The SENSOR Study: A mixed-methods study of SElf-management checks to predict exacerbations of Pseudomonas aeruginosa in patients with long-term respiratory conditions.

Ethics Ref: 14/SC/0298

Date and Version No: v1.5, 19th May 2014

Chief Investigator: Prof Anoop Chauhan

Co-Investigators: Kevin Auton – Managing Director, Aseptika
Claire Roberts – Clinical Research Fellow
Thomas Jones - Clinical Research Fellow
Ben Green - Consultant Respiratory Physician
Samal Gunatilake – Clinical Research Fellow
William Storrar– Clinical Research Fellow
Scott Elliott - Biomedical Scientist Specialist
Sharon Glaysher – Research Scientist
Carole Fogg – Senior Lecturer UoP/PHT
Ann Dewey – Senior Lecturer UoP
Paul Bassett – Statistician
Steven Rule - Research Nurse

Sponsor: Portsmouth Hospitals NHS Trust

Funder: Aseptika Ltd funded by NHS England’s Small Business Research Initiative Healthcare (SBRI Healthcare), managed by Health Enterprise East (HEE) on behalf of the Eastern Academic Health and Sciences Network (EAHSN)

Protocol Development Team: as above, plus Ramon Luengo-Fernandez (Health Economist)

Patient Public Involvement contributors: Eric Compton, Sandra Willsher, Keith Boughton.
CONTENTS

The SENSOR Study: A mixed-methods study of SELF-management checks to predict exacerbations of Pseudomonas aeruginosa in patients with long-term respiratory conditions. 1

ABBREVIATIONS 4

INTRODUCTION 6

The burden of respiratory disease with Pseudomonas aeruginosa 6

Rationale for study and potential impact 7

AIMS AND OBJECTIVES 7

Primary Objective 7

Secondary Objectives 7

Exploratory Objectives 7

METHOD 8

Primary and Secondary Endpoints/Outcome Measures 8

STUDY PARTICIPANTS 8

Inclusion Criteria 8

Exclusion Criteria 9

SAMPLING AND SAMPLE SIZE 9

STUDY PROCEDURES 9

Recruitment 9

Participant/Carer training 10

Study Assessments 11

Sample production and home storage for sputum and urine samples 12

Clinic visits 12

Health economics 12

Qualitative methods 12

Self-administered questionnaire 13

Analysis 13

Discontinuation/Withdrawal of Participants from the study 14
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3G</td>
<td>Third generation mobile network</td>
</tr>
<tr>
<td>HI</td>
<td>Haemophilus Influenzae</td>
</tr>
<tr>
<td>AHSN</td>
<td>Academic Health Science Network</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>APEX</td>
<td>Software used to report laboratory results at PHT.</td>
</tr>
<tr>
<td>IT</td>
<td>Information Technology</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>BMS</td>
<td>Biomedical Scientist</td>
</tr>
<tr>
<td>MC&amp;S</td>
<td>Microscopy, culture and sensitivity</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>ml</td>
<td>Millilitres</td>
</tr>
<tr>
<td>BTS</td>
<td>British Thoracic Society</td>
</tr>
<tr>
<td>NCFB</td>
<td>Non Cystic Fibrosis Bronchiectasis</td>
</tr>
<tr>
<td>CF</td>
<td>Cystic Fibrosis</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute of Clinical Excellence</td>
</tr>
<tr>
<td>CRIS</td>
<td>Community Respiratory Integrated Service project</td>
</tr>
<tr>
<td>NVivo10</td>
<td>Qualitative software package for systematic data management</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>PA</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>EASHN</td>
<td>Eastern Academic Science Health Network</td>
</tr>
<tr>
<td>PEA</td>
<td>Pseudomonas Exotoxin A</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>PHT</td>
<td>Portsmouth Hospitals Trust</td>
</tr>
<tr>
<td>FVC</td>
<td>Full vital capacity</td>
</tr>
<tr>
<td>PIS</td>
<td>Participant Information Sheet</td>
</tr>
<tr>
<td>GINA</td>
<td>Global Initiative for Asthma</td>
</tr>
<tr>
<td>PPI</td>
<td>Public patient involvement</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GLP</td>
<td>Good laboratory practice</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>RMO</td>
<td>Research Medical Officer</td>
</tr>
<tr>
<td>SBRI</td>
<td>Small Business Research Initiative</td>
</tr>
</tbody>
</table>
INTRODUCTION
The burden of respiratory disease with *Pseudomonas aeruginosa*

