HAPOSS Protocol

Version	v5
Version date	10.2.20
Study Title	Hospital Acquired Pneumonia Observational Study of Sputum (HAPOSS)
Sponsor	University of Liverpool
Lead NHS site	Aintree University Hospital NHS Foundation Trust
Funding	University of Liverpool Industrial Strategy Pump Priming grant
Chief Investigator	Dr Dan Wootton
Sites	Liverpool University Hospitals NHS Foundation Trust - Aintree University Hospital and Royal Liverpool Hospital

Signatures

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Amendment history

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2	19.7.19	DW	Wording of SAE reporting changed to reflect comments from external scientific review by GD. Wording of consent process changed to reflect comments from external scientific review by GD.
2	3	3.9.19	DW	In response to comments from UoL sponsorship committee the following changes were made to the protocol: 1. Modification of the method of identifying patients whose samples had been run on FAPP to research team; handwritten logbook replaced with FAPP computer log. 2. Additional comment in consent section to account for the situation where consent is not subsequently obtained for a sample that has been run on FAPP. 3. Extra detail in the explanation of why FAPP may be superior to current lab methodology – specific mention of range of pathogens detected in addition to comments on speed.
3	4	16.9.19	DW	In response to comments from UoL sponsorship committee (deputy chair) the following changes were made to the protocol: 1. Additional comments throughout to account for the situation where consent is not subsequently obtained for a sample that has been run on FAPP. 2. In the 'Participant Confidentiality' section additional information is added to explain the security measures pertaining to the storage of patient identifiers on the FAPP computer log.

4	5	10.2.20	DW	In response to NHS ethics review (email 23.1.20) the following amendments have been made: 1. The exclusion criterion relating to antibiotic administration has been modified to clarify the term “this episode of HAP”. 2. The following sentence “No samples or parts thereof will be stored by the HAPOSS study“ has been added at the end of the paragraph called “Risks”. 3. In the section ‘Consent’ the process relating to registering a sample on the FAPP machine and the details stored in the FAPP sample log have been clarified. 4. Clarification of the security procedures relating to the study data base and its accessibility from a University laptop has been added in the section ”Risks”. 5. The previous paragraph titled anonymisation has renamed pseudo-anonymisation and has been modified to clarify the process of assigning pseudo-anonymised study numbers.

Synopsis

Study Title	**H**ospital **A**cquired **P**neumonia **O**bservational **S**tudy of **S**putum (HAPOSS)	
Trial Design	Observational cohort study	
Trial Participants	Adults (≥ 16 years old) diagnosed with hospital acquired pneumonia (HAP)	
Planned Sample Size	100 patients. This pragmatic sample size reflects the need to recruit across different hospital wards and to detect a comprehensive range of pathogens. We will present summary statistics. We will not conduct inferential testing.	
Follow-up duration	Once a patient has consented to the study there is no further follow-up.	
Planned Study Period	We aim to test 100 patient samples over 8 months. There will then be a 4 month period during which we will analyse the results and generate a modified HAP treatment guideline for use in a future feasibility study and clinical trial.	
Objective	To determine the range and relative frequency of pathogens detected by the BIOFIRE FILM ARRAY PNEUMONIA PANEL when analysing sputum samples from patients with HAP.	
Investigational Device	Device	Pneumonia panel test kits – run on the BIOFIRE FILM ARRAY platform. This is a small, self-contained, close to patient platform for molecular microbiological testing of clinical specimens.
	Sample type	Sputum
	Sample volume	200µL
	Sample preparation	Sample preparation is very simple and takes approx. 2 mins A sterile, absorbent, swab-on-stick is swirled around the sputum sample and absorbs a standard volume. Each test kit comes with the swab, test cartridge and two reagents.
	Test run time	75 mins

Background

This study is the first part of a planned series of studies aimed at improving the outcome for patients who develop hospital-acquired pneumonia (HAP).

