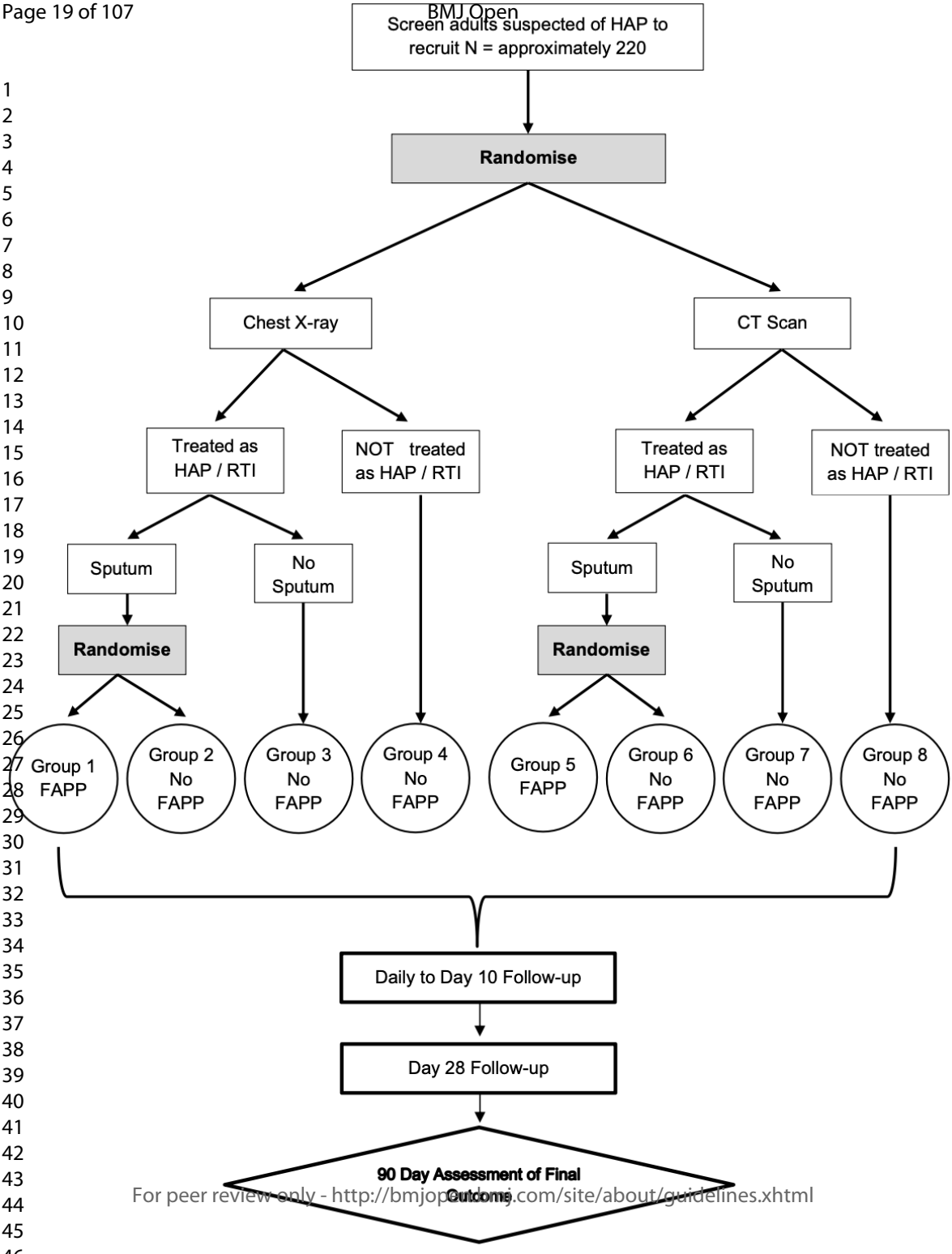
COMPETING INTERESTS STATEMENT

The BIOFIRE® FILM ARRAY® machines for each study site were loaned, free of charge by bioMérieux. FAPP test kits for running on those machines were also provided by bioMérieux. bioMérieux had no role in the content of the funding application, protocol, ethics application for this work nor will they have a role in handling or interpretation of the data or its dissemination.

LT has received consulting fees from MHRA; and from AstraZeneca and Synairgen, paid to the University of Liverpool; speakers' fees from Eisai Ltd, and support for conference attendance from AstraZeneca. AH has received personal consulting fees from Pfizer, and funding from Pfizer paid to the University of Liverpool for a public/practitioner engagement project.

FIGURE LEGEND

Figure 1: Pilot sequential multiple assignment randomised trial (SMART) design



Feasibility study of the clinical and cost-effectiveness of contemporary diagnostics for patients with suspected Hospital-Acquired Pneumonia (HAP).

HAP-FAST Protocol
V3.0, 14/11/2023

Study Sponsor(s):
The University of Liverpool, Clinical Directorate
Thompson Yates Building
The Quadrangle, Brownlow Hill,
Liverpool
L3 5RB

Research Ethics Ref: 22/WA/0315

Sponsor Ref: UoL001676

Funder Ref: NIHR300669

ClinicalTrials.gov: NCT05483309

Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: _____ **Date:** _____

Dr Daniel Wootton
Senior Clinical Lecturer

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of Sponsor:

Signature: _____ **Date:** _____

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of the Lead Statistician:

Signature: _____ **Date:** _____

Dr Ashley Jones
Head of Statistics, Liverpool Clinical Trials Centre

General Information

This document describes the HAP-FAST study including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the study, but sites entering participants for the first time are advised to contact the coordinating centre, Liverpool Clinical Trials Centre, to confirm they have the most up to date version. Clinical problems relating to this study should be referred to the relevant Chief Investigator, Dr Daniel Wootton, via the LCTC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 15.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

Contact Details: Institutions

Sponsor:	**Trial Management, Monitoring and Analysis:**	**Statistics:**
The University of Liverpool, Clinical Directorate, Thompson Yates Building The Quadrangle, Brownlow Hill, Liverpool, L3 5RB Tel: 00 44 (0) 7717 863747 Email: sponsor@liverpool.ac.uk	Liverpool Clinical Trials Centre, 1st Floor, Block C, Waterhouse Building, 1-3 Brownlow Street, University of Liverpool, L69 3GL Telephone Number: 0151 794 9766 E-mail: hapfast@liverpool.ac.uk	Liverpool Clinical Trials Centre, 1st Floor Block C, Waterhouse Building, 1-3 Brownlow Street, University of Liverpool, L69 3GL E-mail: hapfast@liverpool.ac.uk
Dr Daniel Wootton, MRCP, DTM+H, PhD, Clinical Immunology, Microbiology and Immunology, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, 8 West Derby Street, Liverpool, L69 7BE Telephone: 0151 529 3796 E-mail: dwootton@liverpool.ac.uk		

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	
Karen Wilding, Senior Clinical Research Governance Manager, The University of Liverpool, Clinical Directorate, Thompson Yates Building, The Quadrangle, Brownlow Hill, Liverpool, L3 5RB Tel: 00 44 (0) 7717 863747 Email: sponsor@liverpool.ac.uk	Dr Daniel Wootton, MRCP, DTM+H, PhD, Clinical Immunology Microbiology and Immunology, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, 8 West Derby Street, Liverpool, L69 7BE Telephone: 0151 529 3796 E-mail: dwootton@liverpool.ac.uk	

In cases where the CI is unavailable to respond to urgent queries the following individual/s will act as cover:

Medical Expert who will Advise on Protocol Related Clinical Queries:		
Dr Stephen Aston, MBChB, PhD, Senior Clinical Lecturer, University of Liverpool and Honorary Consultant in Infectious Diseases, Liverpool University Hospitals NHS Foundation Trust Email: Saston@liverpool.ac.uk		

Additional Contacts:

The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File.

1 Table of Contents

2 Glossary

AE	Adverse Event
CI	Chief Investigator
CXR	Chest X-Ray
eCRF	Electronic Case Report Form
DTR	Dynamic Treatment Regimens
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
FAPP	FILMARRAY® Pneumonia Panel
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Health Care Professional
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive Web Response System
LCTC	Liverpool Clinical Trials Centre
MA	Marketing Authorisation
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
NIMP	Non-Investigational Medicinal Product
NRES	National Research Ethics Service
PI	Principal Investigator
PSF	Pharmacy Site File
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSI	Reference Safety Information
RSO	Research Support Office
SAE	Serious Adverse Event
SDV	Source Data Verification
SMART	Sequential Multiple Assignment Randomised Trial
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

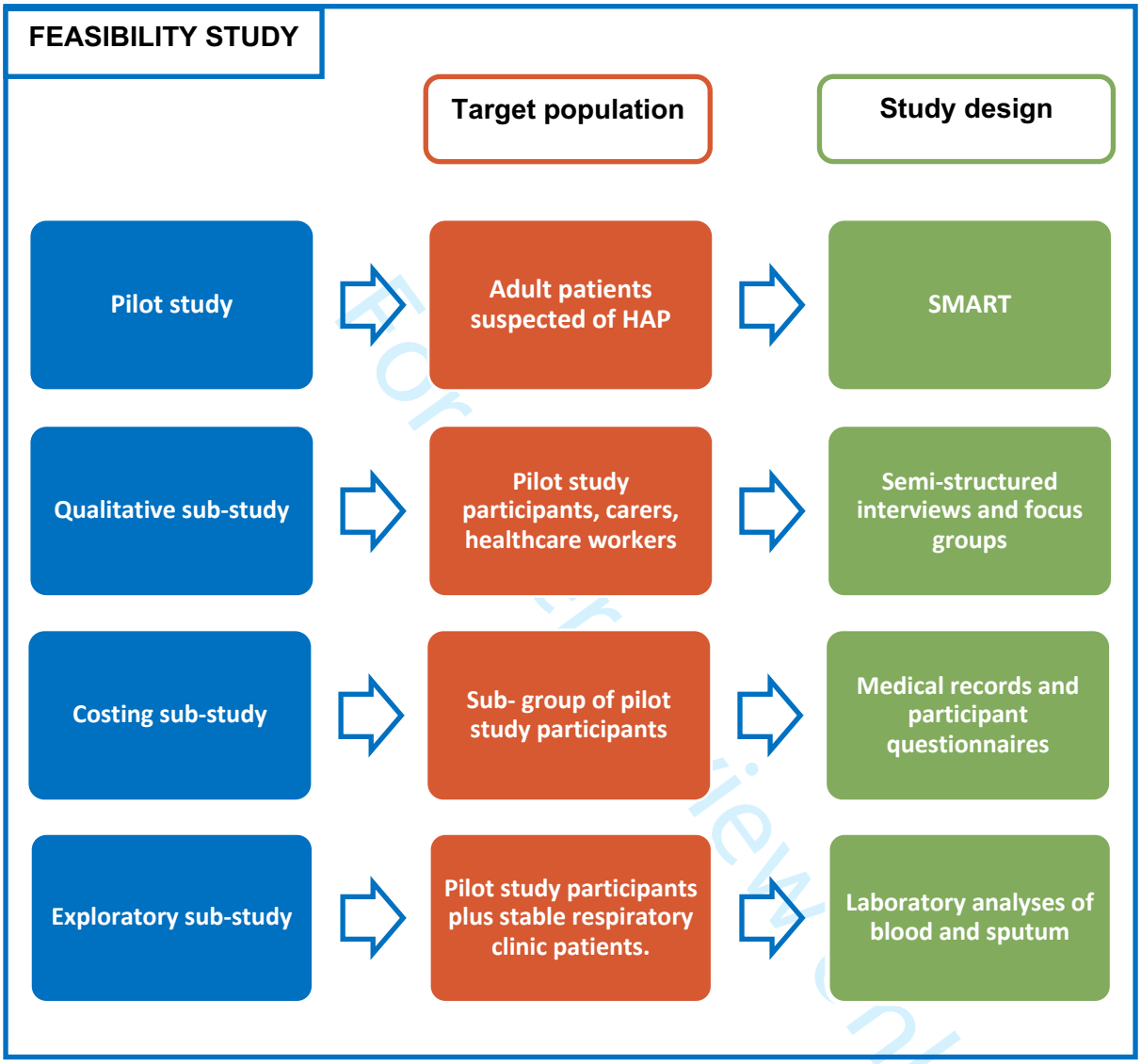
3 Protocol Overview

Full Title:	Feasibility study of the clinical and cost-effectiveness of contemporary diagnostics for patients with suspected Hospital-Acquired Pneumonia (HAP).
Acronym:	HAP-FAST
Phase:	Pilot Study
Target Population:	Adults suspected of HAP
Sample size:	• Pilot Sequential Multiple Assignment Randomised Trial (SMART) = approximately 220 participants from 3 Trusts • Qualitative sub-study = 30 (= 15 pilot participants, 6 carers of participants, plus 9 patients who decline participation). Approximately 30 members of staff for focus groups • Exploratory sub-study = participants from the pilot study and up to 50 participants from respiratory clinics in Liverpool
Inclusion Criteria:	For Pilot Study: Stage 1: • ≥ 18 years • Patients with suspected HAP Stage 2: • The clinician intends to treat the patient for HAP or a hospital acquired respiratory tract infection (RTI) • Sputum has been obtained before 2nd dose of antibiotic
Exclusion Criteria:	For Pilot Study: Stage 1: • Already received a chest X-ray (CXR) to confirm suspected HAP diagnosis • Diagnosis or suspected diagnosis of ventilator acquired pneumonia • Intention to palliate rather than cure • Interventions cannot be completed before administration of second antibiotic dose • Cannot have low-dose, non-contrast CT scan on clinical grounds e.g. strong suspicion of PE • Pregnancy • Previous study participation (patients with second or third episodes of HAP will not be re-recruited) Stage 2: • Following the CXR or CT the clinician decides not to treat with antibiotics for either HAP or a hospital acquired RTI
Study Centres and Distribution:	• Liverpool University Hospitals NHS Foundation Trust • Lancashire Teaching Hospitals NHS Foundation Trust • Manchester University NHS Foundation Trust
Participant Study Duration:	• 12 months of recruitment or until 220 participants are recruited, and 3 months of follow-up