There are an estimated 3 million people in the UK with COPD[1]. Bacteria cause acute exacerbations that characterize the course of COPD, and these exacerbations are associated with substantial morbidity and mortality. In addition, bacteria are present in the lower airways of many adults with COPD, even during clinically stable periods, contributing to the airway inflammation that is a hallmark of COPD.

The observation that *Pseudomonas aeruginosa* (PA) is isolated from sputum samples from 4%–15% of adults with COPD in many cross-sectional studies[2-4] suggests that the bacterium is a relatively common cause of infection in this clinical context. PA is more likely to be isolated from patients with severe disease[4], particularly among patients who require mechanical ventilation for severe exacerbations.

PA may cause chronic infections in patients with COPD that are similar to those seen in patients with cystic fibrosis (CF). Strains of PA that persist in the airways of adults with COPD demonstrate changes characteristic of chronic infection that are similar to changes observed in CF, supporting the conclusion that chronic PA infection occurs in the context of COPD.

The incidence of bronchiectasis in the UK is not certain. Chest x-ray reviews in the 1950s suggested an incidence of 100/100,000 with an increase in prevalence with age[5]. With the advent of advanced imaging techniques up to 30% of patients with COPD and severe asthma are found to have features of bronchiectasis on CT.

Within our centre, exacerbations of COPD and bronchiectasis are managed through a combination of admission to a dedicated 76-bed unit and through self-management by the patient/carer at home. Patients are provided educational literature, a care plan and supplies of antibiotics and steroids for use at home. Patients are encouraged to recognise signs of exacerbation and to begin immediate treatment with antibiotics. They are requested to report when they have initiated antimicrobial therapy at home so that this can be followed-up within 2 days (but often do not report because they feel better). Best practice recommends that patients are followed-up within 3 weeks after being admitted for exacerbation[1].

The PHT Respiratory Centre has created a culture of empowering patients through education and by transferring the skills required for self-management, so as to reduce rates of admission[6]. The costs of providing skilled community staff for home visits has proved uneconomic but the cost burden of unscheduled admissions is equally high, necessitating innovative solutions to assist patients to self-manage.

Aseptika Ltd (Cambridgeshire, UK) has developed a system for patients to self-monitor important physiological measurements including levels of physical activity, peak flow, FEV<sub>1</sub> and 1-3 biomarkers for PA in sputum. In a clinical trial sponsored by Papworth Hospital during 2013, data were collected by 15 CF participants and uploaded electronically to Activ8rlives—a web-based data collection and viewing system developed by the Company. The study indicated that clinical parameters and sputum biomarker changes are likely to enable early detection of exacerbations in CF patients and have a role in highlighting treatment failure[7]. The SENSOR study aims to investigate if these tools can be more widely applied to other respiratory conditions such as COPD and non-CF Bronchiectasis (NCFB). The system includes a sputum assay for bacterial load of PA, physical activity tracker, smart scales, pulse oximeter, peak flow meter and self-assessment score system; these all link via a simple iPad interface directly to the internet. The differing demographics between this study population and the Papworth
population, i.e. the older age of the Portsmouth population, will enable us to learn whether older patients with long-term conditions can be trained to use these monitoring devices.

**Rationale for study and potential impact**

As described above, initial trials with the Aseptika Ltd.’s system with Cystic Fibrosis patients indicate a potential role of this technology in improving patient monitoring and self-management. This is particularly important in patients with chronic respiratory conditions for whom the staff to patient ratio is typically much lower than CF, and for whom innovative solutions to better enable patients to monitor and self-manage their own condition are key to keeping their illness under control.