Pneumonia is a form of severe lung infection and we diagnose hospital-acquired pneumonia (HAP) if it develops in a patient who has been in hospital for greater than 48 hours - having been admitted for some other reason e.g. hip-replacement.[1] To meet the definition the patient must not have had any pneumonia symptoms when they were first admitted to hospital. The reason doctors differentiate HAP from pneumonia that develops outside of hospital (community-acquired pneumonia, CAP) is that we believe the bacteria responsible for HAP are often different to those causing CAP, necessitating different antibiotics. For that reason, a patient admitted from the community with pneumonia who has had a prior admission to hospital within the last 14 days, is also classified as having HAP, the rationale being that during their prior hospital admission they may have become 'colonised' with hospital type bacteria.[2]

HAP occurs in all hospitals – acute hospitals, paediatric, women's, neurological, cardiac or cancer hospitals.[3] HAP occurs on all wards, however there is an association with age, being more common in the elderly and in those with comorbidities such as cardiac, respiratory and neurological problems. It is a common post-operative complication and is associated with socioeconomic deprivation.[4]

The incidence of HAP is higher than all other Healthcare Associated Infections (HCAIs).[5] Moreover, it is responsible for more deaths than any other HCAI with an in-patient mortality of over 25%.[6]

Due to this potential for severity, there is pressure to administer antibiotics promptly following diagnosis. Since sputum cultures take on average 3 days to determine the cause of HAP, the initial antibiotic choice is a best guess as to the likely cause. There have been very few quality studies to help determine what the likely causes are and so our treatment guidelines extrapolate from studies of another type of pneumonia called ventilator-acquired pneumonia (VAP) – which develops in patients who are on ventilators in intensive care. VAP is associated with a wide range of bacteria but particularly Gram-negative bacteria and bacteria that are resistant to standard antibiotics. For this reason, it is current practice to administer two, extended-spectrum antibiotics to all patients with HAP.[1]

There are inherent problems with this empirical (best-guess) approach to antibiotic prescribing for HAP. First, the guess might be wrong and the antibiotic chosen might not kill the bacteria. Secondly, extended-spectrum antibiotics are associated with complications such as *Clostridium difficile* diarrhoea and thirdly, they are responsible for driving anti-microbial resistance.[7]

Ideally, we would use a test that could identify the cause of a patient's HAP before the first dose of antibiotics so we can get the choice right first time. The characteristics of such a test are that it would need to be able to detect all the relevant bacteria that cause HAP and the presence of any antimicrobial resistance genes. However, respiratory viruses are not currently part of our standard testing despite increasing evidence of their involvement in HAP.[8,9] Moreover there are a growing number of studies demonstrating nosocomial transmission of respiratory viruses such as influenza. The ideal HAP microbiology test would therefore not only be quick but also would test for both bacteria, resistance and detect viruses. There are no guidelines as to how soon after a diagnosis of HAP antibiotics ought to be administered but in CAP there is evidence to suggest 4 hours is the longest a patient ought to wait – so extrapolating this to HAP the ideal test would deliver an answer within 4 hours.[1]

The only commercially available platform to test for pneumonia specific pathogens and provide results within 4 hours is the BIOFIRE® FILMARRAY® Pneumonia Panel Plus (FAPP for short). 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. Sample preparation takes 2 minutes, requires no expertise and results are available in 75 minutes. https://www.biomerieux-diagnostics.com/biofire-filmarray-pneumonia-panel

Such a comprehensive, rapid test could dramatically change the way we manage HAP but before it is widely implemented, we must address questions relating to the interpretation of results and health economics within the NHS setting.

Ultimately, these questions will be answered by a large scale, randomised controlled trial of usual care versus management supported by this new test. However, such a trial will require a modified treatment guideline to inform the management of the patients in the intervention arm. This new guideline will help clinicians decide which antibiotic to prescribe their patient based on the bacteria and or viruses detected from the patient's sputum by the FAPP. This modified guideline should be informed by preliminary data demonstrating the likely pattern of bacterial, viral and resistance detections in the context of HAP. This study will generate the data required to create an antibiotic guideline based on FAPP results for use in local trusts participating in future trials of FAPP based management.

Aim

The aim of this study is to use a new diagnostic test to observe the range of bacteria and viruses identified from the sputum of patients with hospital Acquired Pneumonia (HAP) – and to use these observations to inform the design of a modified HAP treatment guideline for use in future trials.