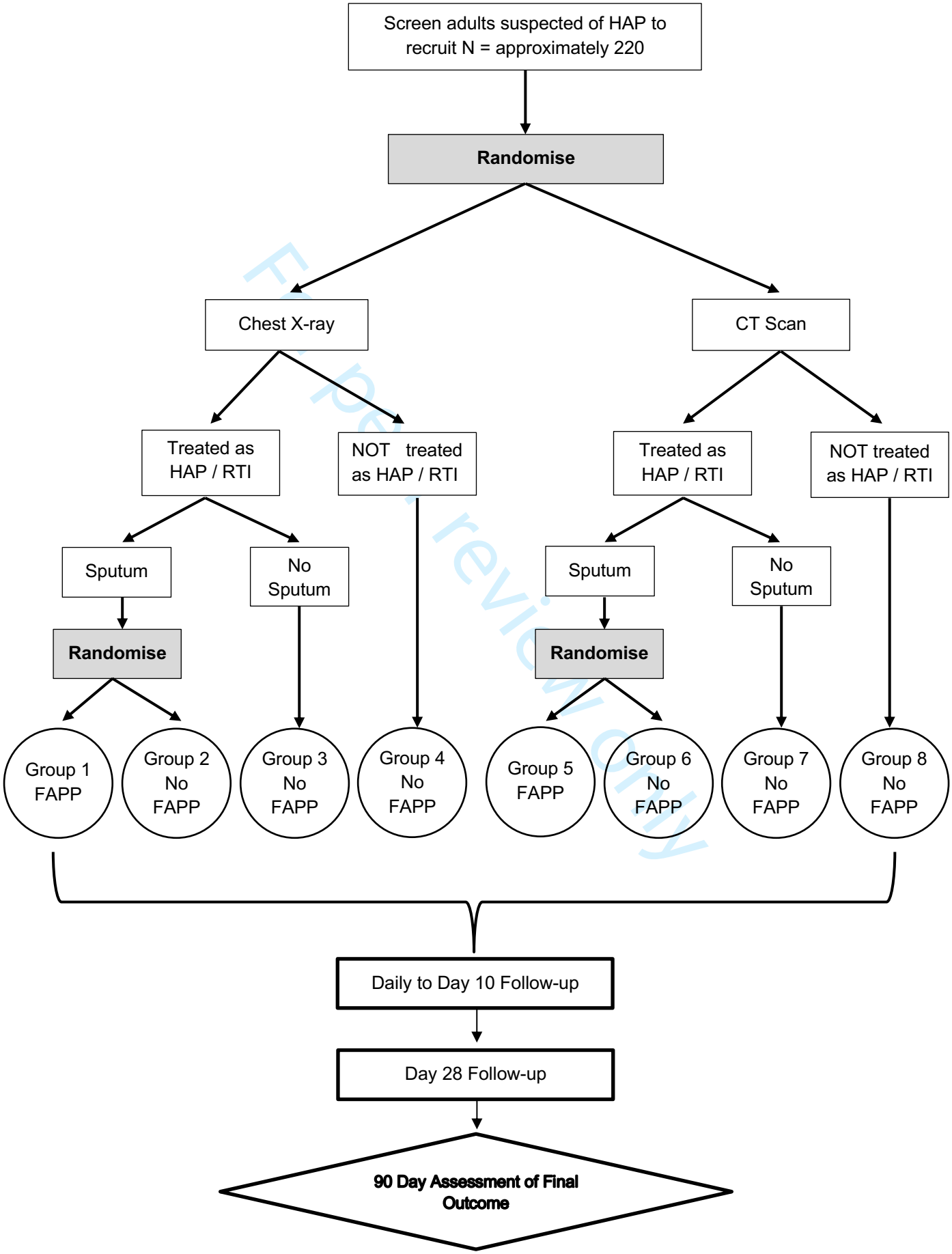
	• Duration of follow-up: 90 Days including 10 days of treatment
Study Duration	Start date: 07/06/2023 End of recruitment: 23/06/2024 End of Follow up: 21/09/2024
HAP Description of Interventions:	Stage 1: Radiographic Diagnosis using chest X-ray vs CT Scan Stage 2: 'FILMARRAY® Pneumonia Panel' (FAPP) vs No FAPP Treatments received by participants will be determined by the diagnostic information obtained during Stages 1 and 2 of the pilot study.
Objectives	
Primary:	The primary objective is to determine the feasibility of a full-scale Randomised Controlled Trial (RCT) comparing different diagnostic dynamic treatment regimens (DTRs) in adult patients suspected of HAP. See section 9 for further details on endpoint/outcome measures.
Secondary:	The secondary objective is the efficacy outcomes that will be investigated in a large scale RCT. These will be determined on the basis of the following outcomes: 1. Inform the sample size of a definitive study 2. To measure key outcome measures (completion rates, missing data, estimates and dispersion) 3. To estimate eligibility, recruitment and consent rates 4. Estimate rates of successful follow up 5. Assess the web-based randomisation process and incorporate clinical and researcher feedback 6. Perform a costing analysis of HAP to inform the cost-effectiveness analysis for any definitive study 7. Assess human factors involved in delivery of the study and how the different diagnostic tests influence clinical decision making by conducting qualitative interviews and focus groups with healthcare workers and researchers 8. Evaluate willingness of clinicians to recruit to the study 9. Evaluate willingness of potential participants or their consultees to be recruited 10. Evaluate adherence to antibiotic guidelines as outlined in the study protocol 11. Assess the study participant and carer experience of participating in the study via qualitative interviews
Exploratory/ Translational:	Describe the dynamics and characteristics of immune cells and inflammatory responses and their associations with severity and outcome among our HAP cohort during HAP.

Schematic of Study Design

3.1.1 Overall Study



3.1.2 Pilot sequential multiple assignment randomised trial (SMART) design



4 Roles and Responsibilities

[redacted] Sponsor

The Sponsor's name is the University of Liverpool and is legally responsible for the study. They will formally delegate specific Sponsoring roles to the Chief Investigator and Clinical Trials Unit.

4.2 Funder

This study is funded by an Advanced Fellowship awarded by the National Institute of Health Research (NIHR) to Dr Wootton.

Funder(s)	Financial and Non-financial Support Given	Role
NIHR Advanced Fellowship (Dr D Wootton)	£1,111,228.00	This funding source had no role in the design of this study and will not have any role in the analyses or interpretation of the data, or decision to submit results.
BioMerieux	Loan of FILMARRAY machines and covering the cost of 50% of the pneumonia kits used.	This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.
University of Liverpool	Fully funded UK PhD	The Institute of Infection, Veterinary and Ecological Sciences within the University of Liverpool has provided tuition, bench, consumable and stipend funds for a UK student to conduct PhD studies relating to immune cell and inflammatory mediators in HAP.

Chief Investigator: Dr Daniel Wootton is the Chief Investigator for the trial and is responsible for overall design and conduct of the study in collaboration with other members of the study team.

Principal Investigators: In each participating centre a principal investigator will be identified to be responsible for identification, recruitment, data collection and completion of eCRFs, along with follow up of study participants and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit: LCTC at the University of Liverpool in collaboration with the Chief Investigator, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, Trial Master File management, data management, randomisation, statistical analysis and participating site coordination.

4.3 Oversight Committees

HAP-FAST is subject to oversight from the following committees:

Trial Management Group (TMG)
A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical), sponsor representatives, PPI representatives and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the study and will be responsible for the day-to-day running and management of the study. The TMG will meet at least monthly at setup stage and then reduce to quarterly throughout the year unless more frequent meetings are required.

Trial Steering Committee (TSC)
The Trial Steering Committee will consist of an independent chairperson, 2 independent experts in the field of pneumonia diagnostics, biostatistician, the CI and PPI representatives. The role of the TSC is to provide overall supervision for the study and provide advice through its independent Chairperson. The decision for the continuation of the study lies with the TSC, with funder input. The TSC will meet prior to onset of recruitment and discuss the future schedule of meetings – but we anticipate this will be at least once during recruitment and once to discuss the final results.

4.4 Protocol Contributors

Name	Affiliations	Contribution to protocol
Dr Daniel Wootton (DW)	University of Liverpool	Lead Author, CI
Stephanie Willshaw	University of Liverpool	Trial Manager
Anica Alvarez Nishio	PPI representative	Patient and public perspective
Dr Ashley Jones	University of Liverpool	Statistical lead
Prof Bridget Young (BY)	University of Liverpool	Oversight of qualitative study
Dr Lance Turtle (LT)	University of Liverpool	Collaborator – exploratory sub-study
Dr Simon Abrams (SA)	University of Liverpool	Collaborator – exploratory sub-study
Liverpool Clinical Trials Centre	University of Liverpool	Protocol development

5 INTRODUCTION

5.1 Background

Hospital-Acquired Pneumonia (HAP) refers to a type of severe lung infection that develops while a patient is in hospital or has been recently discharged. HAP is common, frequently fatal and there is sparse evidence to support its management. Recent guidelines have called for studies focussed on diagnostics.[1]

There are problems diagnosing the condition; HAP diagnosis relies on a chest X-ray (CXR) but misinterpretation leads to over-diagnosis.[2] There are also problems diagnosing the cause of HAP; sputum culture takes too long to meaningfully impact upon antibiotic decisions. Together, these diagnostic inadequacies contribute to poor clinical outcomes and inappropriate antibiotic usage.[3]

CT scans are more accurate than chest X-rays at diagnosing pneumonia but there are no studies to demonstrate impact on outcome in HAP. The close to patient test, 'FILMARRAY® Pneumonia Panel' (FAPP)

can identify 28 pneumonia pathogens from a respiratory sample in 75 minutes – but clinical and cost-effectiveness in an NHS setting has not been evaluated in the context of non-ventilator acquired HAP.

The HAP-FAST study will therefore investigate whether using CT scans or the FAPP, or both together, helps improve antibiotic use and patient recovery while being cost effective.

5.2 **Rationale**

CT scans in pneumonia

Our current method of diagnosing pneumonia, by using a chest X-ray, is inaccurate.[4,5] Using a CT scan as the gold standard, CXR had a positive predictive value of 27% in 3423 US patients with possible Community acquired Pneumonia (CAP).[6] Claessens demonstrated that performing a CT after a CXR in suspected CAP might avoid antibiotics in 14%.[7]

CT scans are particularly useful when a patient is unable to stand for a CXR, as is often the case in suspected HAP. In bedridden patients with suspected pneumonia, a CT scan changed 48% of CXR-based management plans.[8]

Comorbidities, such as chronic obstructive pulmonary disease or congestive cardiac failure are more common in the elderly and can be misdiagnosed as HAP using CXR. Prendki et al. found that using CT scans avoided antibiotic use in 8.5% of elderly Swiss patients with suspected pneumonia.[9]

These studies demonstrate the diagnostic superiority of CT scans in the context of pneumonia. However, the effectiveness of a CT scan compared to CXR has not been investigated.

Rapid microbiological testing in HAP

Current use of antibiotics in HAP is imprecise and hampered by low-quality, often conflicting evidence. A Spanish study demonstrated 60% of bacterial detections were Gram-positive and a retrospective Scottish study found 71% were Gram-negative.[10,11] Neither study tested for viruses but subsequent studies have detected viruses in up to 22% of patients with HAP.[12,13] It is clear there is a wide range of potential pathogens but since HAP trial evidence is lacking, clinical guidelines extrapolate recommendations from the more comprehensive ventilator associated pneumonia (VAP) literature. However, the most comprehensive, comparative study of the aetiology of HAP and VAP indicates the comparison may be invalid.[14] Most recently, the INHALE group compared two rapid molecular diagnostic tests to conventional NHS microbiological testing of respiratory samples from patients with pneumonia on critical care. They reported higher pathogen detection sensitivity of the new rapid tests when compared to conventional methods – and demonstrated once again that viruses are identified in a significant proportion.[15]

In this context, the 2014 pneumonia management guidelines NICE made one research recommendation relating to HAP,

"Can rapid microbiological diagnosis of Hospital-Acquired Pneumonia reduce the use of extended-spectrum antibiotic therapy, without adversely affecting outcomes?"[1]

To clarify 'rapid' in this context, NICE reviewed the evidence for the timing of antibiotics in HAP and found no evidence, however, they recommend antibiotics are commenced within 4 hours of diagnosis in line with strong evidence in CAP. The only commercially available platform to comprehensively test for pneumonia specific pathogens and provide results within 4 hours is the BIOFIRE® FILMARRAY® Pneumonia Panel Plus. https://www.biomerieux-diagnostics.com/biofire-filmarray-pneumonia-panel. This CE marked, United States

Food and Drug Administration (FDA) approved near patient test can simultaneously detect 18 bacterial and 10 viral causes of HAP and the presence of 7 antimicrobial resistance genes.[15] Sample preparation takes 2 minutes, requires no expertise and results are available in 75 minutes. A recent comparison of the FilmArray Pneumonia Panel (FAPP) demonstrated that, when applied to respiratory sample from patients with pneumonia in critical care, it detected more pathogens more rapidly than conventional techniques.[15] This test could dramatically change the way we manage HAP but before it is widely implemented, questions relating to the interpretation of results and cost-effectiveness within the NHS setting need to be addressed.[16]

Outcome measures in HAP trials

We have searched the COMET data-base for core outcome sets in HAP trials.[17] Some groups advocate all-cause mortality assessed on a non-inferiority basis.[18] However, others have made a compelling statistical argument as to why discerning the mortality attributable to HAP, as opposed to underlying comorbidity, is difficult without unfeasibly large trials.[19] Several groups have recently advocated combining mortality with a physiological or patient-based outcome measure. A Delphi exercise to determine HAP trial endpoints suggested a hierarchical, composite, primary outcome of survival at day 28 and 'clinical cure' between days 7-10.[20] Unfortunately, this report did not provide a pragmatic definition of clinical cure. A group convened by the FDA suggested using mortality plus resolution of symptoms.[21]

The evidence summarised above demonstrates that CT scans improve the accuracy of pneumonia diagnosis, and that the new FAPP test could facilitate targeted rather than empirical prescribing. However, what is lacking is any trial evidence that these interventions actually achieve the outcome NICE has asked for which is to improve antibiotic use in a safe and cost effective way. The HAP-FAST study aims to address this evidence gap.

5.3 Risk and Benefits

5.3.1 Potential Risks

Standard of care for this patient population is to diagnose HAP through a chest X-ray. Patients entered into this study will be randomised to either standard chest X-ray or low-dose, non-contrast, thoracic CT scan. CT scans are frequently used as part of the diagnostic work up for patients with pneumonia but here we will trial their systematic use as the first test in those suspected of HAP.

A low dose, non-contrast, thoracic CT scan carries a radiation exposure of 1.5mSv, which is greater than a CXR (0.05 mSv) but lower than annual UK background radiation exposure of 2.7mSv.[9] Thus, the study scans carry very low risk compared to the in-hospital mortality of 27% for HAP. Furthermore, CT scans are more accurate than chest X-rays at diagnosing HAP, which will in turn lead to more accurate treatment of suspected HAP.

A recognised consequence of performing a thoracic CT scan at any point in a patient's acute care is the detection of unexpected abnormalities. These range from rare things such as anatomical variants, to alternative diagnoses for the presenting symptoms such as pulmonary emboli or heart failure. Commonly, thoracic CT scans will detect a pulmonary nodule. Pulmonary nodules are discreet abnormalities which range in size and density and are of unknown aetiology. Their significance derives from the fact that some will turn out to be early stage malignancies. The detection of pulmonary nodules is so common that hospitals have well established pathways for their investigation and follow-up which are supported by national guidelines.[22] The number of scans in the CXR v CT groups will be compared and reported.

Standard of care for the microbiological diagnosis of the cause of HAP is the culture of a respiratory specimen – most commonly a self-expectorated sputum specimen.[23] Culture of sputum is designed to detect the bacterial pathogens which are thought to commonly cause HAP. In the event that a bacterial pathogen is detected, culture provides an opportunity for antibiotic susceptibility testing which provides the clinician with useful information about which antibiotics might and might not help treat the patient.

The FAPP test is a molecular test and it is possible there will be discrepancies between the detections made using the FAPP and those made using culture.[15] However, our study design suggests all samples used in the FAPP should also be sent for culture, and therefore if a pathogen is missed by the FAPP there is an opportunity for it to be detected, as usual, by culture.

It is theoretically possible that, based on a FAPP result, a participant could receive an antibiotic which is not effective against an undetected pathogen. This is always the case with imperfect microbiological tests and is the reason why all patients are closely monitored for response to treatment during the early stages of pneumonia. If a participant were to deteriorate following FAPP guided treatment, the protocol allows for the clinicians treating the participant to escalate or change their therapy as clinically indicated.

More detail regarding management of risks associated with this study are detailed in a separate Risk Assessment maintained in the Trial Master File.

5.3.2 **Potential Benefits**

There is evidence that the use of a CT scan instead of a CXR as the initial radiological test for patients suspected of pneumonia leads to improved management decisions by clinicians.[7] In some instances this might be the confirmation of pneumonia which would not have been apparent on a CXR. In other cases it might be the detection of an alternative explanation for symptoms such as a pulmonary embolus, malignancy or radiological features of heart failure.

Sputum culture takes on average 3 days to produce a result. During this time patients treated for HAP would currently receive empirical antibiotics based on assumptions of the likely pathogen. The FAPP offers the possibility of detecting the causative pathogen and the potential for resistance before antibiotics are started so that the correct choice can be made at the beginning of treatment. Evidence suggests FAPP is considerably more sensitive in detecting respiratory pathogens than conventional culture.[15] Moreover, sputum culture does not detect viruses which are implicated in many cases of HAP – whereas the FAPP test will detect common respiratory viruses.[15] As a consequence, participants in the FAPP arm of this study may incur several benefits such as avoiding unnecessary antibiotics, reduced risk of receiving inadequate antibiotics and avoiding the unnecessary receipt of antibiotics with a high propensity to cause harm.

5.4 **Objectives**

5.4.1 **Primary Objective**

The primary objective is to determine the feasibility of a full-scale Randomised Controlled Trial (RCT) comparing different diagnostic dynamic treatment regimens (DTRs) in adult patients suspected of HAP.

5.4.2 **Secondary Objective(s)**

The primary objective will be determined on the basis of the following objectives:

1. Inform the sample size of a definitive study

2. To measure key outcome measures (completion rates, missing data, estimates and dispersion)
3. To estimate eligibility, recruitment and consent rates
4. Estimate rates of successful follow up
5. Assess the web-based randomisation process and incorporate clinical and researcher feedback
6. Perform a costing analysis of HAP to inform the cost-effectiveness analysis for any definitive study
7. Assess human factors involved in delivery of the study and how the different diagnostic tests influence clinical decision making by conducting qualitative interviews and focus groups with healthcare workers and researchers
8. Evaluate willingness of clinicians to recruit to the study
9. Evaluate willingness of potential participants or their consultees to be recruited
10. Evaluate adherence to antibiotic guidelines as outlined in the study protocol
11. Assess the study participant and carer experience of participating in the study via qualitative interviews

6 STUDY DESIGN

HAP-FAST is a feasibility study consisting of a pilot study, two qualitative studies, and a costing analysis. The study participants will also provide clinical samples to support exploratory analyses of the immune-pathophysiology of HAP.