It is hoped that the results of this study will enable the self-care planning process that currently exist at PHT to be supported with the Aseptika technology to extend the effectiveness of our Home Hospital concept. Qualitative feedback from patients and carers will contribute to the continuing improvement and adaptation of the system.

The eventual addition of the Activ8rlives self-monitoring solution (including tests for sputum PA load), as an “assist” for the patient and clinical staff, and the provision of an IT infrastructure for staff which could simultaneously monitor and mentor many thousand patients with respiratory conditions in the Portsmouth area without the costs incurred through undertaking face-to-face home visits would have a significant impact both on patient health and NHS costs. The development of this infrastructure and subsequent assessment of the effectiveness and cost-effectiveness of the system would be assessed in a further large-scale randomised controlled trial.

**AIMS AND OBJECTIVES**

**Primary Objective**

- To use longitudinal PA sputum biomarker, telemetry and symptom data to develop individualisable models to predict a PA exacerbation in chronic non-CF respiratory disease.

**Secondary Objectives**

- To investigate the correlation between PA biomarkers and telemetry with clinical outcomes during and after treatment of an exacerbation with antibiotics.
- To describe rates of adherence to data input by participants/carers.
- To explore whether the self-management platform provided for data upload is feasible and acceptable for daily use in this clinical population.
- To pilot questionnaires to collect data collection on health care utilisation to describe current health care usage in this population.

**Exploratory Objectives**

- To collect urine samples for future studies which may explore whether biomarkers present in urine can also contribute additional information to the exacerbation prediction model.
- To perform molecular analysis for the HI group to corroborate PA test signals.
METHOD
A mixed methods study:
A longitudinal cohort of participants and their carers (where appropriate) will be asked to collect physiological, biological and disease outcome data over a 6-month period. Neither participants nor the clinicians responsible for participants care will have access to the longitudinal data and this information will not be used to make clinical decisions. The laboratory samples will be analysed in a blinded manner. These data will then be analysed to develop a model for predicting onset of exacerbations that can be built into a self-monitoring system.

Qualitative methods will be used to explore participant and carer experiences of using the technology and performing daily self-monitoring assessments. The expected duration of participant participation in the cohort will be six months, with an invitation to complete a self-administered questionnaire at baseline to inform a face-to-face semi-structured interview with patients with or without carer joint participant at the end of the follow-up period (six months completion).

Primary and Secondary Endpoints/Outcome Measures
Primary endpoint
An exacerbation will be defined as the initiation of antimicrobial therapy for respiratory symptoms either at home or on admission, with or without concomitant steroids or admission. For participants who are already on continuous antibiotics, an exacerbation will be defined as starting a course of different antibiotics due to increased symptoms, or an increase or dose or frequency.

Secondary endpoints
Treatment efficacy will be defined as the day at which antibiotic treatment for that episode is completed.

STUDY PARTICIPANTS
Inclusion Criteria
The participant must meet ALL of the following criteria to be considered eligible for the study:

- Male or Female, aged 18 years or above.
- Diagnosed with at least one (or a combination) of COPD and non-CF bronchiectasis.
- Two or more exacerbations with the same pathogen (PA or HI) proven on culture, treated with antibiotics within the last 12 months, one of which must have been within the last 6 months.
- Exacerbation free for the previous 4 weeks.
- Producing at least 1ml of sputum daily.
- Must be capable of operating the self-monitoring devices and tablet-based IT system, or have a carer capable of undertaking the measurements and collection, storage and transport of samples.
- Participant is willing and able to give informed consent for participation in the study.
Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- A suspected or confirmed diagnosis of Cystic Fibrosis
- Any condition likely to limit participant survival or adherence during the study period in the judgement of the clinician, for example malignancy, cirrhosis of the liver.
- Currently taking part in any other research study.