Study Design

Summary

HAPOSS is a small, pragmatic observational study aimed at supporting future clinical trials. We will analyse a small (200µL) sub-sample of each patient's sputum with a new diagnostic test called the FAPP. The remainder of the sputum sample will be processed normally and the results made available to clinicians in the usual manner but the results of the new test will be stored and analysed retrospectively. Once 100 samples have been through the FAPP we will invite a panel of experts to review the results from the new test and decide on a modified antibiotic prescribing guideline for use in future trials. An example of the readout of the FAPP is provided with this application.

We will not store any samples and participants will have just a single study visit by the research team, to obtain consent, there are no additional study visits. The study will recruit for 8 months at Aintree Hospital and the Royal Liverpool Hospital; there will then be 4 months of analysis and study close will be at 1 year.

Intervention

The new test is the BIOFIRE® FILMARRAY® Pneumonia Panel Plus (FAPP for short). The FAPP is a CE marked, United States Food and Drug Administration (FDA) approved near patient test that can simultaneously detect 18 bacterial and 10 viral causes of HAP and the presence of 7 antimicrobial resistance genes. Sample preparation takes 2 minutes, requires no expertise and results are available in 75 minutes. https://www.biomerieux-diagnostics.com/biofire-filmarray-pneumonia-panel

Study Participants

Inclusion

- Adults of 16 years or older who are treated as HAP within the two recruiting hospitals

Exclusion

- Intention is to palliate rather than cure
- Non-English speaking
- Patients from whom a sputum sample cannot be obtained within 6 hours of the administration of the first dose of antibiotics for this episode of HAP.*

*For the purposes of this protocol, if the patient has had prior instances of HAP during the same or a recent admission, a new episode of HAP is defined as occurring following a 48 hour cessation of prior antibiotics. In that circumstance a patient **will be eligible** for HAPOSS if a sputum sample can be obtained within 6 hours of the first dose of antibiotic for this new HAP episode.
In the circumstance where a patient is diagnosed with HAP whist receiving antibiotics for a non-respiratory infection e.g. cellulitis, if the HAP diagnosis leads to a change in the antibiotic prescription to cover the HAP then that patient will be eligible for recruitment to HAPOSS if the sputum sample was obtained within 6 hours of the first dose of the new/additional antibiotics for HAP. If the diagnosis of HAP does not result in a change in antibiotic then the patient is in-eligible.

Study Procedures

Assessments	Day 1	Visit 1	Visit 2	Visit 3
Obtain sputum sample based on clinical indication (clinical team)	**X**			
Process sputum through the FAPP (clinical team)	**X**			
Discuss and provide information relating to the study (research team)		**X***		
Obtain informed consent (research team)			**X**	
Collection of clinical data from hospital record (research team)			**X**	
Obtain consent[#] from patients that lacked capacity				**X[#]**

*Visit 1 by the research team will occur as soon as they identify a patient's sample has been logged in the FAPP sample log – which will be reviewed each working day. During this visit, the study will be explained to the patient or consultee and a patient (or consultee) information leaflet will be provided. Visit 2 by the research team will be to obtain consent and this will occur after the patient has had time to consider the patient information leaflet and or discuss with family and or friends.
[#]A third visit will only occur in participants who lacked capacity at enrolment. This visit will be triggered by the indication from the clinical team that the participant may have regained capacity. The research team will stay in contact with the ward clinical team for the duration of the participants in patient stay in order to respond to the return of capacity.

Screening and eligibility
Participants will be identified from all wards in two the two participating hospitals. A series of education events will be run prior to and throughout the study period to raise awareness of the study. The decisions about whether to diagnose HAP, obtain a sputum sample for clinical diagnostics and to test a sub-sample of the sputum sample using the FAPP will rest with hospital clinical teams who will be made aware of the eligibility criteria. Eligibility criteria will be posted on all wards and above the FAPP machine. Prior to consent the research team will confirm eligibility.

Consent
The clinical team will obtain a single, clinically indicated sputum sample, as per usual care, and that sample will be immediately sub-sampled and run through the FAPP prior to being sent onwards, as usual, to microbiology. The data from the sample will be stored and the clinical team will have no access to this.