6.1 Pilot Study

The pilot study is designed as a sequential, multiple assignment, randomized trial (SMART) with a 1:1 allocation ratio.[24] Its purpose is to address the main feasibility objectives – specifically secondary objectives 1-5. The flow-diagram in section 3.1 above shows how participants will flow through the study.

Participants are initially randomised between a chest X-ray (CXR) and low-dose thoracic CT scan (CT). Following the imaging, participants whose clinician decides to manage them as either hospital acquired pneumonia (HAP) or hospital acquired respiratory tract infection (RTI), and who are able to produce a sputum sample, are further randomised to 'FILMARRAY® Pneumonia Panel' (FAPP) or no FAPP. All other participants will be managed as per usual care.

The randomisation results in 4 dynamic treatment regimens (DTRs).

Table 1: Definition of DTRs

Dynamic treatment regimen (DTR)	**Phase 1 intervention**	**Phase 2 intervention**	
		Phase 1 indicates HAP/RTI and patient has sputum	**Phase 1 indicates no HAP/RTI and/or patient has no sputum**
DTR 1	CXR	FAPP	No FAPP
DTR 2	CXR	No FAPP	
DTR 3	CT	FAPP	No FAPP
DTR 4	CT	No FAPP	

Screening, baseline and outcome data are collected at distinct time-points according to the schedule detailed in Section 10.9 below.

6.1.1 Blinding

The study is open-label and treating clinicians, researchers and participants will know which treatment / intervention is being administered.

6.1.2 Study Setting

Participants will be identified and recruited from 3 NHS hospital Trusts in the UK. Participants will be assessed by the study team daily until day 10 to track symptomatic recovery, changes in QOL and determine time to clinical cure. Participants will have symptoms and QOL assessed face to face on day 28 (+/- 7 days) as an in or out-patient. Follow up will be conducted as a phone call 90 days (+/- 14 days) following entry into the study to assess symptoms, QOL and to remind them to return a survey booklet on health and social care use up to day 90.

6.1.2.1 Selection of Participating Sites

Participating sites will be opened to recruitment upon successful completion of all global (e.g. REC and HRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

As this is a pilot study, four sites, over three NHS Trusts have already been selected for involvement in the study; Aintree University Hospital and Royal Liverpool University Hospital (Liverpool University Hospitals NHS Foundation Trust), Royal Preston Hospital (Lancashire Teaching Hospitals NHS Foundation Trust) and Wythenshawe Hospital (Manchester University NHS Foundation Trust). Preliminary data demonstrates sufficient number of potential participants within the study's timeframe.

6.1.2.2 Selection of Principal Investigators

Principal Investigators will be required to demonstrate equipoise, relevant experience and commitment during early stage feasibility assessment. All investigators will have the particular medical expertise necessary to conduct the study in accordance to the protocol and all regulatory and ethical requirements. Written agreement to conduct research as such will be obtained prior to site initiation.
A suitable co-investigator should be identified at each site to deputise in case of PI absence.

6.2 Costing Analysis Sub-Study

The purpose of this study is to address secondary objective 6. A sub-group of pilot study participants' clinical pathways from baseline to 90 days will be analysed to investigate the costs associated with patients suspected of HAP. Itemised hospital costs for participants within each intervention group will be obtained using (i) NHS Schedule of costs; (ii) British National Formulary, and (iii) NHS drug prices and local hospital finance department data. Clinical judgement will be used to determine whether individual costs are related to HAP or underlying health conditions or the condition which provoked the original admission to hospital. Where there is ambiguity in attributing a cost, we will clarify with the treating clinical team. Post-hospitalisation costs will be captured up to 90 days following baseline. A bespoke questionnaire will be provided to each participant on discharge – see appendix C. The questionnaire will capture items such as absence from work, domiciliary care costs, visits to the GP and out of hospital prescribing.

Further details are given in section 11.1.

6.3 Qualitative Sub-Study

6.3.1 Patients and Carers

The purpose of this study is to address secondary objectives 9 and 11. Approximately 15 participants (5 from each of the three recruiting Trusts) will be purposively recruited for in-depth semi-structured interviews based on age, gender and underlying comorbidity class (medical admission, surgical admission, acute admission). Carers of 6 study participants (2 per hospital) who lack capacity will also be recruited to be interviewed. The participant and carer interviews will focus on:

- Perceptions of the interventions
- Recruitment and consent – in particular the deferred consent model
- Study documentation and communication
- Care and treatment following randomisation
- Study follow-up

We will also aim to interview approximately 9 participants (3 from each Trust) who decline to participate in the feasibility study. We will attempt to achieve a representative sample of such participants based on the same purposive sampling approach described above but as reasons for declining emerge into themes we may refine this purposive sampling strategy. An open approach to the topics for these interviews will be taken and directed by the core reason for declining but where no obvious reason is offered the above interview focus areas will be explored.

6.3.2 Clinicians

The purpose of this study is to address secondary objectives 7, 8 and 10. We will hold two rounds of focus groups and/or interviews at each hospital – the first after 3 months of recruitment and the next after 9 months of recruitment. We will invite a range of clinical, allied health professional and research staff to participate. We anticipate there being approximately 8 participants in each focus group. Focus groups and interviews will be topic guided, yet conversational and exploratory and conducted in a comfortable private environment.

Further details are given in section 11.2.

6.4 Exploratory Sub-Study

Clinical samples of venous blood, sputum and a nose swab will be taken from participants in the pilot RCT. These samples will be used to explore the role immune cells and inflammatory mediators play in the pathophysiology of HAP and how these vary with pathogen. The samples from the pilot study – which recruits patients suspected of HAP – will be compared with equivalent samples from patients who chronically produce sputum, are not exacerbating, and are being managed as out-patients in respiratory clinics.

Further details are given in section 11.3

7 ELIGIBILITY CRITERIA

The HAP-FAST study aims to recruit approximately 220 participants based on sample size calculations described in Section 13.2.1. Patients will be enrolled into the study under a deferred consent model allowing them to be randomised and provide research samples prior to written informed consent or assent being obtained. This ensures study processes do not delay investigation and management (see Section 10.5 for more information regarding informed consent processes).
As soon as possible after stage one randomisation, written informed consent (or assent in the context of patients lacking capacity) will be sought.

Patients who decline to provide written informed consent after randomisation and no longer wish to continue in the study will be withdrawn (see section 10.7 for more information).

7.1 Stage 1 Randomisation

7.1.1 Inclusion Criteria

For Stage 1, patients must comply with all of the following at randomisation to be eligible for the trial:

- Age ≥ 18 years
- Suspected HAP*

* For the purposes of this study, HAP is defined as per the BTS and FDA definitions i.e. pneumonia which develops 48 hours after an admission to hospital for an alternative diagnosis; or a new presentation to hospital with pneumonia in a patient who has been discharged from an overnight stay in hospital within the last 10 days.[25,26]

7.1.2 Exclusion Criteria

Any patient meeting any of the criteria listed below at randomisation will be excluded from study participation:

- Already received a chest X-ray to confirm suspected HAP diagnosis
- Diagnosis or suspected diagnosis of ventilator acquired pneumonia
- Intention to palliate rather than cure
- Interventions cannot be completed before administration of second antibiotic dose*
- Cannot be randomised to low-dose, non-contrast CT scan on clinical grounds e.g. strong suspicion of PE**
- Pregnancy***
- Previous study participation (patients with second of third episodes of HAP will not be re-recruited)

* In the circumstance where a patient is diagnosed with HAP whist receiving antibiotics for a non-respiratory infection e.g. cellulitis or UTI, if the HAP diagnosis leads to a change in the antibiotic prescription to cover the HAP then that patient will be eligible for recruitment. However, if the diagnosis of HAP does not result in a change in antibiotic then the patient **is not eligible**.

**A non-contrast, low-dose thoracic CT scan is an inappropriate test for a PE and if that is high in the differential diagnosis then tick yes here.

***A urine pregnancy test is required as part of routine care prior to a chest X-ray or CT scan. If the test reveals the patient is pregnant, they will **not be eligible** for the study as they will be unable to receive a CT scan as part of this study. Pregnancy tests are not required at future time points.

7.2 Stage 2 Randomisation

7.2.1 Inclusion Criteria

A patient is eligible to be entered into the 2nd randomisation if:

- The clinician intends to treat the patient for HAP or a hospital acquired respiratory tract infection (RTI)
- A sputum sample has been obtained before 2nd dose of antibiotic

7.2.2 Exclusion Criteria

A patient is not eligible to be entered into the 2nd randomisation if:

- Following the CXR or CT the clinician decides not to treat with antibiotics for either HAP or a hospital acquired RTI

Patients ineligible for randomisation at stage 2 will still be able to participate in the trial.

7.3 Co-enrolment Guidelines

To avoid potentially confounding issues, ideally participants should not be recruited into other intervention trials during their participation in HAP-FAST. However, where recruitment into another study is considered to be appropriate this must first be discussed with the LCTC who will contact the Chief Investigator, Dr Daniel Wootton, for consideration on a case by case basis.

8 TRIAL TREATMENT/INTERVENTIONS

8.1 Introduction

The pilot study has a SMART design, where the randomisation pertains to diagnostic strategies which may or may not affect treatments received. In general, choice of treatment will be determined by the diagnostic information available to clinicians.

8.2 Treatment Definitions

Treatment is determined by the diagnostic information available to clinicians. There are 8 distinct possible routes through the study. These are labelled 1-8 on the pilot study schematic in 3.1.2. Each determines a different approach to treatment.

Participants' treatment will ultimately be at the discretion of the treating clinician. However, for those participants diagnosed with HAP or a hospital acquired respiratory tract infection (RTI) antibiotics should be prescribed with reference to the local treatment policy unless the participant has a sputum sample and is randomised to use the FAPP. If the FAPP is used then antimicrobial treatment can be guided by a study specific, pre-defined treatment algorithm. Where a patient is deemed to have met sepsis criteria, administration of the first dose of antibiotic will be as per sepsis guidelines, with revision of subsequent antibiotics based on the FAPP results. The guideline will indicate that for those who do not meet sepsis criteria, there should be no longer than 4 hours from the time of radiological confirmation of HAP/RTI to the administration of the first dose of antibiotic.

A summary of which approach to take dependent on the participant's flow through the study is given in the table below. See also 8.4 for greater detail regarding diagnostic interventions.

Table 2: Interventions and Treatments

Result of Stage 1 Randomisation	**Result of Imaging**	**Sputum Available?**	**Result of Stage 2 Randomisation**	**Treatment**	**Group**
CXR	Clinician decides to treat for HAP / hospital acquired RTI	YES	FAPP	• Use an aliquot of respiratory specimen in the FAPP • Send remainder of specimen to microbiology for standard tests • Prescribe antibiotics with reference to the FAPP antibiotic guideline	1
		YES	No FAPP	• Prescribe empirical antibiotics based on local guidelines	2
		NO	N/A	• Prescribe empirical antibiotics based on local guidelines	3
	Clinical diagnosis is **not** HAP / RTI	N/A	N/A	• Patient receives usual care and is followed up as per the study schedule	4
CT Scan*	Clinician decides to treat for HAP/ hospital acquired RTI	YES	FAPP	• Use an aliquot of respiratory specimen in the FAPP • Send remainder of specimen to microbiology for standard tests • Prescribe antibiotics with reference to the FAPP antibiotic guideline	5
		YES	No FAPP	• Prescribe empirical antibiotics based on local guidelines	6
		NO	N/A	• Prescribe empirical antibiotics based on local guidelines	7
	Clinical diagnosis is **not** HAP / RTI	N/A	N/A	• Patient receives usual care and is followed up as per the study schedule	8

* Low-dose, non-contrast, CT scan of the thorax “hot reported”.

8.3 Manufacturing and Distribution

The BIOFIRE® FILMARRAY® system and the Pneumonia Panels are manufactured and distributed by BioMerieux. Both the system and panels are CE marked and Food and Drug administration (FDA) approved.

BioMerieux will loan a BIOFIRE® FILMARRAY® system to sites free of charge for use in the study. Pneumonia Panels will be procured centrally by the University of Liverpool and distributed to sites as needed.

At site set up, an initial supply of Pneumonia Panels will be issued. Resupply will be as and when required, totalling one Pneumonia Panel per participant randomised to FAPP.

Requests for re-supply should be made to hapfast@liverpool.ac.uk.

8.4 Administration of Diagnostic Assessments

8.4.1 Standard Chest X-ray (CXR)

This chest X-ray will be carried out by a trained radiographer as per standard NHS practices.

8.4.2 Intervention - CT Scan

This low dose thoracic CT-Scan will be carried out as per standard local protocols and by a trained radiographer as per standard NHS practices.

8.4.3 Standard microbiological testing

Participants will cough into a standard, labelled, sputum pot to provide the sample. Participants will provide this sample as standard of care. A member of the clinical team (e.g. doctor, nurse, HCA, porter) will then take the sample to be processed in the laboratory as per standard NHS practices.

8.4.4 Intervention - FAPP

The BIOFIRE® FILMARRAY® Pneumonia Panel (FAPP) will be used to identify the cause of HAP quickly. It is carried out through the collection of sputum samples from participants directly. Participants will cough into a standard, labelled, sputum pot to provide the sample. Participants will provide this sample as standard of care. A member of the clinical team (e.g. doctor, nurse, HCA, porter) will then take the sample to the FilmArray machine location (site specific) and will either run the sample themselves (if trained and delegated to do so) or find a trained person to run the sample. The FAPP test uses only a small fraction of the sputum sample (500microLitres) and the remaining sample is sent for standard microbiological testing as above.

The procedure for performing a pneumonia panel test using the BIOFIRE® FILMARRAY® is explained in the manual provided in appendix D. In addition to this reference, all relevant staff at sites will have initial training on the machine and tests and will have access to an online video tutorial via the study website (www.hap-fast.org.uk).

BIOFIRE® FILMARRAY® Pneumonia Panel test kits must be stored in a relatively temperature stable environment. In particular they should not be exposed to direct sunlight or subjected to temperatures above 28°C.

8.5 Investigation Modifications

After the patient has entered the study, the clinician is free to give alternative treatment / intervention to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the study for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from the protocol treatment and study follow-up without giving reasons and without prejudicing further treatment, see section 10.7.1.

8.6 Accountability Procedures

Accountability logs will be maintained at site to record the receipt and return of the BIOFIRE® FILMARRAY® system (when provided for use in the study).

Accountability logs will also be maintained for the Pneumonia Panels to record receipt, use and destruction/return.

The LCTC will maintain a master accountability log and perform reconciliation between panels provided to sites, administered and destroyed/returned.

8.7 Concomitant Medications

8.7.1 Data on Concomitant Medication

Concomitant medication information should be collected on a specific electronic case report form and will be used for assessment of cost-effectiveness and as part of the secondary and exploratory analyses of factors affecting outcome in HAP and factors associated with specific pathogens or combinations of pathogens.

9 OUTCOMES

The key objective is determining the feasibility of a future definitive RCT. The secondary objectives of the study will help make a final decision as to whether a definitive study is feasible:

Objective		
Primary Objective		
The primary objective is to determine the feasibility of a full-scale Randomised Controlled Trial (RCT) comparing different diagnostic dynamic treatment regimens (DTRs) in adult patients suspected of HAP.		
Secondary Objective		
Objective	Outcome	Time-point
Inform the sample size of a definitive study	Time to clinical cure*	Day 90
	Antibiotic usage for the HAP episode	Day 90
	EQ-5D-5L	Baseline, day 10, 28 and 90
	Length of hospital stay post HAP diagnosis	Day 90
	Mortality	Day 14, 28 and 90
To measure key outcome measures (completion rates, missing data, estimates and dispersion)	Estimate rates of completion of questionnaires - EQ5D5L, CAP-sym, economic evaluation	Screening Randomisation Follow up End of Treatment End of Study

	Summary statistics and proportion of missing data for time to clinical care, antibiotic usage for HAP diagnosis, EQ-5D-5L, length of hospital stay post HAP diagnosis, mortality	
To estimate eligibility, recruitment and consent rates	Rate of recruitment; Proportion screened that meet eligibility criteria; ** Proportion eligible that consent and where they present; ** Proportion consented and randomised that complete study pathway as per protocol; Proportion consented and randomised that withdraw from study intervention or follow up; **	Screening Randomisation Follow up End of Treatment End of Study
Estimate rates of successful follow up	Proportion consented and randomised that complete study pathway as per protocol; Proportion consented and randomised that withdraw from study intervention or follow up; **	End of Study
Assess the web-based randomisation process and incorporate clinical and researcher feedback	Qualitative conclusions based on staff focus groups	Qualitative analysis
Perform a costing analysis of HAP to inform the cost-effectiveness analysis for any definitive study	Summary statistics for numbers and types of costs with comparison between DTRs	End of Study
Assess human factors involved in delivery of the study and how the different diagnostic tests influence clinical decision making by conducting qualitative interviews and focus groups with healthcare workers and researchers	Qualitative conclusions based on staff focus groups	Qualitative analysis
Evaluate willingness of clinicians to recruit to the study	Qualitative conclusions based on staff focus groups	Qualitative analysis
Evaluate willingness of potential participants or their consultees to be recruited	Qualitative conclusions based on participant and carer interviews	Qualitative analysis
Evaluate adherence to antibiotic guidelines and study protocol	Summary statistics relating to antibiotic use in the pilot study with a comparison between the DTRs	End of Study
Assess the study participant and carer experience of participating in the study	Qualitative interviews	Qualitative analysis

* defined as the number of days from baseline when there is a combination of resolution of signs and symptoms present at enrolment and improvement or lack of progression of radiological signs

** reasons why, and stage will be collected to inform future trial design

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification and Screening

Standard screening logs will not be maintained due to the nature of the study and the urgent need to treat. As soon as a patient is identified as having suspected HAP, they will be assessed for eligibility and included in the study. For participants who are assessed for eligibility but not randomised at stage one, ineligibility reason will be recorded by the online randomisation system as this will provide important information for monitoring purposes.

