Royal Free London NHS
NHS Foundation Trust

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COVID19 AnMach - Study Protocol

FULL/LONG TITLE OF THE STUDY

Evaluation of the impact of using anaesthetic machines for ventilation on COVID-19 patients and professionals. A mixed methods study.

SHORT STUDY TITLE / ACRONYM

COVID19 AnMach

PROTOCOL VERSION NUMBER AND DATE

Version 1.0 – 19 June 2020

RESEARCH REFERENCE NUMBERS

IRAS Number:	**285642**
SPONSOR Number:	*133491*
REC Number:	TBC

CHIEF INVESTIGATOR (CI):

Dr Agnieszka Walecka

Consultant in Intensive Care and Anaesthetics, Deputy College Tutor, Audit Lead

Royal Free Hospital

Pond Street

NW3 2QG

Phone: 07506693222
Email: agnieszka.walecka@nhs.net

Pond Street
London
NW3 2QG
Tel: 020 7794 0500

SPONSOR: **Royal Free London NHS Foundation Trust**

Representative of the Sponsor:

Lucy H H Parker
R&D Manager
Royal Free London NHS Foundation Trust
Pond St
London
NW3 2QG
Phone: 07956530411
Email: lucy.parker2@nhs.net

Funding Source: Royal Free Charity

Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorisation from Royal Free London's R&D Office or its affiliates.

SIGNATURE PAGE

Chief Investigator Declaration

The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except where departures from it are mutually agreed in writing.

The Investigator agrees to conduct the trial in compliance with the approved protocol, GCP, the Data Protection Act (1998), the Trust's Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd Edition), the Sponsor's SOPs, and other regulatory requirements as appropriate.

This protocol has been written in accordance to the Sponsor's procedure identified as: SOP029 'Applying for Royal Free Sponsorship' and is intended for use at UK sites **only.**

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For and on behalf of the Study Sponsor:		
Signature:		Date: 26../ 06../ 2020
Name (please print): Lucy H H Parker		
Position: R&D Manager		
Chief Investigator: *Agnieszka Walecka*		
Chief Investigator Site: *Royal Free Hospital* Signature: Type text here Agnieszka Walecka		Date: ...../...../..... 29/06/2020
Name: (please print): Agnieszka Walecka		

Acknowledgements and Protocol contributories

Agnieszka Walecka (AW), Annalisa Casarin (AC, NIHR Research Design Service, University of Hertfordshire) conceived the study; AW, AC, James Noble Johnston (JNJ, Royal Free Hospital) initiated the study design; AW, AC, JNJ prepared the study protocol, and all helped with implementation. AW, AC are grant holders, AC provided statistical expertise in clinical study design and AW, AC, JNJ are conducting primary statistical and thematic analysis. All authors contributed to refinement of the study protocol and approved the final manuscript.

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1.0 LIST OF ABBREVIATIONS/GLOSSARY OF TERMS

AE	Adverse Event
AnMach	Anaesthetic Machines
CI	Chief Investigator
COVID19 or COVID-19	Coronavirus Infectious Disease 2019
CRF	Case Report Form
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
ITU	Intensive Therapy Unit
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS R&D	National Health Service Research & Development
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
RFL	Royal Free London
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment

2.0 ROLES AND RESPONSIBILITIES

Chief Investigator (CI): Dr Agnieszka Walecka, Intensive Care and Anaesthetics Dept

Royal Free Hospital, Pond Street, NW3 2QG

E-mail: agnieszka.walecka@nhs.net
Phone: 07506693222 Fax: N/A

Trial Management Group: Dr Agnieszka Walecka, CI, quantitative component

Dr Annalisa Casarin, monitoring, quantitative and qualitative component, statistics

Dr James Noble Johnston, quantitative and qualitative component, statistics

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NW3 2QG
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3.0 STUDY SUMMARY