The patients' sample will be logged in the FAPP machine by means of a unique, 5-digit 'sample id'. Sample ids will consist of a site prefix followed by 3-digit consecutive sample numbers. For example, at Aintree all sample ids will have the prefix 01 and at the Royal Liverpool all sample ids will have the prefix 02 such that the first sample run at Aintree will be 01001 and the first at the Royal will be 02001 – the second Aintree sample will be 01002 and the second Royal sample will be 02002. The FAPP computer that holds this data will be password protected such that only members of the research team will be able to access this information. This FAPP log will be checked daily by the research team and new potential participants will be approached by the research team as soon as is practically possible. During this visit consent, or assent from a consultee will be obtained to analyse the stored sample data and for access to the standard medical record. In the situation where a patient declines consent or the consultee declines assent then the patient's data will not be included in the study.

Delivering interventions in an emergency setting makes HAP studies difficult and explains why there are so few. HAP has an inpatient mortality of over 25% and so it is important that research studies do not introduce undue delays to the clinical processes. Patients with HAP are more likely to be elderly and to have underlying cognitive impairment such as dementia. Moreover, HAP itself can cause transient delirium that impairs capacity. HAP occurs at any time of day and on any day of the week.

The above consent process represents a hybrid between a 'research without prior consent' model to process the sputum in the FAPP machine and a standard consent model with respect to the use and storage of data obtained from the analysis of the sputum. The 'research without prior consent model' is used frequently in intensive care and emergency scenarios where the delivery of the intervention is time critical. There are very limited risks associated with testing the sputum sample and so this model will place minimal burden on patients. Recent studies have revealed that patients and families are keen to embrace such consent models in order to conduct research aimed at improving outcome in HAP.[10]

Patients without capacity to consent
HAP is more common in people with cognitive impairment. Moreover, HAP itself can induce delirium with consequent transient loss of capacity. Therefore, we must study patients who lack capacity in order for the findings of this study to be applicable to future research and to HAP in its usual clinical context.

The research has the potential to benefit future patients who have HAP and lack capacity. Our aim is to move from our current practice of empirical (best guess) antibiotic prescribing to a scenario where we prescribe the right antibiotic for the pathogen.

The benefits of this precision / personalised prescribing are that:
a) getting the antibiotic right will improve efficacy of treatment
b) avoiding broad spectrum antibiotics reduces the risk of antibiotic related adverse events such as C Diff diarrhoea
c) reducing overall use of broad-spectrum antibiotics slows the development of antibiotic resistance

The research team will decide on a patient's capacity to consent to the study processes. All individuals specified with this role in the delegation log will be experienced in both clinical and clinical research settings and will be GCP trained.

If a patient is deemed to lack capacity to consent, we will contact a consultee in order to gain their assent to store the patient's information on our research data-base. The choice of consultee will default to the registered next of kin or person with legal power of attorney. Where neither of the above is available, a doctor, independent of the research team will be asked to consider the patients participation and act as a consultee. Ideally, this discussion will happen face-to-face and the consultee will sign an 'assent' form. When it is not possible to meet a consultee face-to-face we will speak to them on the phone and record their wishes on a date and timed 'assent form' along with the signature of the research team member involved. If no consultee is available then the patient's clinical consultant responsible for their care will be asked to consider their suitability for the study and to sign the assent form.

In the context of transient loss of capacity - at the point at which the patient regains capacity, they will be offered a patient information leaflet, the study will be explained by the study team and the patient will be asked to provide written informed consent. If the patient does not want to have their information stored as part of the study, all details will be removed from the study and their wishes will overrule any prior opinions of consultees.

Pseudo-anonymisation
Patients will be assigned 4-digit study numbers using the following system:

Aintree Hospital recruits will have the prefix 1 followed by the consecutive 3-digit recruitment number – so the first recruit at Aintree will be 1001 and the second 1002 etc. The Royal Liverpool Hospital recruits will have the prefix 2 followed but consecutive 3-digit recruitment numbers – so that the first recruit at the Royal Liverpool will be 2001 and the second 2002 etc.