10.2 Eligibility Assessment and Confirmation

Eligibility for randomisation can only be confirmed by an appropriately qualified medical professional. Eligibility criteria are described in detail in Section 7.

Eligibility confirmation will be performed by the study team and recorded via the randomisation system and must be documented in the participant's medical notes. Details must include at a minimum who confirmed full eligibility and when this was confirmed.

It is not required to obtain written informed consent to complete eligibility assessments. This study is using a deferred consent model for recruiting participants.

10.3 Randomisation / Registration

Participants will be assigned a unique study number via an online platform accessible from networked hospital computers on relevant wards. The Liverpool Clinical Trials Centre (LCTC) will coordinate and supervise the online randomisation process and hold the randomisation sequence. Randomisation will be two stage – first to CXR or CT – then to FAPP or not FAPP.

Please note, participants may be randomised (at stage 1 and stage 2) prior to obtaining written informed consent. This study is using a deferred consent model for recruiting participants.

10.3.1 Randomisation Process

There are 2 stages of randomisation in the pilot study. Both will use a secure (24-hour) web-based randomisation systems controlled centrally by the LCTC.

Randomisation 1: Choice of imaging
Participants will be randomised to undergo either CT scan or chest X-ray (in a ratio of 1:1).

Randomisation 2: FAPP or No FAPP
Once imaging has been completed, and a clinical judgement is made, participants who:

- Are to be treated as HAP or a hospital acquired RTI and
- Are able to produce a sputum sample will be randomised to FAPP or No FAPP (in a ratio of 1:1).

Clinical staff with a .NHS email address prefixed with one of the recruitment site prefixes (e.g. joe.bloggs@luhft.nhs.uk) will be able to access to the randomisation system(s). When the system requirements (i.e. eligibility) are confirmed at the stage 1 randomisation, the participant DTR allocation and a unique study number (randomisation number) will be displayed on a secure webpage. When a randomisation has occurred two emails will automatically be sent.

The first email is a "HAP-FAST randomisation confirmation" and will go to three addresses: the member of staff who performed the randomisation, the LCTC trial co-ordinator and the site research team. The aim of this email is primarily to alert the site research team to the randomisation and enable them to locate the participant in order to complete the baseline eCRF, provide study information and seek written informed consent (or assent).

The second email will be sent to the site research team and the LCTC trial coordinator and will include the email address of the staff member who performed the randomisation process. The aim of this mail is to enable the site to keep an auditable log of who is performing randomisations.

In the event that informed consent is declined after stage 1 randomisation but before stage 2 randomisation, a system barrier will prevent stage 2 randomisation from occurring. See section 10.5.4 for details on declined consent.

10.3.2 **Randomisation System Failure**

In the event of a randomisation system failure, the centre should contact the coordinating team at the LCTC (Monday to Friday between 9:00 to 17:00 excluding bank holidays) to try to resolve the problem. If the problem cannot be resolved the LCTC will perform central randomisation and randomise the participant using the back-up randomisation system. The back-up randomisation system is an exact replica of the live system but is based on a standalone PC at LCTC.

10.4 **Sampling**

10.4.1 **Sample Collection**

Sputum samples will be requested and collected using standard clinical materials and techniques from all participants as is standard clinical practice in patients suspected of HAP. Each sputum request will be flagged to the local laboratory as being part of the HAP-FAST study. Residual sputum from the clinical sample will be retained for use in the exploratory sub-study. Two additional research specific sputum samples will be taken using standard clinical materials and techniques.
Research specific blood samples will be taken using standard procedures e.g. vacutainer tubes. Where possible, these research-specific samples will be coordinated with clinical samples.
Research specific nasal swabs will be taken using the standard clinical method (as is done for e.g. COVID-19 lateral flow or PCR tests).

10.4.2 **Sample Storage and Handling**

Sputum: participants randomised to the FAPP arms will have their sputum samples sub-sampled (= approx. 500microL) for the FAPP machine and then the remainder will be passed to the local Microbiology department for standard testing. The method for sub-sampling a sputum sample and running it on the FAPP will be made clear in the laboratory manual and the procedure will be summarised on laminated posters above each machine and is also explained in detail in the video which will appear on the study website (www.hap-fast.org.uk) which will be accessible from all networked computers in participating Trusts.

Participants randomised to the non-FAPP arms will have their samples passed to the local hospital's microbiology department. After the NHS microbiology laboratory has performed their tests, any remaining

sputum belonging to a HAP-FAST participant will be stored for subsequent use in the exploratory sub-study; see section 11.3 for further details on this sub-study.

Blood: some of the research specific samples will be sent to NHS laboratories and some will have initial processing prior to storage on site as specified in the laboratory handbook. Stored samples at each site will then be sent to University of Liverpool laboratories.

Nasal swabs: these will be stored on site prior to dispatch in batches to University of Liverpool laboratories.

10.4.3 **Custodianship**

Stored samples will be subject to standard practices at each hospital site.

10.5 Informed Consent

10.5.1 **Deferred Informed Consent Process**

Due to the potential severity of HAP there is a short timeframe of eligibility between HAP being suspected and diagnostic tests being carried out. Moreover, eligible patients, as a consequence of their acute illness and or underlying comorbidities may have impaired capacity to provide written informed consent and consequently require a consultee for assent.

Because of these factors, it is not reasonably practicable to obtain written informed consent from the patient or a legal representative prior to randomisation to study interventions and procedures. The HAP-FAST study consent process for the study will therefore incorporate a deferred consent model as has been used in other emergency situations.[27-29] The use of deferred consent model for HAP trials has been studied previously and deemed acceptable by patients and the public.[29]

10.5.2 **Obtaining Written Informed Consent/Assent**

Patients who are randomised to the study interventions by the clinical team will be approached by a member of the local research team to obtain written informed consent as soon as possible before they are discharged. A written information sheet that forms part of the ethically approved Patient Information Sheet (PIS) and Consent form will be provided. This will include a detailed explanation of the HAP-FAST study (and associated sub-studies) and will make clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The research staff will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise. In the rare circumstance where a participant is discharged to home having been randomised to the study under deferred consent, all data captured will be analysed and processed using task in the public interest as the legal basis for processing. However, every effort should be made by the research team to obtain written informed consent even after discharge. To facilitate informed consent being obtained after a patient has been discharged, informed consent may be obtained via post. The researcher will discuss the trial by telephone or video conferencing and details of the discussion will be recorded in the patient notes. The ethically approved Patient Information Sheet and Consent form should be signed by the patient at home and then returned to the research site. The researcher who carried out the informed consent discussions should sign the consent form upon receipt. A copy of the fully signed consent form must be posted back to the patient for their records, the original filed in the ISF and a final copy must be sent to the LCTC.

10.5.3 **Patients who lack capacity**

Patients with underlying cognitive impairment are at risk of HAP and patients with HAP can have delirium as part of their pneumonia syndrome. As a consequence, it is not uncommon for patients who have HAP to lack the capacity to consent to clinical trials such as HAP-FAST. In order to be representative of the HAP population as a whole – and in order to allow patients who lack capacity the chance to gain the potential benefits of joining the HAP-FAST study, we will recruit patients who lack capacity to provide written informed consent. In this instance, a personal consultee will be sought. The personal consultee will be someone who knows the person who lacks capacity in a personal capacity and is able to advise the researcher about the person who lacks capacity's wishes and feelings in relation to the project and whether they should continue to participate in the research. After taking reasonable steps to identify a personal consultee, if the research team discover the person who lacks capacity has no close relatives in regular contact, it would be more appropriate to identify a nominated consultee. The researcher will nominate a third party unconnected with the research who is willing to act as a nominated consultee such as a member of the clinical team.

In the event that a patient dies before informed consent has been obtained, the participant's next of kin will be contacted to notify them of participation in the trial. An appropriate and sensitive interval, such as six weeks after the patient's death, will be left before contacting the grieving family to inform them of their relative's participation. It is important to recognise that relatives and friends are not able to consent on behalf of the deceased participant. The data captured whilst the deceased participant was alive will remain in the study unless the relatives express recollection of the participant having very strong negative views about research in which retention of data will be considered on a case by case basis.

10.5.4 **Consent Form Completion**

After verbal and written information has been provided, the individual seeking consent will ensure that the patient/consultee has fully understood all the information and will ask if they are happy to consent to continue in the study. If required, potential participants will be given up to 24 hours to decide if they would like to sign the consent form.

Where this is the case, written informed consent will be obtained by means of a dated signature on the consent form. This should be countersigned and dated by the person who obtained informed consent i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

All efforts must be made to obtain written informed consent / assent before the participant is discharged. Written informed consent must be obtained before patient questionnaires (EQ-5D-5L and CAP Sym) are completed. Biological samples (sputum, blood and nasal) must not be analysed until written informed consent has been obtained (see section 11.3 for sample processing). Samples will be sent to the University of Liverpool Biobank where informed consent will be confirmed before the samples are released for analysis. Samples are to be destroyed if consent is not in place (see lab manual).

The original signed document will be retained in the trial site's Investigator Site File (ISF) and copies will be made:

- One copy provided to the patients/consultees for their information
- One copy transferred securely to the LCTC
- One copy filed in the participant's medical records

N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.
Each participant's GP will be notified via letter of their patient's involvement in the research study.

10.5.5 Participants who decline to consent

Patients who are randomised but decline consent to continue with the study will have the reason for declining recorded on a withdrawal eCRFs.

All data captured up until this point will still be included in the analysis and processed using task in the public interest as the legal basis for processing. Refer to section 10.7.1 for more details.

10.5.6 Loss of Capacity.

If the participant that has consented then becomes unable to give informed consent, the previously obtained consent remains valid. They will be monitored for any signs of objection or distress during research visits. Any signs that would prompt a reconsideration of their continued participation will be communicated to the research nurse at these visits. This would also be the case if their nominated relative raised concerns regarding their continued participation.

10.5.7 Adults who Gain Capacity during the Course of their Participation

When a patient's participation has been consented for by a legal representative and the participant then regains capacity, the research team will provide the Patient Information Sheet and request consent from the participant. Participants will be advised that consent is voluntary and they may withdraw without any detriment to their care. If a participant regains capacity once discharged from hospital they will be approached to ask whether they would like to continue participating at their next scheduled research assessment. If they choose to continue to participate in the study they will be requested to sign the consent form.

10.6 Baseline Assessments

Baseline assessments should be completed as per the Schedule of Assessments (Section 10.99) in order to accurately complete the Baseline eCRF and collect the necessary information for the study analyses. This includes the following assessments:

- Concomitant medications
- Past medical history
- Admission related data
- Patient demographics
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate, oxygen saturation, NEWS2 score)
- Details of antibiotic use
- Clinical symptom assessment
- Clinical respiratory exam
- Routine blood tests results (haemoglobin, platelets, white blood count, neutrophils, lymphocytes, creatinine, c-reactive protein and urea)
- EQ-5D-5L
- Nasal swab*
- Research blood sample*
- CAP-Sym
- Survival status

*optional sub-study assessments

These assessments will be transcribed from the patient's medical notes into the Baseline eCRF as close to stage 1 randomisation as possible.

Baseline research blood samples MUST be collected within 24 hours of stage 1 randomisation or be classed as a missed visit.

The baseline EQ-5D-5L MUST only be completed once written informed consent (or assent) has been obtained, and within 4 days of stage 1 randomisation.
The CAP-Sym MUST only be completed once written informed consent (or assent) has been obtained.

10.7 Intervention Discontinuation and Participant Discontinuation/Withdrawal

Participants will undergo trial activities such as follow-up assessments, data collection, and sample collection and retention. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

10.7.1 Participant Withdrawal from Follow Up

Participants/consultees are free to withdraw from follow up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The LCTC should be informed via email and via completion of a Withdrawal eCRF to be returned to the LCTC within 7 days.

If participants/consultees express a wish to withdraw from follow up, the research team at site should ascertain if this is for all elements of study follow-up, or if for example, data from routine assessments can still be collected for the study. In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the participant's condition becomes stable.

10.7.2 Participant Transfer

If a participant moves from the area, every effort should be made for the participant to be followed-up at another participating study centre and for this study centre to take over responsibility for the participant or for follow-up via GP.
A copy of the participant eCRFs should be provided to the new site. The participants/consultees remain the responsibility of the original site until the new site PI has signed the Transfer eCRF. However, data collected up until the point of transfer remains the responsibility of the original site's PI who will be required to manage data queries relating to that data.

10.7.3 Loss to Follow-up

A participant will be considered lost to follow up if they fail to return for the scheduled visit and are not contactable by the site research team.

If a participant fails to attend/facilitate a required study visit the following actions must be taken:

- Site will attempt to contact the participant and reschedule the missed visit within 7 days and advise the participant on the importance of maintaining the assigned visit schedule

- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the participant (i.e. 3 telephone calls and, if necessary, a headed letter to last known address). These efforts should be recorded in the patient medical notes
- If the participant continues to be unreachable they should be considered withdrawn from the study with a primary reason of lost to follow up and this should be recorded on the appropriate eCRF

10.8 End of Trial

The end of the study is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the study database. The study may be closed prematurely by the Trial Steering Committee (TSC).

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the study closes as planned or prematurely. This includes activities such as:

1) End of Trial notification to REC
2) Trial-related materials reconciled and returned/disposed of as appropriate
3) All site data entered onto the study database, discrepancies raised and satisfactory responses received
4) Quality Control checks of the Investigator Site Files and Trial Master File as appropriate

10.8.1 Study Discontinuation

In the event that the study is discontinued, participants will continue to be treated as per standard of care at each NHS institution. The design of the study should mean that study discontinuation would not have an impact on treatment received.

10.9 Schedule for Assessments and Follow-up

All assessments and follow up are to be conducted in line with the Schedule of Assessments below:

Specific Activity	Stage 1 randomisation Day 0	Stage 2 Randomisation	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 28 (+/- 7 days)	Day 90 (+/- 14 days)
Assessment of eligibility	X	X												
Concomitant medication check	X													
Randomisation	X	X												
Urine pregnancy test as required pre Chest X-ray/CT scan	X													
Chest X-ray	X													
CT scan	X													

HAP-FAST Protocol V3.0, 14/11/2023
Based on protocol template v1.0 20/02/2020

Sputum sample		X			[3]X								[3]X	
FAPP		X												
Informed consent		[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X
Past Medical history	X													
Admission related data (date, time, symptoms, co-morbidities, ward type, reason for admission, clinical frailty score)	X													
Patient demographics (age, sex, postcode, height, weight, calculated BMI)	X													
Details of antibiotic use	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (temperature, blood pressure pulse rate, oxygen saturation rate, respiratory rate, NEWS2 score)	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Record clinician's description of symptoms	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Record clinician's respiratory exam findings	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Blood test results (haemoglobin, platelets, white blood count, neutrophils, lymphocytes, creatinine, c-reactive protein and urea)	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		

CAP-sym score	[4]X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	X	X
Record survival status	X		X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L	[4]X											[1]X	X	X
Nasal swab	[35]X				[3]X								[3]X	
Research blood sample	[35]X				[3]X								[3]X	
Post-discharge Indirect Cost Survey														X
Record microbial results from admission														X
Record any further imaging and findings														X

[1] collected until day 10 or discharge

[2] collected as soon as possible up until discharge

[3] collected for the exploratory sub-study only

[4] not to be collected until written informed consent is obtained

[5] must be collected within 24 hours of stage 1 randomisation

11 SUB-STUDIES

11.1 Costing analysis

11.1.1 Background

This feasibility study will test a number of diagnostic pathways, referred to here as dynamic treatment regimens (DTRs), for managing patients suspected of Hospital Acquired Pneumonia (HAP). Following this feasibility study, we will design a definitive RCT to determine which DTR is most effective. However, for that future study to generate a complete assessment of the effectiveness of each different DTR, the relative cost of each DTR must be known. This will enable a cost effectiveness analysis of clinical efficacy versus cost to conclude which DTR should become NHS standard of care in the future.