Official title:	Evaluation of the impact of using anaesthetic machines for ventilation on COVID-19 patients and professionals. A mixed methods study.
Brief title /Acronym:	COVID19 AnMach
Sponsor reference number:	133491
Study Population/disease condition	Phase 1. Patients ventilated on anaesthetic machines during COVID-19 surge in April and May 2020. Phase 2. Professionals who managed patients on an anaesthetic machines on the above-mentioned period.
Research Question	What is the impact of ventilating patients on an anaesthetic machine?
Study design	Observational non-interventional retrospective data collection, survey and qualitative study
Eligibility criteria:	***Inclusion criteria:*** Phase 1. Adult patients >18 years old admitted to RFH ITU from the 1st of April 2020 until the 30th of October 2020; ventilated with an anaesthetic machine during their ITU admission. Phase 2. ITU professionals who managed patients ventilated using anaesthetic machines at the RFH ITU between the same period.
	Exclusion criteria: Phase 1. Patients ventilated with ITU grade ventilators from admission. Phase 2. Professionals who did not managed patients on an anaesthetic machine.
Anticipated start date	01/07/2020
Anticipated end date	30/11/2020
Target number of subject's/data sets	Maximum 15 patients related datasets
Target number of participants	Maximum 20 professionals' interviews
Primary aim	The study aims to identify issues with ventilation of COVID-19 positive critically ill patients on anaesthetic machines that are not described in available guidelines.

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	Adverse events affecting patient's management and the staff experience of using anaesthetic machines are explored.
Sources of funding	***Royal Free Charity***
Sponsor	**Royal Free London NHS Foundation Trust**
Contact name	***Sponsor representative : Lucy H H Parker*** ***Email: lucy.parker2@nhs.net*** ***Tel:07956530411*** ***Fax : NA*** ***Chief Investigator:*** Dr Agnieszka Walecka ***Email: agnieszka.walecka@nhs.net*** ***Tel:*** 07506693222 ***Fax: N/A***

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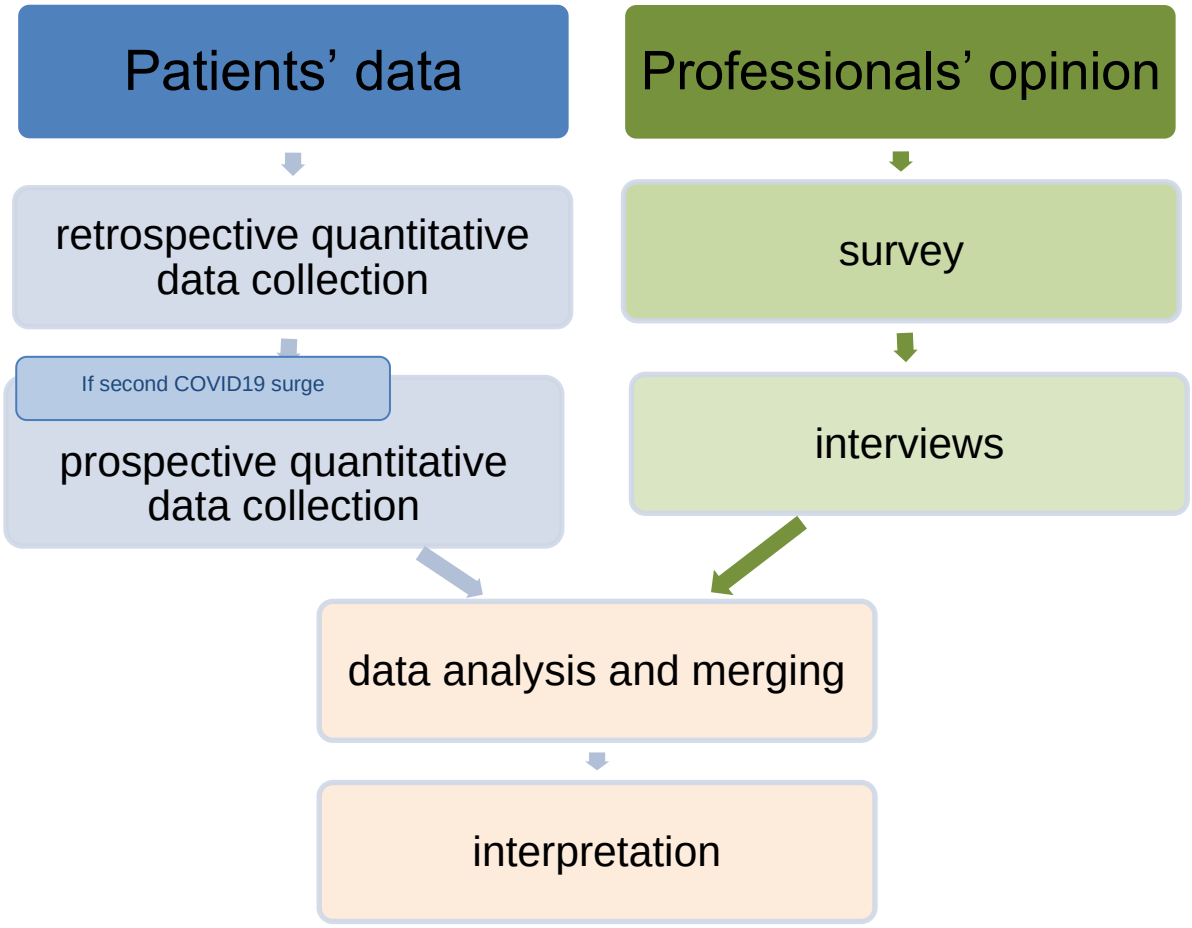
4.0 STUDY FLOW CHART