Participants will be identified only by their 4 digit study number in all but three circumstances: 1) the recruitment log where study numbers will link back to patient identifiers 2) the patient's consent form 3) the FAPP machine log where potential participants whose sputum has been run through the FAPP will be identified by name, hospital number and ward. At the end of the study the FAPP log will be permanently destroyed.

Collection of hospital data
Once consent has been obtained, routinely available data recorded in hospital notes and on the hospital results system will be recorded in the case report form (CRF) by the research staff. This will include

demographics, the original reason for admission, routine medications and any antibiotics received since admission, lab results (full blood count, CRP, U+E at the time of HAP), known comorbidities.

Definition of the end of study

The end of study is the date of agreement of the modified antibiotic guideline for the FAPP and it is anticipated this will be 12 months from the start of the study.

Withdrawal of participants

Each participant has the right to withdraw consent from the study at any time. For those participants without capacity to consent to the study at the time of admission and who entered are the basis of assent gained from a consultee, withdrawal from the study may either be at the participant's own request (if they regain capacity) or at the request of a consultee. The participant and the consultee will be made aware that this will not affect the participant's future care. The reasons for leaving the study will be requested and recorded, but participants are not obliged to give reasons. Participants will be assured that withdrawal will not affect the future care they receive. All patient identifiers will be removed from the FAPP computer in the event of withdrawal from the study. All records of the patients FAPP sample will be removed from the study database and no clinical information relating to the patient will be stored.

Safety Reporting

The definition of a serious adverse event (SAE) is problematic in the context of HAPOSS since participants will frequently be ill frail patients and mortality is high in this group.

All SAEs (defined below) will be recorded in the CRF but only those deemed to be SARs (defined below) will be reported.

<u>The principal investigator at a site will need to distinguish between an SAE that is possibly, probably or definitely related to the intervention (= a suspected adverse reaction (SAR) – see definition below) and an SAE that arises from disease progression or has another cause.</u>

Serious adverse events (SAEs) Definitions

A serious adverse event is any untoward medical occurrence in a patient who receives a study intervention, which does not necessarily have to have a causal relationship with the intervention, in this case the testing of sputum by the FAPP, and that:

- Results in death,
- Is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Other important medical events (NOTE: Other events that may not result in death are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.)

Serious Adverse Reaction (SAR)

All untoward and unintended responses to a study intervention. The phrase "responses to the study intervention" means that a causal relationship between the study intervention and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the trial intervention qualify as adverse reactions.

Since the results of the FAPP will not be available to the clinicians or the research team until after the last participants disease episode is over – the FAPP test itself will have no impact on patient care.

The only possible scenario we can foresee (and will mitigate against) is that, following testing on the FAPP the remaining sputum sample is lost and does not proceed to the microbiology lab – therefore depriving the patient of the potential of important diagnostic information. In the event that this occurred and the patient went on to suffer an SAE this could be interpreted as a SAR and would be reported.

Reporting

Serious unexpected adverse reactions (SARs, defined above) are expected to be rare in this observational study but should be reported on an SAE form within 24 hours of being made aware of the event to the Sponsor. **All other SAEs will be recorded in the CRF but not reported.**

Statistical considerations

This is an observational study and we will not be conducting and inferential analysis. We will describe the relative frequency of observation of bacterial, viral and antibiotic resistance gene detections. We will describe the relative frequency of demographics, cases per-ward, per-hospital etc. i.e. summary statistics.

Number of participants

The sample size is pragmatic. Our recent audits of HAP cases demonstrate that Aintree hospital makes approximately 100 HAP diagnoses per-month with a slight seasonal bias towards an increase incidence in the winter. The Royal Liverpool has very similar rates. At both sites the rate of acquisition of sputum samples in routine clinical practice is 20%. Therefore, it there are 200 cases per month across both sites and sputum is acquired from 20% this means there will be 40 samples which could be tested per month. Assuming a 30% recruitment rate, this implies 12 samples per-month across the two sites. At this rate, our target of testing 100 samples will take approximately 8 months. This will enable us to recruit through a winter and into the summer to cover any seasonal variation in detections. Both hospitals are similar in terms of services, populations and protocols (and are now part of same trust) there is no scientific reason to insist on balanced recruitment. Recruitment will therefore continue until the target of 100 is reached.