At present, the cost of HAP within an NHS setting is not known nor are the individual components which contribute to that overall cost. Moreover, it is likely that a small number of costs have a disproportionate impact on the overall cost of HAP, for example length of stay, but we do not know the extent to which these will vary across DTRs. To address these evidence gaps, a costing analysis of HAP will be embedded within the feasibility study. This costing analysis will seek to capture in detail the direct costs incurred in hospital. However, we will also capture post-discharge indirect costs with a bespoke questionnaire. We will evaluate the performance of this questionnaire which we have developed with reference to a range of similar studies.[30-33] We will capture item completion rates, and discuss participant and carer's views of the questionnaire in order to refine it for the future full scale RCT.

11.1.2 **Aim**

The aim will be to determine the design and analysis plan for a cost effectiveness analysis of the different DTRs to be embedded into the future definitive RCT.

11.1.3 **Objectives**

1. Itemise costs associated with the different DTRs in the feasibility study
2. Determine which costs are directly attributable to HAP – and generate an estimate and standard deviation for the cost of HAP within the NHS
3. Determine which are the largest and most influential costs in HAP and how they vary across DTRs
4. Determine the effect of recruitment site on the above costs
5. Use a patient questionnaire to estimate the post hospitalisation indirect costs in HAP and how these are affected by the DTRs
6. Evaluate the performance and participant experience of the post discharge questionnaire in order to refine it for use in a future RCT

11.1.4 **Methods**

1. Itemise hospital costs for participants within each DTR. The time point for beginning each subject's costing analysis will be the date and time of diagnosis of HAP. Prospective, micro-costing of healthcare materials and processes will be obtained from the following databases:
    i. NHS Schedule of costs
    ii. British National Formulary
    iii. NHS drug prices and local hospital finance department data
2. By consulting the patients record, clinical judgement will be used to determine whether individual costs are related to HAP or underlying health conditions or the condition which provoked the original admission to hospital. Where there is ambiguity in attributing a cost, we will clarify with the treating clinical team.
3. Micro-costing data will undergo sensitivity analysis to determine the key drivers of costs to take forward into a future definitive RCT. As part of this, we will generate a summary of key cost driver statistics, the variability between DTRs and the effects size of each DTR on cost and the scope of hospital activity which represents the biggest contributor to overall cost of a HAP episode.
4. We will evaluate any differences in DTR costs between the 3 recruiting hospital Trusts. This will allow us to generalise HAP costs within the NHS and determine the extent to which any large costs are site specific.
5. In accordance with the NICE guide to methods of technology appraisal (Section 2.2.9), we will capture personal social services costs and describe how these differ between DTRs.
https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781
6. Indirect costs will be captured up to 90 days following the diagnosis of HAP. A bespoke questionnaire will be provided to each subject on discharge – see appendix C. The questionnaire will capture items such as absence from work, domiciliary care costs, visits to the GP and out of hospital prescribing.
7. Validate and refine the content and format of the post-hospitalisation indirect costing questionnaire in order to improve it for use in the future full-scale RCT.

11.2 Qualitative sub-study

11.2.1 Background

We will conduct a qualitative study nested within the above pilot RCT study to systematically gather the views of a range of study stakeholders and use the findings to inform the design and methodology of a future fully powered RCT. Qualitative studies have previously been used to enhance trial design from participants' perspectives and improve future participants' experiences within trials. In particular we are keen to understand potential barriers to recruitment – from both the patient, carer, healthcare worker and researcher perspectives. Moreover, we want to analyse the perceptions of these same stakeholders with respect to our consent model. As explained above, written consent will be deferred until after randomisation. This is due to the inability to predict the onset of HAP and the urgency of performing diagnostic tests and administering treatment.[28]

11.2.2 Aim

To inform and refine the protocol to ensure optimal recruitment and retention to a future fully powered randomised control trial.

Research questions to be addressed in interviews and focus groups

- Among research practitioners
  What are the perceived barriers to recruitment and retention within the pilot study protocol and how might these be overcome?
  What was their experience of the deferred consent model?[29,34]
- Among participants, their carers and eligible patients who declined to participate
  What was their experience of participation and follow-up within the pilot study protocol and how might this experience be improved? In particular, how do they feel about the deferred consent model and what are the perceived benefits and downsides of the two interventions?
  What were the perceived barriers to participation and follow-up within the pilot study protocol and how might these be overcome?[35]
- Among healthcare workers involved in the management of hospital acquired pneumonia
  What were doctors' experience of randomisation within the pilot study protocol and what are their suggestions for refining the process?
  How do doctors describe the decision-making process around the prescription of antibiotics for study participants with HAP/RTI and how this was influenced (or not) by the FAPP and the CT scan?
  Among radiographers, nurses, physios – what are their experiences of the pilot study, perceived barriers to its delivery and how might the study be improved to enhance recruitment, efficiency, and retention?
  How do healthcare workers talk about participation conduct and the perceived 'worth' of research and their role in it – and how might that influence the successful conduct of a trial? https://academic.oup.com/fampra/article/24/3/269/484626?view=extract

Objectives to address the aim and answer the research questions

1. Conduct and analyse semi structured interviews with a purposive sample of participants and their carers and use the findings to refine trial design.
2. Conduct and analyse semi structured interviews with a sample of eligible patients who declined to participate.
3. Conduct and analyse a series of focus groups and interviews with a purposive sample of healthcare workers and researchers to learn from their experience of conducting the study and improve the design for a future RCT.

11.2.3 **Methods**

Recruitment and sampling

Assessment of study participant and carer experience of participating in the study

Sampling

To maximise variation in terms of age, gender and underlying comorbidity (medical admission, surgical admission, acute admission), 5 participants from each of the 3 recruiting Trusts (i.e. an initial sample of 15 participants) will be purposively sampled for these in-depth semi-structured interviews. More participants may need to be interviewed as required to reach data saturation. We will similarly interview the carers of 6 participants (2 per hospital) who lack capacity.

Recruitment and consent

Written informed consent for participation in qualitative interviews will be requested from all patients who are approached about the pilot study. Due to the nature of qualitative research, remote (e.g. telephone, MS Teams/Zoom) interviews may be required - in which case we will seek verbal recorded consent.

Participants will be made aware that not everyone will be selected for an interview and participants will have the option on the consent form to opt in or out of the qualitative interview irrespective of their participation in the pilot study. Those who volunteer will have their contact details shared with an experienced post-doctoral qualitative study researcher. The researcher will then liaise with recruiters to establish when the participant will be discharged from hospital. 14 days after hospital discharge, the researcher will contact the participant to offer more information as required and arrange an initial interview date and time.

Interview design and conduct

Given the high proportion of frail and elderly participants who develop HAP our preference is that most interviews will be face-to-face in their homes, residential care settings, rehab units, or other preferred place, as permitted by social distancing restrictions at the time. If restrictions are still in place, or if participants prefer, they will be interviewed by telephone or video-call.

Interviews will be topic guided, yet conversational and exploratory and conducted in a comfortable private environment. Interviews will be conducted by the qualitative researcher under the supervision of the qualitative lead (BY). Patient and carer topic guides will be periodically revised in light of the ongoing analysis to ensure exploration of unanticipated but important issues. However, the starting point for topic guides will be developed collaboratively with public contributors and we anticipate that interviews would explore the following areas:

- Perceptions of the interventions;
    - in particular the process of having a CT scan
    - perceptions around the increased radiation exposure associated with CT scans
    - perceptions around the identification of unexpected findings by CT scans
    - perceived value – or not – of the FAPP test and its influence on pathogen identification and antibiotic prescribing
- Recruitment and consent – in particular the deferred consent model
- Study documentation and communication
- Care and treatment following randomisation
- Study follow-up

Eligible patients who decline to participate in the feasibility study

We will interview a sample of 9 patients (3 from each Trust) who decline to participate in the feasibility study, aiming for a diverse sample of such patients based on the same purposive sampling approach described

above, but as interviewing progresses and our analysis of the views and experiences of those who decline develops, we may refine this purposive sampling strategy. A flexible and sensitive approach will be taken interviewing patients who decline the feasibility study. For example, if the patient prefers, an interview could take place during the admission – so long as the patient is stable enough to take part and an appropriately private environment can be found. In this case, it may be that a member of the wider research team, with the relevant interviewing experience and where delegated by the PI, conducts the interview. In some instances, it may be possible for a qualitative researcher to conduct in-patient interviews on site in the hospital – for example on a non-acute rehabilitation ward – or via a phone interview where a suitable environment permits. Where in-patient interviews are neither preferred nor possible – out-patient interviews as described above will be offered.

Exploration of clinical and research teams' views of the study and its implementation

Focus groups as well as interviews have been chosen to capture not only a range of views but the interaction of different cadres of staff – which will be informative given the possible power dynamics and differing points of view within clinical environments.

Sampling

We will hold 2 rounds of focus groups at each Trust– the first after 3 months of recruitment and the next after 9 months of recruitment (i.e., a total of 6 focus groups). We will invite a range of clinical, allied health professional and research staff to participate. We anticipate there being approximately 8 participants in each focus group. Interviews will also be conducted if required.

Recruitment and consent

The site PI will identify a representative range of healthcare workers and research practitioners who have had experience of the pilot RCT. Information leaflets will be offered and those who are interested will agree to have their contact details shared with a qualitative post-doctoral researcher who will coordinate the focus group or interview. Our aim will be for consent to be written and the focus group or interview to be in person. However, due to the ongoing pandemic and associated restrictions we may need to perform remote, video assisted (e.g., MS Teams/Zoom) focus groups/interviews - in which case we will seek verbal recorded consent.

Focus group and interview design and conduct

Focus groups and interviews will be topic guided, yet conversational and exploratory and conducted in a comfortable environment. They will be conducted by an experienced qualitative researcher, under the supervision of the qualitative lead (BY). We anticipate key area to explore will be:

- Recruitment and consent process
  A particular focus will be on the deferred consent model and the process of randomisation and the degree to which these were practical and acceptable.
  What, if any, are the perceived barriers to recruitment and how might these be addressed and the process improved.
- Interventions
  Implementation of early CT scans and their reporting
  Implementation of the FAPP
  We will focus on an exploration of attitudes to obtaining sputum samples – their perceived benefit in the usual care Dynamic Treatment Regimens (DTRs) versus the FAPP containing DTRs.
  What are the perceived barriers or obstacles to obtaining sputum samples and how can they be overcome?
- Antibiotic prescribing

How clinical decision making has been influenced by the CT scans and the FAPP?
What are the factors that affect adherence to antibiotic guidelines?

11.2.4 **Analysis**

Data analysis

We will draw on recommendations regarding the design, conduct, analysis and reporting of qualitative research, including those on qualitative studies embedded in feasibility trials, to ensure the methodological integrity and utility of the qualitative work.[36,37]

Interviews and focus groups will be audio-recorded, checked and anonymised by the research team before being transcribed by a professional agency. Once transcripts have been checked, all audio-recordings will be deleted. All audio recordings, transcripts and associated spreadsheets with participant data will be encrypted, securely stored and appropriately access restricted.

Professional qualitative data analysis computer software will be used to assist with coding the transcripts. The qualitative researcher will lead the analysis in collaboration with DW and they will meet regularly with BY to review a proportion of transcripts and compare coding and interpretations.

The interviews and focus groups will initially be analysed as separate sets to avoid, for example, interpretations of the staff interviews overshadowing those of the patients and relatives or vice-versa. Analysis of transcripts will be interpretative and draw on thematic approaches suited to the pragmatic aim of this qualitative research which is to inform a future study. Analysis will primarily be inductive but may incorporate deductive elements to assess the resonance of the findings to other studies. Rather than take the expressed views at face value we will compare and interpret across interviews to understand the psychological factors behind the way in which colleagues and participants speak about this research. As the analysis progresses, we will seek to develop categories and themes that integrate across the patient, relative and staff datasets by comparing across these, whilst also highlighting divergence in their perspectives.

11.3 **Exploratory sub-studies**

Laboratory based exploratory sub-studies will be performed on research blood, sputum and nasal swab samples obtained from the pilot study participants (see schedule of events) and compared to a sample of up to 50 stable, sputum producing participants without pneumonia. The work will be carried out by University of Liverpool PhD students supervised by DW, SA and LT.

Aim

Explore associations between immune cells, causative pathogens, inflammatory responses, severity and outcome among our HAP cohort.[38-46]

Objectives

1: Characterisation of immune cells and inflammatory responses in whole blood, sputum and nasal swabs from up to 50, non-exacerbating, sputum producing volunteers from clinic.

2: Measure immune cells and inflammatory responses in samples from the cohort of HAP patients and explore associations with clinical outcome.

3: Use regression analysis to explore associations between immune cell numbers and characteristics, inflammatory responses, markers of coagulation and different pathogens identified using the FAPP from the pilot study cohort.

4: Collaborate with NHS immunology laboratory to translate research assays above into the NHS laboratory to support future clinical and clinical research work.

11.3.1 Inclusion criteria for stable, sputum producing patients identified from NHS clinics and sampled for the exploratory study

Inclusion

- ≥18 years
- Ongoing follow up in a respiratory clinic
- Chronic sputum production
- Fit either of the two categories:
    - no colonising organisms found in sputum during stable state on at least 2 consecutive occasions at least 3 months apart
    - same organism identified in sputum while clinically stable on at least 2 occasions at least 3 months apart

Exclusion

- Not willing or able to provide 3 paired blood, sputum and nasal swab samples each ≥ 2 weeks apart
- Patients taking the following drugs:
    - Long term oral steroid use (any dose)
    - Methotrexate
    - Cyclophosphamide
    - Anti-TNF drugs, Rituximab or other biological therapies
- Exacerbation or infection requiring acute antibiotics and or oral steroids within the last 4 weeks*

*If a patient exacerbates in between the three planned samples – e.g. between the first and second – then 4 weeks should elapse following completion of any treatments before any subsequent samples are taken i.e. patient should be at a self-reported baseline level of symptoms.

11.3.1.1 Screening stable sputum producing patients for exploratory work

Research teams within the participating NHS Trusts will screen clinics for patients meeting the above criteria.

11.3.1.2 Recruitment and consent of stable sputum producing patients for exploratory work

Patients identified by the research teams as potential recruits will be flagged to clinicians during planned clinic visits. Clinicians carrying out clinic appointments will ask patients if they would mind talking to the research team before or after their appointment.
The research team will provide a Patient Information Sheet and explain the research and what is involved. If the patient agrees to provide samples they will sign a consent form.

11.3.1.3 Samples for stable sputum producing patients for exploratory work

Blood samples taken to support these exploratory sub-studies will be identical to those described in the main pilot study of patients with HAP i.e. 32.5 ml Research blood sample comprising:

2 x 9 ml EDTA
2 x 2.5 ml PAX-gene
1 x 5 ml serum gel
1 x 4.5 ml citrate (clotting)

Sample collection

Sample timing is flexible and should be arranged to suit both the participant and the available research and laboratory staff, however samples should not be taken less than 14 days apart. If the participant is willing, then the first paired blood, sputum and nasal swab samples could be obtained during the same visit as the consent is obtained. Blood samples will be taken by the research team or phlebotomy service present in clinic. If the participant would prefer to come back on another occasion for sampling then the time and date can be arranged with the research team.

Sample storage and handling

See also the laboratory manual

Some samples will be sent to the NHS clinical laboratories. Other samples will have an initial stage of processing within the research laboratory at Liverpool University Hospitals NHS Foundation Trust or the laboratory at Ronald Ross building of the University of Liverpool. Some assays will occur immediately within the above research laboratories – others will occur later, on stored, frozen aliquots of these samples.

12 SAFETY REPORTING

As this study only incorporates well-established and non-invasive diagnostic investigations that would normally be carried out as standard of care, safety events will not be recorded as part of this study.

12.1 Contact Details and Out-of-hours Medical Cover

Emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for HAP-FAST participants. All participants will be provided with a contact card and copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

13 STATISTICAL CONSIDERATIONS

13.1 Introduction

This section relates primarily to the pilot study aspects of the feasibility study. Questions of sample size and analysis regarding the sub-studies are outlined in section 11.

13.2 Sample Size

13.2.1 Sample Size Calculation

Since this is a feasibility/pilot study, a sample size justification is given rather than a calculation. Prospective audits of HAP at Liverpool University Hospitals NHS Foundation Trust and Lancashire Teaching Hospitals NHS Foundation Trust reveal 1200 and 706 cases per year respectively. Assuming 30% of cases are eligible of whom 40% are recruited we estimate 220 participants. This is at the top end of pilot study size described in the audit of UK CLRN database but we feel it is justified by the above objectives, in particular to establish a signal of efficacy and to inform decisions regarding outcome selection.