Carers who will also be included in the qualitative interview and to aid participants with data upload. A carer in this study is defined as an adult (≥18yrs) relative or friend who has frequent contact with the participant and will assist the participant to perform measurements or use the iPad mini to upload data.

SAMPLING AND SAMPLE SIZE

Using the sputum biomarker(s) to predict exacerbations, the sample size was based on showing a difference in exacerbation frequency in time periods when an exacerbation was predicted compared to time periods when no exacerbation was predicted. This will give an Odds Ratio of exacerbation following detection of sputum biomarkers.

Time periods will consist of approximately 10 days; of which it will be estimated that there may be on average 12 per participant (assuming an average of 4-months of follow-up). It is estimated that an exacerbation will occur in 60% of time periods in which it is predicted, and 10% of time periods in which it is not predicted. It is also assumed that a predicted exacerbation will be made in only 1 in 12 time points (8% of all time points). Using a 5% significance level and 90% power it is calculated a total of 120 time periods will be required.

However, as there are multiple time periods from the same participant, the data values are unlikely to be independent of each other, and thus the sample size requires inflating. Assuming intra-class correlation of 0.18, a design effect of approximately 3 is calculated. This implies that 360 time periods are required for the analysis. This equates to a total of 30 participants for the study.

The proposed 30 participants will consist of:
- 20 participants with chronic PA infection:
  - 10 with primarily COPD
  - 10 with non-CF bronchiectasis
- 10 participants with Haemophilus infection.

STUDY PROCEDURES

Recruitment

Potentially eligible patients, identified from clinical databases, will be contacted by a member of the research team and invited to attend an information event or specialist research recruitment clinic.

The information event will be held locally on a Saturday or in the evening to make the event more convenient for patients and their carers. The event will allow patients to meet the research team, have an educational talk and find out about the study. They will also be able to look at the devices and iPad app as well as ask any questions. Patients interested in participating in the study will be given a patient information sheet (PIS) and invited to come to a research clinic for screening and enrolment.
At the research clinic patients will be reviewed by a clinical research fellow and screened for suitability for the study by the research team. Patients and carers will be able to view and try out the self-monitoring devices and tablet-based IT system. Capacity to operate these systems will be assessed as part of screening using a checklist, assessing the patient/carer confidence in using the devices and ability to perform the measurements. Those who meet eligibility criteria will be given a Participant Information Sheet (PIS) and a Carer Information Sheet (CIS) if necessary.

After adequate time to read, understand and ask questions (at least 24 hours) patients will be invited back to the research clinic to give informed consent.

Baseline data will be captured on paper CRF’s and uploaded to a local study database, separate to the self-monitoring database held by Aseptika Ltd.

**Participant/Carer training**

Volunteers will be trained by a Research Nurse and Aseptika personnel during a visit to the participant’s home. A home visit will clarify which 3G cellular network is available in their location (for internet access) and will ensure that the participant has space to install a small dedicated freezer and that there is access for delivery.

Each participant will be provided with the following items, and training for the participant/carer provided on their use:

- **Physical Activity Tracker.** This will be set-up for them and they will be shown how and when to wear it.
- **Smart scales.** The participant will be instructed how to weigh themselves and how this measures their body composition. They will be instructed to perform this in bare feet.
- **Blood Pressure.** The participant will be instructed how to take their own blood pressure and what the results mean.
- **Pulse oximeter.** The use of a pulse oximeter and how it works will be explained.
- **Temperature.** The participant will be provided with a non-contact infrared thermometer and will be shown how to take their temperature.
- **Participants will be shown how to measure their Peak Flow and FEV1 using a simple, automated device. This instruction will be undertaken by the research nurse.**
- **Sputum and urine sample.** The participant will be taught how and when to take a sample and how to store the sample in the containers provided in the freezer that will be supplied.
- **iPad mini and questionnaire.** The participant will be trained on how to charge the iPad mini, how to switch it on and off etc. A short questionnaire about symptoms, medications and health-care usage will be completed on the iPad mini using a colourful self-explanatory series of screens. The display will be brightly coloured and any text (which will be kept to a minimum) will be large in size.