5.0 INTRODUCTION

5.1 BACKGROUND

The COVID-19 pandemic dramatically increased the demand for the ventilator beds in the United Kingdom (UK), generating, at the same time, Intensive Therapy Unit (ITU) ventilators shortages (Lauer et al., 2020). Anaesthetic machines (AnMach) have been commonly used as a solution to supplement ventilator capacity. The use of AnMach as a long-term ventilator is considered an off-label use but emergency use of these devices is justified when there is no available alternative because the benefits outweigh the risks (Government UK, 2020; Food and Drug Administration Staff 2020). This occurred at the Royal Free Hospital (RFH), London, in April and May 2020.

Modern AnMach are capable of providing mechanical ventilation to patients with respiratory failure, however they neither are ITU grade ventilators nor their use as such has been verified and validated

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(GE Healthcare, 2020). Safe and effective use of AnMach as ventilators requires understanding of the differences between AnMach and ITU ventilators and their limitations in mimicking ventilation strategies (APSF/ASA, 2020).

Both machines provide air and oxygen from a wall to patients at desired ventilation settings and oxygen concentration. The AnMach have a rebreathing system where the expired air goes through a filter (soda lime, that has a limited capacity of absorption and needs replacing) that catches the carbon dioxide and the ‘’cleaned’’ air goes back to the patient. To do this they need high flow volume, more than 50% of the patients’ minute volume (air volume given to patients each minute). The ITU ventilators are non-rebreathing systems so exhaled breath is dispersed to the atmosphere and a new air mix is given to patients at every breath. AnMach are designed to be full time attended because they have limited ability to generate alerts. Also, they may contain residual anaesthetic gas in the system that could interact with other patients’ medication. AnMach need testing every 24hours and need to be set ready to ventilate while ITU ventilators are ready to go as soon as the patient is connected (GE Healthcare, 2020).

Although regulatory authorities approved the emergency use of AnMach as ventilators, it has been stated that healthcare professionals using these machines must be appropriately trained (Government UK, 2020; Food and Drug Administration Staff 2020). Similar statements have been issued by the manufacturers (Lauer et al. 2020; GE Healthcare, 2020; Getinge, 2020). To outline the potential risks related to the use of AnMach as ventilators, the UK MHRA issued a Medical Device Alert in early April 2020 highlighting the actions required to minimise hazards (Government UK, 2020). At the end of April 2020, NHS England and NHS Innovation published a new comprehensive clinical guidelines for use of AnMach to provide continuous invasive ventilatory support for adult patients during the coronavirus pandemic. The guidelines were long awaited and launched when the UK passed the surge. The guidelines described the major differences between AnMach and ITU ventilators as well as highlighted potential issues with ventilation using AnMach and provided advice how to deal with them (NHS England, 2020). It has been recommended that anaesthetic machines should be used in patients with the lowest critical care acuity scores and relatively good lung compliance. The guidelines also acknowledge that if a patient`s lung compliance (the extent to which the lungs will expand) deteriorates it may be necessary to transfer a patient on to ITU grade ventilator.

The most common issues with ventilating patients on AnMach, according to the NHS England guidance, are (NHS England, 2020):

1. Problems with altering the fresh gas flows (FGF) and the degree of rebreathing: the FGF should be set to avoid rebreathing and generation of excess humidity. Moreover, the amount of oxygen given to the patients depends on the FGF and the amount of rebreathing. An increase in FGF every 4 hours is recommended to help dry the internal components of the machine.

2. Need of changing soda lime for absorption of CO2: the risk of CO2 rebreathing occurs in case of exhaustion of soda lime activity.