Ethics

Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki.

ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

Approvals

Study documents including the protocol, consent documentation and participant information sheet will be submitted via IRAS to the NHS Research Ethics Committee (REC). Required documents will also be submitted to HRA, and host institution(s) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The FAPP computer will be password protected such that a sample can only be run by a study team member identified in the delegation log. Before a sample can be run on the FAPP, the team member will log into the FAPP computer. The patient's hospital bar code will be scanned so that the sample data can be paired with the correct identifiers. At the end of the study, and prior to this in the event that a patient or consultee declines or withdraws consent or assent, patient identifiers will be permanently removed from this computer.

Each consenting participant will be assigned a Participant ID number, allocated at randomisation, for use on study documents and the study database. The documents and database will also use the patient's initials. The patient's date of birth will also be entered into the database. The study database will be password protected and held on computers behind hospital and University of Liverpool security and firewalls.

The participants will be identified only by participant ID number on the study database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act.

Other Ethical Considerations

Risks

In this study, the patient is consenting for the use of data obtained from analysis of their sputum. All data will be stored anonymously by using random, four-digit study numbers and only the study team will have access to a randomisation code linked to patient identifiable information. After the study has completed, all data will be 'wiped' from the FAPP machine. Anonymous data will be held on password protected study computers behind NHS firewalls at the two recruitment sites. The password protected study database will also be accessible from a laptop provided by the University of Liverpool. The study database will hold no patient identifiers. University laptops are password protected, have mandatory, centrally managed robust security software via the University Windows Managed Services security system.

All patient samples are precious but in the context of HAP many patients find it difficult to produce sputum and a second sample is rarely available. For this reason, we will be using the same sample that the clinical team obtain for the FAPP analysis rather than relying on a second sample. It is important that that the sputum sample is handled carefully and that there is the shortest possible delay in delivering it onwards to the microbiology laboratory. In this context, it is important that those who handle the sputum sample and take the sub-specimen for the FAPP have had robust training. Since samples will be generated from all areas of the hospital it is not practically possible to train all clinical staff and so we will restrict the handling of the FAPP to a team of senior nurses who work on the acute medical unit

(AMU). The FAPP will be placed in a swipe-card protected room on the AMU close (30 metres) to the main laboratory specimen reception. No samples – parts thereof will be stored by the HAPOSS study.

Summary of FAPP procedure

- A member of staff brings sputum from patient's ward to the trained, senior nurse on the AMU.
- The nurse will take the sputum sample to the FAPP
- Logs into the FAPP computer and scans patient data to identify sample with patient
- Put on gloves
- Put on a simple face mask
- Clean the surface of the desk where the FAPP sits
- Use the sterile swap provided with the FAPP kit to stir once around the sputum sample
- Place the swap (no containing approximately 200µL sputum) into the sample cartridge
- Place the cartridge into the machine
- Scan the patient details into the machine
- Start the machine
- Deliver the sputum sample to the specimen reception for delivery to microbiology as per usual.

For those familiar with the analysis of blood samples for blood gas analysis – this is a very close analogy i.e. a test placed near to patients in a clinical environment, handled by a limited number of trained individuals from the clinical team.

A standard risk associated with processing microbiological specimens is contamination of the sample by the person processing it – this is no different in this study. The procedure outlined above mitigates against this small risk of the nurse contaminating the sputum sample e.g. if they have a cold. It ensures consistency and regularity of training by reducing the number of people who use the machine and handle samples. It keeps the extra time added to the delivery of samples to the lab to a minimum – estimated to be between 10 and 30 mins maximum and this will have no impact on the routine investigation of that sample.

Burdens

We will not take any new samples in this study nor will be record any new information that is not part of the standard patient record. There are no follow up visits. The only burden therefore is the time and effort taken by the patient to discuss the study with the study team. The study team is composed of highly experienced research nurses who are empathetic and considerate and will ensure they do not cause undue stress to patients who are already unwell.