Participants will be able to use the iPad mini for personal use as well as for daily study use, within the limits specified and agreed to in the participant consent form (point 5). Participants will be requested to take this equipment with them to hospital if they are admitted and to continue recording these data in hospital. Initial training will take approximately 60 minutes.

Following training, questions about use of the equipment will be handled by the research nurse and referred to the Company in the event of technical difficulties with the IT system. The iPads will be
supplied pre-configured with all software installed and an account for the volunteer already created and defined. A remote access technical support solution will also be pre-installed allowing the company to remotely access the iPad to resolve problems in the event of significant failures. If required, follow-up visits to the participants will be undertaken. Every effort will be made to ensure that the volunteer is adequately trained and supported for the duration of the study.

Study Assessments

Participants will be asked to undertake the following once a day every day during a 6 month follow-up period, with assistance from carers as appropriate. The following picture illustrates the equipment that will be provided to the participant to facilitate these assessments.

Each participant will be provided with a 3G enabled tablet (iPad) and will upload peak flow, FEV₁, pulse rate, oxygen saturation, blood pressure, temperature and physical activity data on a daily basis. The participants will be provided with a set of instructions about uploading the data onto the iPad. The participants will be blind to their continuous data over the duration of the study but will see the values generated daily on the screens of the devices.

There will be no requirement for the participant to enter numerical values into the software. The data collected on the iPad is automatically transmitted to the Cloud databases. No information is stored on the iPad and if the iPad is lost, there is no risk that these data could be made available. The Company is able to track the iPad’s location in the event that it is stolen or lost.

The information uploaded by the volunteers will be reviewed daily and remotely to ensure that data has been uploaded on a daily basis and there are no technical problems. Aseptika’s Directors will undertake this. In the event of technical problems, most will be remedied remotely by the Aseptika
technical staff. In the case of information not being uploaded, Aseptika’s investigator will initially inform the research nurse who will contact the volunteer by telephone to enquire if there have been any difficulties.

Should any volunteers find the technology difficult to manage, they will be offered a further home visit for instructions and training.

**Sample production and home storage for sputum and urine samples**

- Containers will be pre-labelled with the participant study number, expected contents (sputum / urine) and the day and date.
- Participants will be asked to fill the supplied pot with sputum and ensure the lid is correctly sealed.
- Participants will be asked to collect urine in the bulk container and secure the lid
- They will then use the Vacutainer and connect it to the cap of the urine container (as per supplied instructions) – the Vacutainer will begin to fill with urine.
- Bulk urine collection pot is to be discarded.
- Store both containers in sputum and urine collection bags inside of the supplied minus 20°C freezer.
- After 1 month, these will be transferred for bulk storage at the QAH hospital in a designated -70°C freezer and a new batch of containers will be provided.

**Clinic visits**

Participants will be requested to attend the clinic for a follow-up visit at months 3 and 6 (study completion) +/- 2 weeks.

Participants will attend their normal review with the medical team that usually involves lung function, sputum sample for culture and clinical review. They will then have a research visit which will involve disease specific control and quality of life questionnaires (QOL-B, SF-36, SGRQ, EQ5D) as well as noting any changes to treatment and exacerbations.

The data collected from these visits will be recorded on paper CRFs which will then be uploaded by a member of the research team to a local study database with restricted access.

**Health economics**

In preparation for a future cost-effectiveness trial of the self-management system, a questionnaire to collect health care utilisation data will be piloted to capture resource use. These data will be analysed descriptively.

The daily questionnaire on the iPad will ask if participants have been in contact with a health professional or been in hospital for the last 24 hours. If they answer yes, they will be prompted to give more information about who they saw and for what reason. This will capture data on the participants’ health care utilisation for their respiratory condition as well as other conditions.