13.2.2 Sample Size considerations

Two factors further affect recruitment targets:-

- Seasonality: our hospital audits demonstrate that HAP incidence is greater in the winter than the summer. To account for seasonal variation in pathogens it is important that we recruit across a full calendar year.
- Differences between hospitals: we do not know whether recruitment will be similar in each hospital. We will recruit from more than one hospital since the definitive study will need to be multi-centre, and one of our aims is to demonstrate feasibility in 2 hospitals with different characteristics.

13.3 Method of Randomisation

13.3.1 Allocation Sequence Generation

For each randomisation system, a randomisation list will be created by an independent statistician.

13.3.2 Allocation Sequence

Participant allocations will be irrevocably generated upon completion of the web-based randomisation form.

Interim Analyses
There are no planned interim analyses for this study.

Analyses of the accumulating data will be performed at regular intervals (at least annually) for review by the review committees (TMG/TSC). These analyses will be performed at the LCTC. The committees will be asked to give advice on whether the accumulated data from the study, together with results from other relevant trials, justifies continuing recruitment of further participants or further follow-up. A decision to discontinue recruitment, in all participants or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the study and the general clinical community.

13.4 Analysis Plan

13.4.1 Pilot Study

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the SAP are summarised below:

Feasibility and overall recruitment rate will be assessed for each participating site and overall by calculating the total number of participants randomised per month and the ratio of successful recruitment to eligible patients approached.

Much of the analysis will be performed using summary statistics and graphical representations of outcomes at each time-point and by DTR. Formal assessments of efficacy, will be made for each outcome, for the following treatment arms comparisons: FAPP vs no FAPP (groups 1 and 5 vs groups 2 and 6); and CXR vs CT (groups 1-4 vs groups 5-8). No inference will be drawn – all results will be treated as hypothesis generating.

Continuous data will be presented using median (interquartile range) and mean (standard deviation) as appropriate, with boxplots summarising measurements at each time-point by treatment group. Categorical

data will be presented as frequencies and percentages. Time-to-event data will be presented with Kaplan-Meier curves, and summarised by median (95% confidence interval) if possible.

All analyses shall be carried out on an intention to treat basis, retaining all participants in their initially randomised groups irrespective of any protocol deviations.

As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis. Such methods will be fully described in the SAP.

14 DATA MANAGEMENT AND TRIAL MONITORING

For the HAP-FAST study the responsibilities for Data Management and monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans will detail regarding the internal processes that will be conducted at the LCTC throughout the study. Justification for the level of monitoring is provided within those documents and the study-specific risk assessment. All data will be managed as per local LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

14.1 Source Documents

Data will be entered directly on to the database without the use of a paper case report form. As such, for data items where no prior record exists the eCRF on the database will be considered the source document. A HAP-FAST source document list will be produced for each site to be kept in the ISF and provide detail of what constitutes HAP-FAST-specific source data.

Date of written informed consent processes (including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (and possible treatment arms) should be added to the patient's medical record chronologically.

14.2 Data Collection Methods

Data are to be entered into the study database by members of the research team at site. The database includes validation features which will alert the user to certain inconsistent or missing data on data entry. If any problems are identified via automated validation or central monitoring, a query will be raised within the database and the site will be notified. A complete log of discrepancies and data amendments is automatically maintained including the date of each change, the reason for the change and the person who made the change, thus providing a complete audit trail. Automated email reminders can be generated by the database if follow up data from a scheduled participant visit is overdue.
Training will be provided as necessary prior to data entry.

14.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the study and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with Sponsor.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of monitoring will be conducted.

This will be dependent on the documented risk assessment of the study which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to study interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the study are detailed in Roles and Responsibilities see section 0.

14.3.1 **Central Monitoring**

There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the study data, to be detailed in the Trial Monitoring Plan. Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to participant rights and safety will also be regularly performed as per LCTC processes. Where discrepancies are found, data queries will be raised by the LCTC and sent to site staff to resolve or explain discrepancies, with appropriate corrections made on the database.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

14.3.2 **Clinical Site Monitoring**

In order to perform their role effectively, the trial coordinator and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the PISC. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

1) assessing compliance with the study protocol
2) discussing any emerging problems that may have been identified prior to the visit
3) checking eCRF and query completion practices

14.4 **Risk Assessment**

(ICH GCP 5.18.3) "The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the study. In general there is a need for on-site monitoring, before, during and after the study; however …central monitoring in conjunction with procedures such as investigators' training and meetings and extensive written guidance can assure appropriate conduct of the study in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified."

A bespoke trial risk assessment will be conducted for HAP-FAST, which will inform the level of monitoring to be implemented.

14.5 **Confidentiality**

This study will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the study

(e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

eCRFs will be labelled with a unique trial randomisation number. Verification that appropriate written informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the LCTC by recruiting sites. This transfer of identifiable data is disclosed in the PISC.
N.B. Consent forms must be transferred separately to any other study documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by the LCTC will be notified promptly to the study Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

Research sites will be responsible for administering questionnaires to study participants 3 months following completion of assessments and therefore will be required to receive contact details including name, address, email and telephone details. Access to these contact details will be restricted.

14.6 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of study-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the study specific training. A greenlight checklist will verify all approvals are in place prior to study initiation at LCTC and the individual centre.
- The study will be conducted in accordance with procedures identified in the protocol.
- The independent members of the TSC will provide independent oversight of the study.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the study Data Management Plan.

14.7 Records Retention

The retention period for the HAP-FAST data and information is 10 years from the official End of Trial date.

The PI at each investigational site must make arrangements to store the essential study documents (as defined by ICH GCP guidelines) including the Investigator Site File and the applicable participant medical records, for the full length of the study's retention period and will arrange for confidential destruction at the end of this period as instructed by the Liverpool Clinical Trials Centre.

The PI is also responsible for archiving all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the study will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g. laboratories, third-party vendors, etc.).

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All eCRFs and study data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

15 REGULATORY AND ETHICAL CONSIDERATIONS

15.1 Statement of Compliance

The procedures detailed within this protocol are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken.

15.2 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone ethical review by an independent Research Ethics Committee and has received a favourable opinion.

15.3 Approvals

The protocol, PISC and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA) and host institution(s) for written approval.
Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

15.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and MHRA and REC requirements are handled based on their nature and severity.

15.4.1 Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

15.4.2 **Serious breaches**

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the study become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committee (TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.
The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the study. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to the REC.

Breaches confirmed as 'serious' will be reported to the REC within 7 days by the LCTC on behalf of the University of Liverpool and notified to the TMG and TSC at their next meeting.
Any requests for additional information from the Sponsor, TMG, TSC, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.
Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

16 **INDEMNITY**

The University of Liverpool holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

17 **PUBLICATION AND DISSEMINATION**

17.1 **Publication Policy**

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the study's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this study will be attached to any publications resulting from this study and members of the TSC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

17.1.1 **Authorship**

Contributors to all 4 of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the HAP-FAST Consortium which will also be named at the manuscript head.

17.2 **Dissemination to Key Stakeholders**

On completion of the research, a Final Trial Report will be prepared and submitted to the REC. The results of HAP-FAST will be published regardless of the magnitude or direction of effect.

17.3 **Data Sharing**

At the end of the study, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank eCRF) will be prepared in order to be shared with external researchers. All requests for access to the IPD will be reviewed by the Sponsor.

18 **CHRONOLOGY OF PROTOCOL AMENDMENTS**

18.1 **Version 3.0 (15/Sept/2023)**

Summary of Amendment from Protocol v2.0 to Protocol v3.0		
Protocol Section Number	Protocol Section Title	Summary of Changes
6.1.2	Study Setting	Addition of a +/- 7 day window for the day 28 follow-up visit.
6.3.2	Clinicians	Option for interviews to be conducted with health care professionals as well as focus groups.
7.1.1	Inclusion Criteria	Definition for Hospital Acquired Pneumonia added.
7.2.1	Inclusion Critiera	Requirement that sputum has been obtained prior to the 2nd dose of antibiotic.
7.2.2	Exclusion Crtieria	Removal of “A sputum sample cannot be obtained before 2nd dose of antibiotic" as an exclusion criteria as this is covered in the inclusion criteria.
10.4.1	Sample Collection	Clarification of where sputum samples will be obtained from.

10.5.2	Obtaining Written Informed Consent/Assent	Postal consent added.
10.5.4	Consent Form Completion	Clarification that samples cannot be analysed until informed consent has been obtained.
10.9	Schedule for Assessments and Follow-up	Removal of requirement for stage 2 randomisation to be done within 8 hours of stage 1 randomisation. Removal of requirement for concomitant medications checks to be done every day for 10 days and at day 28.
11.2.3	Methods	Verbal consented added for patients taking part in the qualitative sub-study.

18.2 **Version 2.0 (30/Nov/2022)**

Summary of Amendment from Protocol v1.0 to Protocol v2.0		
Protocol Section Number	Protocol Section Title	Summary of Changes
1.1.2	Exclusion Criteria	Ventilator acquired pneumonia has been added to the exclusion criteria for stage one randomisation.
10.5.2	Obtaining Written Informed Consent/Assent	Clarification that data captured up until discharge will be kept for analysis if informed consent has not been obtained.
10.5.3	Patients who lack capacity	A personal consultee or a nominated consultee will be appointed to provide informed consent is a patient lacks capacity. Patient's next of kin will be informed of their participation in the trial if they pass away before informed consent is obtained.

18.3 **Version 1.0 (12/09/2022)**

Original Approved version.

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20 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

20.1 Appendix A: CAP-sym questionnaire

Participant Identification Number: _____

Date: _____

In the past 24 hours, how much have you been bothered by:

	Patient did not have the symptom/problem	Patient had the symptom/problem and it bothered him/her...				
		Not at all	A little	Moderately	Quite a bit	Extremely
*1. Coughing?	0	1	2	3	4	5
*2. Chest pains?	0	1	2	3	4	5
*3. Shortness of breath?	0	1	2	3	4	5
4. Coughing up phlegm/sputum (secretion from the chest)?	0	1	2	3	4	5
5. Coughing up blood?	0	1	2	3	4	5
*6. Sweating?	0	1	2	3	4	5
*7. Chills?	0	1	2	3	4	5
*8. Headache?	0	1	2	3	4	5
*9. Nausea?	0	1	2	3	4	5
10. Vomiting?	0	1	2	3	4	5
11. Diarrhea?	0	1	2	3	4	5
12. Stomach pain?	0	1	2	3	4	5
*13. Muscle pain?	0	1	2	3	4	5
*14. Lack of appetite?	0	1	2	3	4	5
*15. Trouble concentrating?	0	1	2	3	4	5
16. Trouble thinking?	0	1	2	3	4	5
*17. Trouble sleeping?	0	1	2	3	4	5
*18. Fatigue?	0	1	2	3	4	5

* Indicates items that are included in the CAP-Sym 12.

20.2 Appendix B: EQ-5D-5L Quality of Life Questionnaire

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

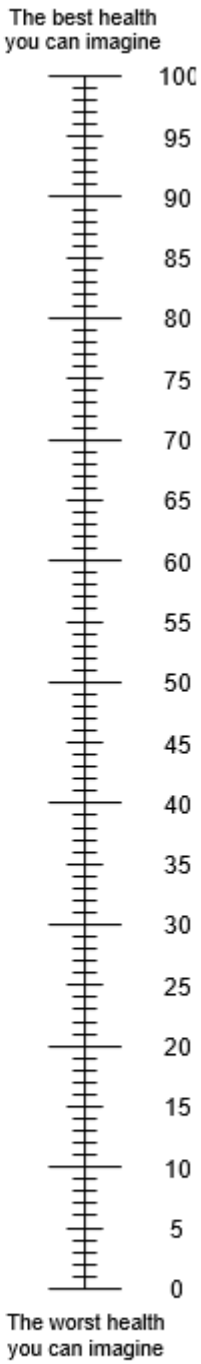
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



20.3 Appendix C: POST-DISCHARGE INDIRECT COST SURVEY

Thank you for completing this survey. The idea of this survey is to get an idea of how events in hospital influence what happens once a patient goes home. We are interested in the period up to 90 days (three months) from the date you joined the study

We would recommend you add notes to this questionnaire every week as it is easy to forget the details about what has happened.

We have provided you with an addressed envelope to return the questionnaire. In case it gets lost in the post we will give you a call at around 90 days to go through it with you.

1.

Since your discharge from hospital, have you had a GP appointment?	Yes □	No □
If yes, how many appointments?	_____ appointments	
What were the reasons for these appointments?		

2.

Since your discharge, have you had to go back to hospital?	Yes □	No □
What were your symptoms that prompted you to go back to hospital?		
How long were you in hospital for?	_____ days	

3.

Since your discharge from hospital, have you had any further investigations (for example blood tests, scans, breathing tests or camera tests)?	Yes □	No □
Do you know why the doctor ordered these tests?		

4.

After you left hospital did you go to a respite or rehabilitation bed?	Yes □	No □
If yes, what kind of facility did you go to?	Care home □ Nursing home □ Rehabilitation bed □ Other:_____	
How many days were you there?	_____days	

5.

Since your discharge, have you gone to a hospital clinic appointment?	Yes □	No □
If yes, what was the reason for the clinic appointment		

6.

Have you had *NEW* any help from the following community services?	How long do their visits last?	How many times a week do they come to help?	What is the reason you need this help?
Home carer □	_____ hours	_____ per week	
District nurse □	_____ hours	_____ per week	
Cleaner □	_____ hours	_____ per week	
Social worker □	_____ hours	_____ per week	
Health visitor □	_____ hours	_____ per week	
Physiotherapist □	_____ hours	_____ per week	
Occupational therapist □	_____ hours	_____ per week	
Other:_____	_____ hours	_____ per week	
Other:_____	_____ hours	_____ per week	

7.

Since your discharge from hospital, have you started taking any new medications prescribed by your GP?	Yes □	No □
If yes, what were these medications?	Course length (if long term, please leave blank)	
Medication name:	_____ days	
Medication name:	_____ days	
Medication name:	_____ days	
Medication name:	_____ days	
Other:		

8.

Have you missed work due to being ill since your discharge from hospital?	Yes □	No □
If yes, how many days have you missed?	_____ days	
How much do you earn an hour? Approximately	£_____	
How many hours do you work in a normal working day?	_____ hours	
What is the reason you had had time off work?		

9.

Since your discharge from hospital, have friends or family had to take time off work to help you?	Yes □	No □
If yes, how many days have they missed	_____ days	
How much do they earn an hour? Approximately	£_____	
How many hours do you work in a normal working day	_____ hours	
What is the reason you need their help?		

20.4 Appendix D: BioFire® FilmArray® Pneumonia Panel Testing

BioFire® FilmArray® Pneumonia Panel Testing

Purpose

This procedure provides instructions for testing sputum-like specimens (induced or expectorated sputum, or endotracheal aspirates) or bronchoalveolar lavage (BAL)-like specimens (BAL or mini-BAL) using the BioFire Pneumonia Panel kit.

Background

The BioFire Pneumonia Panel is a multiplexed nucleic acid test intended for use with BioFire® FilmArray® 1.5, BioFire® FilmArray® 2.0, or BioFire® FilmArray® Torch systems for the simultaneous detection and identification of multiple respiratory viral and bacterial nucleic acids, as well as select antimicrobial resistance genes, in sputum-like specimens (induced or expectorated sputum, or endotracheal aspirates) or bronchoalveolar lavage (BAL)-like specimens (BAL or mini-BAL) obtained from individuals suspected of lower respiratory tract infection.

The following bacteria are reported semi-quantitatively with bins representing approximately 10^4, 10^5, 10^6, or ≥10^7 genomic copies of bacterial nucleic acid per milliliter (copies/mL) of specimen, to aid in estimating relative abundance of nucleic acid from these common bacteria within a specimen:

Bacteria reported with bins of 10^4, 10^5, 10^6, or ≥10^7 copies/mL		
Acinetobacter calcoaceticus-baumannii complex	Klebsiella oxytoca	Serratia marcescens
Enterobacter cloacae complex	Klebsiella pneumoniae group	Staphylococcus aureus
Escherichia coli	Moraxella catarrhalis	Streptococcus agalactiae
Haemophilus influenzae	Proteus spp.	Streptococcus pneumoniae
Klebsiella aerogenes	Pseudomonas aeruginosa	Streptococcus pyogenes

The following atypical bacteria, viruses, and antimicrobial resistance genes are reported qualitatively:

Atypical Bacteria		
Chlamydia pneumoniae	Legionella pneumophila	Mycoplasma pneumoniae
Viruses		
Adenovirus	Human Rhinovirus/Enterovirus	Parainfluenza Virus
Coronavirus	Influenza A	Respiratory Syncytial Virus
Human Metapneumovirus	Influenza B	
Antimicrobial Resistance Genes		
CTX-M	NDM	*mecA/C* and MREJ
IMP	OXA-48-like	
KPC	VIM	

Principle of the Procedure

The BioFire® FilmArray® Pneumonia Panel pouch is a closed-system disposable that stores all the necessary reagents for sample preparation, reverse transcription, polymerase chain reaction (PCR), and detection in order to isolate, amplify, and detect nucleic acid from multiple lower respiratory pathogens within a single bronchoalveolar lavage (BAL)-like (BAL or mini-BAL) or sputum-like (sputum or ETA) specimen. After sample collection, the user injects hydration solution and sample combined with sample buffer into the pouch, places the pouch into a BioFire® FilmArray® Instrument, and starts a run. The entire run process takes about one hour. Additional detail can be found in the appropriate FilmArray Operator's Manual.