Benefits

There will be no direct benefit of this research to participants although it is recognised that evidence exists that patients who participate in clinical research enjoy better outcomes. The benefit of this research is that it facilitates further research into HAP, which may eventually have a major impact on

future patients across the NHS. Given that there is limited direct benefit to participants, it is crucial that any detriment is minimised. For the reasons we have articulated above we believe the risks to individual patients are minimal.

Data handling and record keeping

All study data will be entered onto a Microsoft excel spreadsheet (previously referred to in this document as 'study database'. Access to the spreadsheet will be restricted using password protection. Copies of the spreadsheet will exist on password protected site computers behind the NHS firewall and on a password protected University of Liverpool laptop behind its firewall and Sophos security.

The spreadsheet will be backed up to the University of Liverpool server.

Financing and Insurance

This study is funded by an Industrial Strategy Pump-priming grant from the University of Liverpool. University of Liverpool will act as the sponsor for this study.

Publication Policy

Findings will be published in peer-reviewed scientific journals and be presented at local, national and international meetings. Findings will also be shared with relevant patient interest groups.

References

1. Woodhead M. Pneumonia: Diagnosis and management of community and hospital-acquired pneumonia in adults. http://www.nice.org.uk/guidance/cg191/evidence/cg191-pneumonia-full-guideline3. 2014. Date last accessed: 3/9 2015.

2. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M, Woodhead MA. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64 Suppl 3: iii1-iii55.

3. Public Health England. Healthcare associated infections (HAI): point prevalence survey, England. https://www.gov.uk/government/publications/healthcare-associated-infections-hcai-point-prevalence-survey-england. Date last updated: 8/1/2016 2016. Date last accessed: 10/30 2018.

4. Kumar S, Wootton DG. A prospective, observational study reveals Hospital Acquired Pneumonia (HAP) to be a blind-treated, high mortality, hospital wide disease associated with cardio-respiratory comorbidity. https://www.his.org.uk/media/1774/97.pdf. 2019. Date last accessed: 02/12 2019.

5. Walter J, Haller S, Quinten C, Karki T, Zacher B, Eckmanns T, Abu Sin M, Plachouras D, Kinross P, Suetens C, Ecdc Pps Study G. Healthcare-associated pneumonia in acute care hospitals in European Union/European Economic Area countries: an analysis of data from a point prevalence survey, 2011 to 2012. *Euro Surveill* 2018; 23: 10.2807/1560-7917.ES.2018.23.32.1700843.

6. Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank HP, Ducomble T, Haller S, Harder T, Klingeberg A, Sixtensson M, Velasco E, Weiss B, Kramarz P, Monnet DL, Kretzschmar ME, Suetens C. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. *PLoS Med* 2016; 13: e1002150.

7. Brown K, Valenta K, Fisman D, Simor A, Daneman N. Hospital ward antibiotic prescribing and the risks of Clostridium difficile infection. *JAMA Intern Med* 2015; 175: 626-633.

8. Loubet P, Voiriot G, Houhou-Fidouh N, Neuville M, Bouadma L, Lescure FX, Descamps D, Timsit JF, Yazdanpanah Y, Visseaux B. Impact of respiratory viruses in hospital-acquired pneumonia in the intensive care unit: A single-center retrospective study. *J Clin Virol* 2017; 91: 52-57.

9. Hong HL, Hong SB, Ko GB, Huh JW, Sung H, Do KH, Kim SH, Lee SO, Kim MN, Jeong JY, Lim CM, Kim YS, Woo JH, Koh Y, Choi SH. Viral infection is not uncommon in adult patients with severe hospital-acquired pneumonia. *PLoS One* 2014; 9: e95865.

10. Corneli A, Perry B, Collyar D, Powers JH,3rd, Farley JJ, Calvert SB, Santiago J, Donnelly HK, Swezey T, Dombeck CB, De Anda C, Fowler VG,Jr, Holland TL. Assessment of the Perceived Acceptability of an Early Enrollment Strategy Using Advance Consent in Health Care-Associated Pneumonia. *JAMA Netw Open* 2018; 1: e185816.