**Qualitative methods**

Qualitative methodology will be used in order to explore the psycho-social questions: How do the participant and main carer experience self-managing their condition under routine care; what is the
participant’s expectation of taking part in the study and how do they experience collecting daily self-monitoring data and using the devices provided? Qualitative research [8,9] seeks to describe, understand and explain a particular phenomenon to make explicit the experiences and perceptions of the research subjects. This is achieved by exploring the data (usually words) for conceptual definitions on how people perceive situations to provide explanations of why something happens in a particular way as well as looking for typologies or classifications of grouping of people (or situations) that tend to have common characteristics, opinions and experience. Qualitative data will be collected at the end of the study (six months) through face to face semi-structured interviews with participants, or paired interviews with carers, based on participant preference. Carers will not be interviewed separately.

All interviews will be guided by a semi-structured topic guide although free discussion of experiences and ideas will also be encouraged. The semi-structured interviews will be audio taped and field notes taken to describe context, interview process and initial theme development. A choice of venue, either at home or suitable hospital room, will be used. All qualitative interviews will be conducted by the same trained research fellow supported and supervised by another experienced qualitative researcher.

It is anticipated that the semi-structured face to face interviews will take between 45 minutes to one hour to complete, depending on what the participant wishes to share. The interview will be terminated at any point the participant wishes to stop and this will not influence their subsequent treatment. As a small token of appreciation for time given to take part in the interviews, each participant will be offered a £10 gift voucher on completion.

The interviews will be digitally recorded, transcribed verbatim and entered into NVivo 10, a qualitative software package for systematic and transparent data management. All participants’ names will be removed from the transcripts to retain confidentiality. Care will be taken to always ensure any direct quotes used in study reports or papers to illustrate the findings will not be directly attributable to individuals.

Self-administered questionnaire
After consent, and on entry to the main study, all patients, but not carers, will be asked to complete a self-administered questionnaire (to be developed with advice from the PPI team members) with open and closed questions regarding self-awareness/perception of burden of disease, self-management including use of medication, identifying signs and symptoms of deterioration, problem-solving, seeking support/health care professional input during usual care as well as rationale and expectation of participation in the study, perceived barriers and enablers to successful completion in the study. We anticipate that this short self-administered questionnaire will take approximately 30 minutes to complete. The purpose of administrating this self-administered questionnaire is to use individual responses to act as an “aide memoire” at the follow up interviews.

Analysis
Data analysis will use the Framework Approach[10] which provides a systematic, auditable and rigorous analysis of qualitative data. It is also more deductive than other thematic analysis approaches and ensures that focused data is collected to answer the clear research objectives of the study. Experienced facilitators will independently code all data. Scrutiny of the framework matrix will be sought to see if there is agreement with the categories generated. In addition, a member of the steering group, not involved in data collection, will be asked to independently read through a sample
of the transcripts to generate a preliminary framework without seeing the original researchers’ list. In the case of disagreement, a solution will be sought to clarify the meaning of a code/theme developed until mutual consent is reached. The aim of this stage is to attempt to enhance the validity of the development of the conceptual framework and to guard against researcher bias. A narrative summary will be developed from the findings which include comparison within case and across patient and carer’s perception and experience.

**Discontinuation/Withdrawal of Participants from the study**

Participants not complying with study requirements or failing to upload data or collect a sample will be re-trained. Significant non-adherence (e.g. non-collection of data and samples for a period of several weeks) may lead to withdrawal of the participant from the study by the study team. If participants/carers are not willing to continue data collection, they may decide to withdraw from the study, and will return all the equipment.

**Definition of End of Study**

The end of study is the date of the last sample and data upload of the last participant follow-up date, or the last qualitative interview, whichever comes last.

**ASSESSMENT OF SAFETY**

This is a non-interventional study and is therefore considered to be of no additional safety risk compared with usual clinical practice. All patients are expected to have a number of co-morbidities and ongoing symptoms due to their illness. All study procedures in use are the usual standard of care for this population and are not novel. The test used to observe the variation in levels of Exotoxin A is a new test but one that is validated and in itself provides no risk of harm to the participants; it is not performed on the participant themselves but on their sputum, which they would ordinarily be producing daily, and it will not change any clinical treatment as the results will not be available to the participant or their clinical team.