Overview

The following is an overview of the operations and processes that occur during a pouch run. During a run, the BioFire® FilmArray® System:

- Lyses the sample by agitation (bead beading).
- Extracts and purifies all nucleic acid from the sample using magnetic bead technology.

- Performs nested multiplex PCR by:
  - First performing reverse transcription and a single, large-volume, massively multiplexed reaction (PCR1).
  - Then performing multiple singleplex, second-stage PCR reactions (PCR2) to amplify sequences within the PCR1 products.
- Uses endpoint melting curve data to detect and generate a result for each target on the BioFire Pneumonia Panel array.
- For the BioFire Pneumonia Panel, the system also uses real-time amplification data from the assays relative to a Quantified Standard Material (QSM) included in the pouch to provide an estimated value in genomic copies per milliliter (copies/mL) for bacterial analytes.

Specimen

Specimen Type	Bronchoalveolar lavage (BAL)-like specimens • Including BAL and mini-BAL collected according to standard technique Sputum-like specimens • Including induced and expectorated sputum, as well as endotracheal aspirate (ETA) collected according to standard technique
Minimum Sample Volume	Approximately 0.2 mL (200 µL) of specimen material will be captured by the Sample Swab for transfer into the test
Transport and Storage	Specimens should be tested with the BioFire® FilmArray® Pneumonia Panel as soon as possible If storage is required, specimens can be held: • Refrigerated for up to 1 day (2–8 °C)

NOTE: BAL-like or sputum-like specimens should not be centrifuged, pre-processed, treated with any mucolytic or decontaminating agents (e.g. MycoPrep, Sputasol, Snap n' Digest, DTT, sodium hydroxide, oxalic acid, trypsin, etc.), or placed into transport media before testing.

Note: In accordance with good laboratory practice recommendations, institutions should follow their own established rules for acceptance/rejection of sputum specimens (e.g. using Gram stain/Q-score) and therefore apply appropriate guidelines locally for acceptance/rejection of a sample for testing.

NOTE: Bleach can damage organisms/nucleic acid within the specimen, potentially causing false negative results. Contact between bleach and specimens during collection, disinfection, and testing procedures should be avoided.

Materials

Materials Provided	Materials Required But Not Provided
Each kit contains sufficient reagents to test 30 samples (30-test kit; RFIT-ASY-0144) or 6 samples (6-test kit; RFIT-ASY-0145): • Individually-packaged BioFire® FilmArray® Pneumonia Panel pouches • Single-use (1.0 mL) Sample Buffer ampoules • Single-use, pre-filled (1.5 mL) Hydration Injection Vials (blue) • Single-use Sample Injection Vials (red) • Individually-packaged Sample Swabs	• BioFire® FilmArray® System including: BioFire® FilmArray® 1.5, BioFire® FilmArray® 2.0, or BioFire® FilmArray® Torch and accompanying software • Pouch Loading Station • 10% bleach solution or a similar disinfectant

Procedure

Refer to the BioFire Pneumonia Panel Quick Guide, the FilmArray Training Video, or the FilmArray Operator's Manual for more detail and pictorial representations of these instructions.

Use clean gloves and other Personal Protective Equipment (PPE) when handling pouches and samples. Only prepare one BioFire Pneumonia Panel pouch at a time and change gloves between samples and pouches. Once sample is

added to the pouch, promptly transfer to the instrument to start the run. After the run is complete, discard the pouch in a biohazard container.

Prepare Pouch

1. Thoroughly clean the work area and the Pouch Loading Station with freshly prepared 10% bleach (or suitable disinfectant) followed by a water rinse.
2. Remove the pouch from its vacuum-sealed package by tearing or cutting the notched outer packaging and opening the protective aluminum canister.

NOTE: The pouch may still be used even if the vacuum seal of the pouch is not intact. Attempt to hydrate the pouch using the steps in the Hydrate Pouch section. If hydration is successful, continue with the run. If hydration fails, discard the pouch and use a new pouch to test the sample.

Check the expiration date on the pouch. Do not use expired pouches.

Insert the pouch into the Pouch Loading Station, aligning the red and blue labels on the pouch with the red and blue arrows on the Pouch Loading Station.

Place a red-capped Sample Injection Vial into the red well of the Pouch Loading Station.

3. Place a blue-capped Hydration Injection Vial into the blue well of the Pouch Loading Station.

Hydrate Pouch

1. Unscrew the Hydration Injection Vial from the blue cap.

Remove the Hydration Injection Vial, leaving the blue cap in the Pouch Loading Station.

Insert the Hydration Injection Vial's cannula tip into the pouch hydration port located directly below the blue arrow of the Pouch Loading Station.

Forcefully push down in a firm and quick motion to puncture seal until a faint "pop" is heard and there is an ease in resistance. Wait as the correct volume of Hydration Solution is pulled into the pouch by vacuum.

- If the Hydration Solution is not automatically drawn into the pouch, repeat Step 2 to verify that the seal of the pouch hydration port was broken. If Hydration Solution is again not drawn into the pouch, discard the current pouch, retrieve a new pouch, and repeat from Step 1: Prepare Pouch.

Verify that the pouch has been hydrated.

- Flip the barcode label down and check to see that fluid has entered the reagent wells (located at the base of the rigid plastic part of the pouch). Small air bubbles may be seen.
- If the pouch fails to hydrate (dry reagents appear as white pellets), repeat Step 2 to verify that the seal of the pouch hydration port was broken. If hydration solution is still not drawn into the pouch, discard the current pouch, retrieve a new pouch, and repeat from Step 1: Prepare Pouch.

Prepare Sample Mix

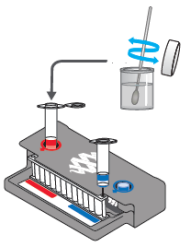
1. Add Sample Buffer to the Sample Injection Vial.
   - Hold the Sample Buffer ampoule with the tip facing up.

NOTE: Avoid touching the ampoule tip during handling, as this may introduce contamination.

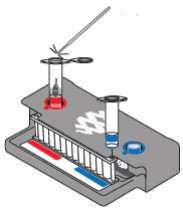
- Firmly pinch at textured plastic tab on the side of the ampoule until the seal snaps.
- Invert the ampoule over the red-capped Sample Injection Vial and dispense Sample Buffer using a slow, forceful squeeze followed by a second squeeze.

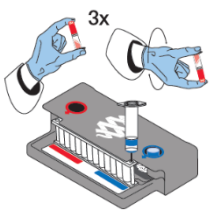
NOTE: Avoid squeezing the ampoule additional times. This will generate foaming, which should be avoided.

Using the Sample Swab provided in the test kit, thoroughly stir the BAL-like or sputum-like specimen for about 10 seconds.



2. Place the swab end of the Sample Swab into the Sample Injection Vial, then break off the swab handle.
3. Tightly close the lid of the Sample Injection Vial and discard the swab handle into the appropriate waste container.
4. Remove the Sample Injection Vial from the Pouch Loading Station and invert the vial at least 3 times to mix.

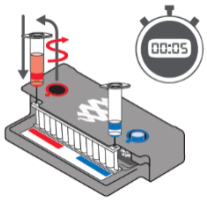




5. Return the Sample Injection Vial to the red well of the Pouch Loading Station.

Load Sample Mix

1. Slowly twist to unscrew the Sample Injection Vial from the red cap and wait for 5 seconds with the vial resting in the cap.



NOTE: Waiting 5 seconds decreases the risk of dripping and contamination from the sample.

2. Lift the Sample Injection Vial, leaving red cap in the well of the Pouch Loading Station, and insert the Sample Injection Vial cannula tip into the pouch sample port located directly below the red arrow of the Pouch Loading Station.
3. Forcefully push down in a firm and quick motion to puncture seal (a faint "pop" is heard) and sample is pulled into the pouch by vacuum.
4. Verify that the sample has been loaded.
   - Flip the barcode label down and check to see that fluid has entered the reagent well next to the sample loading port.
   - If the pouch fails to pull sample from the Sample Injection Vial, the pouch should be discarded. Retrieve a new pouch and repeat from *Step 1: Prepare Pouch*.
5. Discard the Sample Injection Vial and the Hydration Injection Vial in appropriate biohazard sharps container.
6. Record the Sample ID in the provided area on the pouch label (or affix a barcoded Sample ID) and remove the pouch from the Pouch Loading Station.

Run Pouch

The BioFire® FilmArray® Software includes step-by-step on-screen instructions that guide the operator through performing a run.

BioFire® FilmArray® 1.5 and BioFire® FilmArray® 2.0

1. Ensure that the BioFire 1.5 or BioFire 2.0 system (instrument and computer) is powered on and the software is launched.
2. Follow on-screen instructions and procedures described in the Operator's Manual to place the pouch in an instrument. Enter pouch, sample, and operator information.
3. Pouch identification (Lot Number and Serial Number) and Pouch Type information will be automatically entered when the barcode is scanned. If it is not possible to scan the barcode, the pouch Lot Number, Serial Number, and Pouch Type can be manually entered from the information provided on the pouch label into the appropriate fields. To reduce data entry errors, it is strongly recommended that the pouch information be entered by scanning the barcode.

NOTE: When selecting a Pouch Type manually, ensure that the Pouch Type matches the label on the BioFire® FilmArray® Pneumonia Panel pouch.

4. Enter the Sample ID. The Sample ID can be entered manually or scanned in by using the barcode scanner when a barcoded Sample ID is used.
5. Select and confirm the appropriate protocol from the Select Protocol dialog box. The BioFire Pneumonia Panel uses two different protocols that should be selected according to the sample type (BAL or sputum) that is being tested.
6. Enter a user name and password in the Name and Password fields.

NOTE: The font color of the username is red until the user name is recognized by the software.

7. Review the entered run information on the screen. If correct, select Start Run.

Once the run has started, the screen displays a list of the steps being performed by the instrument and the number of minutes remaining in the run.

NOTE: The bead-beater apparatus can be heard as a high-pitched noise during the first minute of operation.

8. When the run is finished, follow the on-screen instructions to remove the pouch, then immediately discard it in a biohazard waste container.
9. The run file is automatically saved in the BioFire® FilmArray® Instrument database, and the test report can be viewed, printed, and/or saved as a PDF file.

BioFire® FilmArray® Torch

1. Ensure that the BioFire Torch system is powered on.

2. Select an available Module (instrument) on the touch screen or scan the barcode on the pouch using the barcode scanner.
3. Pouch identification (Lot Number and Serial Number) and Pouch Type information will be automatically entered when the barcode is scanned. If it is not possible to scan the barcode, the pouch Lot Number, Serial Number, and Pouch Type can be manually entered from the information provided on the pouch label into the appropriate fields. To reduce data entry errors, it is strongly recommended that the pouch information be entered by scanning the barcode.

NOTE: When selecting a Pouch Type manually, ensure that the Pouch Type matches the label on the BioFire Pneumonia Panel pouch.

4. Enter the Sample ID. The Sample ID can be entered manually or scanned in by using the barcode scanner when a barcoded Sample ID is used.
5. Insert the pouch into the available Module (instrument).
   - Ensure that the pouch fitment label is lying flat on top of pouch and not folded over. As the pouch is inserted, the Module (instrument) will grab onto the pouch and pull it into the chamber.
6. Select and confirm the appropriate protocol from the Select Protocol dialog box. The BioFire® FilmArray® Pneumonia Panel uses two different protocols that should be selected according to the sample type (BAL or sputum) that is being tested.
7. Enter operator user name and password, then select Next.

NOTE: The font color of the username is red until the user name is recognized by the software.

8. Review the entered run information on the screen. If correct, select Start Run.

Once the run has started, the screen displays a list of the steps being performed by the Module (instrument) and the number of minutes remaining in the run.

9. At the end of the run, remove the partially ejected pouch, then immediately discard it in a biohazard waste container.

NOTE: The bead-beater apparatus can be heard as a high-pitched noise during the first minute of operation.

10. The run file is automatically saved in the Biofire® FilmArray® Instrument database, and the test report can be viewed, printed, and/or saved as a PDF file.

Quality Control

Process Controls

Two process controls are included in each pouch:

1. RNA Process Control
   - The RNA Process Control assay targets an RNA transcript from the yeast *Schizosaccharomyces pombe*. The yeast is present in the pouch in a freeze-dried form and becomes rehydrated when sample is loaded. The control material is carried through all stages of the test process, including lysis, nucleic acid purification, reverse transcription, PCR1, dilution, PCR2, and DNA melting. A positive RNA Process Control result indicates that all steps carried out in the BioFire Pneumonia Panel pouch were successful.
2. Quantified Standard Material (QSM) Control
   - The QSM assay detects a quantified standard synthetic nucleic acid that is subject to all stages of the test process following sample lysis (bead beating). A positive QSM control result indicates that the expected level of QSM is present (approximately 10^6 copies/mL) for use in determining assay and bin results for bacterial analytes.

Monitoring Test System Performance

The BioFire® FilmArray® Software will automatically fail the run if the melting temperature (Tm) for either the RNA Process Control or the QSM is outside of an acceptable range (80.3–84.3°C for the RNA Process Control and 82.7–86.7°C for the QSM). If required by local, state, or accrediting organization quality control requirements, users can monitor the system by trending Tm values for the control assays and maintaining records according to standard laboratory quality control practices. Refer to the appropriate FilmArray Operator's Manual for instructions on obtaining control assay Tm values.

Interpretation

The BioFire Software automatically analyzes and interprets the assay results and displays the final results in a test report (see the BioFire® FilmArray® Pneumonia Panel Quick Guide to view an example of a test report). The analyses performed by the BioFire Software and details of the test report are described below.

Assay Interpretation

When PCR2 is complete, the BioFire® FilmArray® Instrument performs a DNA melting analysis on the PCR products and measures the fluorescence signal generated in each well (for more information see appropriate FilmArray Operator's Manual). The BioFire Software then performs several analyses and assigns a final assay result. The steps in the analyses are described below.

Analysis of melt curves. The BioFire Software evaluates the DNA melt curve for each well of the PCR2 array to determine if a PCR product was present in that well. If the melt profile indicates the presence of a PCR product, then the analysis software calculates the melting temperature (Tm) of the curve and compares it against the expected Tm range for the assay. If the software determines that the Tm of the curve is within the assay-specific Tm range, the melt curve is called positive. If the software determines that the Tm of the curve is not in the appropriate Tm range, the melt curve is called negative.

Analysis of replicates. Once positive melt curves have been identified, the software evaluates the replicates for each assay to determine the assay result. For an assay to be called positive, two associated melt curves must be called positive and both Tms must be similar. Assays that do not meet these criteria are called negative.

Analysis of assay results for bacteria. The assays in the BioFire Pneumonia Panel for detection of bacteria that are reported semi-quantitatively are designed to amplify genes that are present in single copies within the chromosome of the target bacterium and are used to estimate genomic copies of bacterial nucleic acid per milliliter (copies/mL) of specimen. The BioFire Software calculates an approximate value for each gene target based on real-time PCR amplification data relative to the QSM (internal reference of known quantity). Assays with no measurable amplification or a value below 10^3.5 copies/mL are called negative. Assays with a value equal to or greater than 10^3.5 copies/mL are called positive.

Organism and Antimicrobial Resistance Gene Interpretation

Each positive and negative assay result is interpreted by the BioFire Software to provide results for the identification of specific bacteria, atypical bacteria, viruses, and antimicrobial resistance (AMR) genes as shown in Table 3. For most analytes detected by the BioFire Pneumonia Panel, interpretations are based on the result of a single assay. However, results for *Staphylococcus aureus*, Adenovirus, and the AMR genes require interpretation based on more than one assay result, as discussed in the relevant sections below.