There is therefore no clear rationale for additional safety monitoring during the study period, or for the expedited reporting of any serious adverse events. However, as study procedures are being conducted more frequently by the patients in their homes (as part of their daily routine), there may be an increased frequency of expected side effects/adverse events for some patients. The most likely AE during procedures is an increased risk of fainting for those participants who are susceptible to fainting during Spirometry (specifically daily peak flow, which requires blowing rapidly and forcefully into a spirometer).

Therefore, the following risk-adapted safety monitoring procedures are to be followed during the study period.

Participants will be asked to report any of the expected adverse events to the research team if they occur at a level which causes significant discomfort to the participant, so that the research team can provide any further training or adjustments to the way in which the measurements are taken, or reduce the frequency at which the participant is to take the measurement:

- Dizziness / light-headedness
- Fainting
The Chief investigator and study team will record and monitor any adverse events caused due to the increased frequency of the self-monitoring assessments. If there is any concern over these events or if they become unacceptable and in any circumstance cause the risk to benefit ratio to tip they should be expedited to the Sponsor and may subsequently reviewed by the Research Quality Committee (RQC).

**DATA HANDLING AND RECORD KEEPING**

**Data Collection Forms**

The anonymous daily data generated by participants using the technology provided to them will be uploaded directly to the web servers of Aseptika Ltd via 3G built into the iPad tablets provided to the participants (see section Screening & Enrolment). The anonymised data collected at the hospital visits at baseline, 3 & 6 months will be recorded on study specific Case Report Forms (CRF’s). The data recorded on these forms will then be uploaded, by a member of the research team, onto the local study database held at Portsmouth Hospitals Trust. This database will be password protected and kept on a secure NHS server with restricted access on a computer with restricted access in a locked room.

**Data Management**

Each volunteer will be given an account within Activ8rlives online system. Their names, NHS number, address or any other identifying information will not be entered. Anonymity will be assured by giving each participant a unique study ID which will not be traceable to the participant. The unique study ID will be formed of two letters and two numbers (e.g. SE01 for the first participant recruited into the study, SE02 for the second participant recruited and so on).

Aseptika Ltd.’s servers are located in the UK and have appropriate security measures. Access to these data will be restricted to Director-level personnel within Aseptika Ltd and to the Research Nurse, for the purposes of technical support and to track progress of the study. Patients/carers, clinical staff and laboratory staff will have no access to these data.

Data generated from sputum and urine analysis will be output to Excel spreadsheets and will be imported into the account for each volunteer to be correlated with other telemetry data.

Other clinically relevant information (start of antimicrobial therapy, admission or other treatment which is associated with an endpoint will be entered into the Activ8rlives system.

**DATA ANALYSIS**

**Description of Analysis Populations**

The study is a non-randomised cohort of a single group of patients. All subjects recruited into the study will be included in the data analysis.

**Analysis of Endpoints**

The first stage of the data analysis is to use data on the collected parameters (e.g. peak flow, pulse rate, oxygen saturation, activity data) to predict when an exacerbation is likely. Control charts will be used to determine the boundaries of ‘normal’ behaviour for each parameter. Separate control charts will be used for each participant, as what constitutes ‘normal’ behaviour will vary from participant to participant. When a parameter strays from ‘normal’ behaviour (e.g. exceeds 99% control limits) an
exacerbation will be predicted. To examine the association between predicted exacerbation and actual exacerbation, participant follow-up will be divided into periods of time (e.g. 7-10 days). A comparison of actual exacerbation when exacerbation has and has not been predicted will be made. To allow for the repeat measurements over time from the same participants, the analysis will be performed using multilevel logistic regression.

Additionally, the sensitivity and positive predictive value of the predictions will also be calculated. Estimated values will be presented along with corresponding confidence intervals. Healthcare utilisation data will be presented descriptively, for example the frequency and type of healthcare contacts over the study period for different participant groups.

Procedure for Dealing with Missing, Unused and Spurious Data
The primary analysis will be restricted to collected data only, without any data imputation. The distributions of the parameters collected will be assessed, and implausible values may be excluded from the analysis. Any data exclusions will be justified both clinically and statistically.

Procedures for Reporting any Deviation(s) from the Original Statistical Analysis
Any deviations to the Statistical Analysis Plan will be carefully documented and justified.

ETHICS
The study will not be initiated before the protocol and all study relevant material such as informed consent forms, participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research& Development (R&D) department. Any changes to protocol or relevant study documents will be approved by the Sponsor. Should an amendment be made that requires REC approval, defined by REC as a substantial amendment, the changes will not be instituted until the amendment has been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor amendments, defined by REC as non-substantial amendments, may be implemented immediately and the REC will be informed.

Participant Confidentiality
Study staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by initials and a participant’s ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

Benefits and Burdens to Participants
This study requires a high engagement and compliance rate from the study participants. The additional daily measurements, monitoring and downloading of the information onto the study’s website for six months will be an additional time burden for the participants and may add
significantly to their already onerous treatment burden. Clear instruction, in-depth training and on-going technical support for all of the study equipment, along with regular input from an experienced and committed research team will help to mitigate any burden.

Participants will be required to store the various study equipment including a small study freezer, iPad mini and self-monitoring gadgets in their own homes which may be a burden for some participants, especially those living in smaller properties. Participants will be made aware of the equipment they will be provided with and information on how much space they will need to store the equipment, prior to consent. The capability to store the study equipment will be evaluated as part of a participant eligibility assessment prior to giving out participant information.

A Research Nurse and Aseptika trainer will need to complete a one-off visit to participants’ homes to deliver, install and train the participant in the various study technology. To minimise the burden of this visit, participants will only ever be contacted by the research team, not the company and a visit time will be scheduled in advance, at a time that is convenient to the participant.

On completion of the entire study, each participant and their carer will be shown the data and what has been learned from their participation in the study.

Participant benefits include being compensated £1 a day for successfully completing the measurements and collecting samples, retaining the iPad mini and freezer, being provided with 3G connectivity for 6 months following completion of the study and retain ownership of the monitoring devices. Participants will be encouraged to continue the self-monitoring process “unblinded” thereafter and will have full access to the data they generate.

The study will be reviewed by the Research Quality Committee at regular intervals.

PATIENT PUBLIC INVOLVEMENT (PPI)

The study design is similar to that of a previous study carried out with 15 cystic fibrosis patients in Cambridge. Adaptations of the content and methods of data collection and the final design of the questionnaire on the iPad will be informed by a group of PPI members convened for the purposes of this study. These members will be patients at PHT with similar respiratory conditions and will be invited to attend the group by their respective clinicians. PPI members have also given input on the study design and implementation issues, reviewed the Participant information sheet (PIS) and the informed consent form (ICF). Some key issues raised by the group are listed below, and these will be addressed in the preparation of study implementation:

- How big is the freezer - concern over space at home
- How often will samples be collected - concern about storage of samples and consumables and possible expenses to bring samples to the hospital, plus ensuring that any staff who collect samples from the house will have appropriate ID.
- Ease of use of the Vacutainer urine collection system for participants with co-morbidities such as arthritis.
- Recommended pre-printing of labels.
• Some apprehension about using an iPad.
• Whether the participants who take part will get to know the results of the study.
• What happens if participants wish to go on holiday

RESULTS
The SENSOR study is now in data analysis. It is anticipated results will be available by the end of 2016. The use of technology by study participants was successful, with high upload figures and product reliability.

REFERENCES
1. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. NICE guidelines [CG101].
6. Green B. Improving patient care through a community respiratory integrated service (CRIS) in South East Hampshire. BTS awards for integration, innovation and education, BTS summer meeting 2012.