Table 3. Analytes Detected by the BioFire® FilmArray® Pneumonia Panel

Bacteria		
Acinetobacter calcoaceticus-baumannii complex	Klebsiella oxytoca	Serratia marcescens
Enterobacter cloacae complex	Klebsiella pneumoniae group	Staphylococcus aureus
Escherichia coli	Moraxella catarrhalis	Streptococcus agalactiae
Haemophilus influenzae	Proteus spp.	Streptococcus pneumoniae
Klebsiella aerogenes	Pseudomonas aeruginosa	Streptococcus pyogenes
Atypical Bacteria		
Chlamydia pneumoniae	Legionella pneumophila	Mycoplasma pneumoniae
Viruses		
Adenovirus	Human Rhinovirus/Enterovirus	Parainfluenza Virus
Coronavirus	Influenza A	Respiratory Syncytial Virus
Human Metapneumovirus	Influenza B	
Antimicrobial Resistance Genes		
CTX-M	NDM	*mecA*/*C* and MREJ
IMP	OXA-48-like	
KPC	VIM	

Interpretations and Semi-quantitative Bin Results for Bacteria

The BioFire Pneumonia Panel provides a Detected or Not Detected result as well as a semi-quantitative bin result (10^4 copies/mL, 10^5 copies/mL, 10^6 copies/mL, or ≥10^7 copies/mL) for most bacteria. The bin result represents the approximate number of specific bacterial genomes in the specimen and is intended to provide a simple assessment of relative abundance of nucleic acid from different bacteria in a lower respiratory specimen based on a molecular method. For bacteria, negative assays (no measurable amplification or value less than 10^3.5 copies/mL) are reported as Not Detected. Positive assays are reported as Detected and a bin result is assigned based on the assay value. Each bin is defined by discrete upper and lower limits spanning a 1-log range of values (see Table 4) such that the bin result reflects the assay value within the nearest ±0.5-log.

Table 4. BioFire Pneumonia Panel Bin Results for Bacteria

Assay Result		**Reported Result and Bin Result**	
Negative OR	<10^3.5 copies/mL	Not Detected	
Positive AND	≥10^3.5 – <10^4.5 copies/mL	Detected	10^4 copies/mL
Positive AND	≥10^4.5 – <10^5.5 copies/mL	Detected	10^5 copies/mL
Positive AND	≥10^5.5 – <10^6.5 copies/mL	Detected	10^6 copies/mL
Positive AND	≥10^6.5 copies/mL	Detected	≥10^7 copies/mL

1.0 Staphylococcus aureus

The BioFire Pneumonia Panel pouch contains two different assays (Saureus1 and Saureus2) for the detection of *Staphylococcus aureus*. The BioFire® FilmArray® Software interprets each of these assays independently (as described above), and if one or a combination of the assays is positive, the result will be *Staphylococcus aureus* Detected with the appropriate bin result. If both assays are negative, the result will be *Staphylococcus aureus* Not Detected.

NOTE: Detection of bacterial nucleic acid may be indicative of colonizing or normal respiratory flora and may not indicate the causative agent of pneumonia. Semi-quantitative Bin (copies/mL) results generated by the BioFire® FilmArray® Pneumonia Panel are not equivalent to CFU/mL and do not consistently correlate with the quantity of bacterial analytes compared to CFU/mL. For specimens with multiple bacteria detected, the relative abundance of nucleic acid (copies/mL) may not correlate with the relative abundance of bacteria as determined by culture (CFU/mL). Clinical correlation is advised to determine significance of semi-quantitative Bin (copies/mL) for clinical management.

Interpretations for Atypical Bacteria and Viruses

Results for most atypical bacteria and viruses are reported as Detected or Not Detected based on an individual corresponding assay result. If the assay is positive the result will be Detected, and if the assay is negative, the result will be Not Detected. However, Adenovirus detection is reported based on the results of multiple assays, as described below.

2.0 Adenovirus

The BioFire Pneumonia Panel pouch contains three different assays (Adenovirus2, Adenovirus3, and Adenovirus7) for the detection of all species and serotypes of Adenovirus. The BioFire® FilmArray® Software interprets each of these assays independently (as described above) and the results are combined as a final result for the virus. If one or any combination of assays is positive, the result will be Adenovirus Detected. If all assays are negative, the result will be Adenovirus Not Detected.

Interpretations for Antimicrobial Resistance (AMR) Genes

Results for AMR genes are also reported qualitatively (Detected/Not Detected) based on corresponding assays, but only if an applicable bacterium (i.e. potential carriers of the AMR gene;

Table 5) is also detected (≥10^3.5 copies/mL) in the sample.
The results for each of the antimicrobial resistance genes will be listed as either:
Detected—when an applicable bacterium is detected AND the antimicrobial resistance gene assay(s) are positive.
Not Detected—when an applicable bacterium is detected AND the antimicrobial resistance gene assay(s) are negative.
N/A—when all applicable bacteria are Not Detected, regardless of the result for the antimicrobial resistance gene assay(s).

Table 5. Antimicrobial Resistance (AMR) Genes and Applicable Organisms

AMR Gene Result	**Applicable Bacteria**
mecA/C and MREJ	Staphylococcus aureus
CTX-M IMP KPC NDM VIM	Acinetobacter calcoaceticus-baumannii complex Enterobacter cloacae complex Escherichia coli Klebsiella aerogenes Klebsiella oxytoca Klebsiella pneumoniae group Proteus spp. Pseudomonas aeruginosa Serratia marcescens
OXA-48-like	Enterobacter cloacae complex Escherichia coli Klebsiella aerogenes Klebsiella oxytoca Klebsiella pneumoniae group Proteus spp. Serratia marcescens

Each AMR gene result is associated with a single corresponding assay except for the *mecA/C* and MREJ result, which is dependent on both the *mecA/C* assay and the MREJ assay (see Table 6). Detection of both *Staphylococcus aureus* and the *mecA/C* and MREJ markers is indicative of methicillin resistant *Staphylococcus aureus* (MRSA).

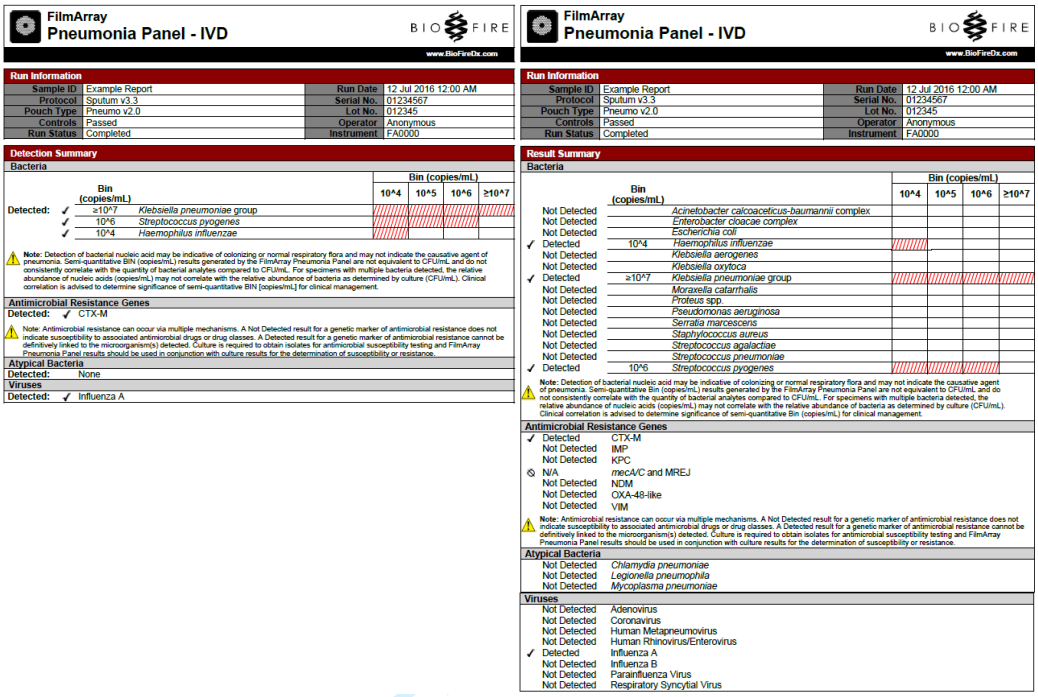
Table 6. Possible Assay Results and Interpretation for mecA/C and MREJ

BioFire Pneumonia Panel Results		**Staphylococcus aureus**	***mecA/C* Assay**	**MREJ Assay**
Staphylococcus aureus *mecA/C* and MREJ	**Detected** **Detected**	Detected	Positive	Positive
Staphylococcus aureus *mecA/C* and MREJ	**Detected** **Not Detected**	Detected	Positive	Negative
Staphylococcus aureus *mecA/C* and MREJ	**Detected** **Not Detected**	Detected	Negative	Positive
Staphylococcus aureus *mecA/C* and MREJ	**Not Detected** **N/A**	Not Detected	Any Result	Any Result

NOTE: Antimicrobial resistance can occur via multiple mechanisms. A Not Detected result for a genetic marker of antimicrobial resistance does not indicate susceptibility to associated antimicrobial drugs or drug classes. A Detected result for a genetic marker of antimicrobial resistance cannot be definitively linked to the microorganism(s) detected. Culture is required to obtain isolates for antimicrobial susceptibility testing, and BioFire® FilmArray® Pneumonia Panel results should be used in conjunction with culture results for the determination of susceptibility or resistance.
BioFire Pneumonia Panel Test Report

HAP-FAST Protocol V3.0, 14/11/2023
Based on protocol template v1.0 20/02/2020

The two-page BioFire® FilmArray® Pneumonia Panel report is displayed upon the completion of a run and contains three sections: Run Information, Detection Summary, and Result Summary. It can be saved as a PDF file and/or printed if desired.



Run Information

The Run Information section is displayed at the top of both pages of the test report. It provides information about the sample and the run, including Sample ID, Protocol (sample type), pouch information (Pouch Type, Lot Number, and Serial number), run date, run status (completed, incomplete, aborted, instrument error, instrument communication error, or software error), the identity of the operator who performed the test, and the instrument used to perform the test. Control results are reported as Passed, Failed, or Invalid. Table 7 provides additional information for each of the possible control field results.

Table 7. Interpretation of Controls Field on the BioFire® FilmArray® Pneumonia Panel Test Report

3.0	Control Result	4.0	Explanation	5.0	Action
6.0	Passed	7.0 8.0 9.0	The run was successfully completed AND Both pouch controls were successful.	10.0 11.0	None. Report the results provided on the test report.
12.0	Failed	13.0 14.0 15.0	The run was successfully completed BUT At least one of the pouch controls (RNA Process Control and/or QSM) failed.	16.0 17.0	Repeat the test using a new pouch. If the error persists, contact Customer Technical Support for further instruction.

3.0	Control Result	4.0	Explanation	5.0	Action
18.0	Invalid	19.0	The controls are invalid because the run did not complete. (Typically, this indicates a software or hardware error).	20.0	Note any error codes displayed during the run and the Run Status field in the Run Information section of the report. Refer to the appropriate FilmArray Operator's Manual or contact Customer Technical Support for further instruction.
				21.0	Once the error is resolved, repeat the test or repeat the test using another instrument.

Detection Summary

The Detection Summary section is displayed on the first page of the report and lists the Detected results under each category (bacteria, antimicrobial resistance genes, atypical bacteria, and viruses), including the semi-quantitative "Bin (copies/mL)" results for bacteria. If there are no Detected results in a specific category, the result shown is Detected: None.

Results Summary

The Results Summary is displayed on the second page of the report and provides a full list of test results for each organism and antimicrobial resistance gene including the "Bin (copies/mL)" result for bacteria. Possible results for each organism are Detected, Not Detected, Invalid, and N/A.

Table 8 provides an explanation for each interpretation and any follow-up necessary to obtain a final result.

Table 8. Reporting of Results and Required Actions

Result	Explanation	Action
Detected	The run was successfully completed AND The pouch controls were successful (Passed) AND The assay(s) for the organism were POSITIVE.[a]	Report results.
Not Detected	The run was successfully completed AND The pouch controls were successful (Passed) AND The assay(s) for the organism were NEGATIVE.[b]	Report results.
Invalid	The pouch controls were not successful (Failed) OR The run was not successful. (Run Status displayed as: Aborted, Incomplete, Instrument Error, or Software Error.)	See Table 7 for instruction.
N/A (Antimicrobial Resistance Genes only)	The run was successfully completed AND The pouch controls were successful (Passed) AND The assay(s) for the organism(s) associated with the antimicrobial resistance gene were NEGATIVE so the results of the antimicrobial resistance gene are not applicable to the test results.	Report results.

[a] For bacteria, the organism calculated value must be greater than or equal to 10^3.5 copies/mL for the assay to be POSITIVE.

[b] For bacteria, a NEGATIVE assay result may indicate no amplification or amplification with an organism calculated value less than 10^3.5 copies/mL.

Change Summary

It is possible to edit the Sample ID once a run has completed. If this information has been changed, an additional section called **Change Summary** will be added to each page of the test report. This Change Summary section lists the field that was changed, the original entry, the revised entry, the operator that made the change, and the date that the change was made. Sample ID is the only field of the report that can be changed.

Change Summary				
Field	Changed To	Changed From	Operator	Date
[1]Sample ID	Positive_example_XYZ	Positive _example	Jane Doe (JD)	16 Sept 2017

References/Related Documents

BioFire® FilmArray® Pneumonia Panel Instruction Booklet (RFIT-PRT-0575), BioFire Diagnostics, LLC.

Table 4: Schedule for Assessments and Follow-Up

Specific Activity	Stage 1 randomisation Day 0	Stage 2 Randomisation	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 28 (+/- 7 days)	Day 90 (+/- 14 days)
Assessment of eligibility	X	X												
Concomitant medication check	X													
Randomisation	X	X												
Urine pregnancy test as required pre Chest X-ray/CT scan	X													
Chest X-ray	X													
CT scan	X													
Sputum sample		X			[3]X								[3]X	
FAPP		X												
Informed consent		[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X	[2]X
Past Medical history	X													
Admission related data (date, time, symptoms, co-morbidities, ward type, reason for admission,	X													

clinical frailty score)														
Patient demographics (age, sex, postcode, height, weight, calculated BMI)	X													
Details of antibiotic use	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (temperature, blood pressure pulse rate, oxygen saturation rate, respiratory rate, NEWS2 score)	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Record clinician's description of symptoms	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Record clinician's respiratory exam findings	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
Blood test results (haemoglobin, platelets, white blood count, neutrophils, lymphocytes, creatinine, c-reactive protein and urea)	X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X		
CAP-sym score	[4]X		[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	[1]X	X	X
Record survival status	X		X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L	[4]X											[1]X	X	X

Nasal swab	[35]X				[3]X								[3]X	
Research blood sample	[35]X				[3]X								[3]X	
Post-discharge Indirect Cost Survey														X
Record microbial results from admission														X
Record any further imaging and findings														X

[1] collected until day 10 or discharge
[2] collected as soon as possible up until discharge
[3] collected for the exploratory sub-study only
[4] not to be collected until written informed consent is obtained.
[5] must be collected within 24 hours of stage 1 randomisation

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Pg 1, line 1-5
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Pg 2, line 56
	2b	All items from the World Health Organization Trial Registration Data Set	Pg2, line 56-60
Protocol version	3	Date and version identifier	Pg2, line 57
Funding	4	Sources and types of financial, material, and other support	Pg2, line 58
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pg1, line 9-24
	5b	Name and contact information for the trial sponsor	Pg 2, line 59
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Pg 13, lines 358-364

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pg 3-4, lines 74-152
	6b	Explanation for choice of comparators	Pg 3-4, lines 97-129
Objectives	7	Specific objectives or hypotheses	Pg 4-5, lines 154-176
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Pg 5, line 186-189
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Pg 5, line 179-184
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Pg 5-6, lines 214, 222
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pg 5-10 lines 191 - 321
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Pg 9, line 266-267
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Pg13, 349-354
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Pg 6, Table 1
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	TABLE 3

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 2, Table 4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Pg 5, lines 192-197
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Pg 5, line 182-184
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Pg7, lines 250-254
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Pg7, lines 250-254
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Pg7, lines 250-254
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pg7, lines 250-254
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pg 10-11, lines 323-334

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Pg 5, 212-215
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Pg 10-11, lines 323-334
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pg 8, lines 273-282
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pg 8, lines 266-271
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Pg 8, 279-282
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Pg 13, lines 350-355
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Pg 14, lines 391-395
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Pg 10, 318-320
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Pg 14, lines 370-378

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Pg 14, lines 379-390
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Pg 5, lines 198-213
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Pg 10, 209-210
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Pg 13, lines 349-355
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Pg 17, lines 550-558
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Pg 17, line 548
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Pg 14, line 396-398
	31b	Authorship eligibility guidelines and any intended use of professional writers	Pg 534, line 534-545
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Attached full protocol as supplementary
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached as supplementary

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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