3. Potential to deliver hypoxic mixture at low flows: low flows are not recommended for long term ventilation of ITU patients.

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4. Absence of a pressure relief valve to limit the maximum pressure of the air flow given to the patients that put the receiver at increased risk of barotrauma.

5. Increasing resistance to gas flow due to saturation of filters with water: water vapour is produced by CO2 absorbers. If the water is not expelled, monitors may indicate easily overlooked flow tracing errors (prolonged expiratory phase, slurring of the expiratory capnography) and increased airway pressure may occur. Periodic drainage of water from the circuit is required which may result in an alternative means of ventilation being used.

6. Collection of water in dependent areas (part of tubes where water sits lower by gravity) of the breathing system: pressure/flow oscillations may be sensed by the ventilator as patient inspiratory effort which in turn will make a total respiratory rate greater than the set one and have a detrimental effect on patient`s ventilation.

7. Lack of leak compensation in case of a leak of air flow: this may result in loss of inspiratory pressure and end-expiratory pressure and falling of the bellows (the bag where air flow goes in to be subsequently pushed into patient`s lungs) resulting in inadequate ventilation. Several strategies need to be employed including manual ventilation during suctioning of secretions.

8. A ‘backup mode’ of ventilation is not always present: the lack of the apnea mode (if patients doesn’t breathe the system starts ventilating for him) may result in prolonged apnea if patient loses respiratory drive while on spontaneous mode of ventilation.

During the pandemic, the rapid deployment and repurposing of available devices were not the only actions taken to tackle care challenges. The increased demand for ITU beds also resulted in ITU staff shortages and subsequent deployment of non-ITU trained staff to help to look after ITU patients. This caused a significant change in approach to patient care, capacity management and training on ITU (Nursing and Midwifery Council, 2020) to guarantee quality of care. The guidance by the American Society of Anaesthesiologists states ‘’Intensivists [ed. the ones that are not anaesthetists], ICU nurses and respiratory therapists are not trained to manage anaesthesia machines and are likely to be overextended and stressed’’ (APSF/ASA, 2020). Undoubtedly the expanding pandemic, significant and rapid change to working pattern, and the lack of experience with managing AnMach were personally and professionally challenging for both ITU staff and redeployed professionals and may have caused some of them to experience moral injury or mental health problems (Greenberg et al., 2020).

5.2 RATIONALE

In order to meet the increased demand for ITU beds, in many hospitals in the UK, and in particular at the RFH, general care wards were transformed into ITUs in preparation for the surge. The ward 2North A (2NA) and the main recovery room at the RFH has been equipped with AnMach with a view to admit COVID-19 surge ventilated patients. Patients were looked after by either anaesthetic or intensive care consultants as well as ITU and non-ITU nurses and doctors.

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Evidence around the use of AnMach for long-term ventilation and weaning of critically ill patients is scarce. Published studies are dated and based on test lung model and compare the performance of the AnMach and ICU ventilators in the laboratory settings (Jaber et al., 2006; Tung et al., 2005). Despite recently disseminated guidelines, professionals who managed surge patients admitted to 2NA/main recovery may have not been familiar with the equipment and not been aware of the newly published evidence.

This study aims to explore the clinical outcome of patients admitted to 2NA/main recovery in April and May 2020, identify possible adverse events related to the use of AnMach as ventilators, and capture the experience of staff using unfamiliar equipment and managing non typical cases. The results of our study will potentially allow us to identify additional risks of using AnMach as ITU ventilators rather than the ones published in the guidelines and to recognise hidden areas for improvement of care and staff support to address.

6.0 RESEARCH QUESTION

What is the impact of ventilating patients on an anaesthetic machine in term of adverse events and ITU professionals experience?

6.1 PRIMARY AIM

This observational study is set to evaluate the impact of using anaesthetic machines for ventilation of COVID-19 positive ITU patients admitted to the RFH 2NA and main recovery location. The study aims to identify issues with ventilation of critically ill patients on anaesthetic machines that are not described in available guidelines. Adverse events affecting patient's management and the staff experience of using anaesthetic machines are explored.

6.2 OBJECTIVES

- To collect quantitative data from the charts of patients admitted to 2NA/main recovery from the 1stApril 2020 to the 30th October 2020.
- To survey ITU staff in order to identify professionals that manage patients ventilated via anaesthetic machines.
- To interview consenting professionals that rotated in 2NA/main recovery in the study period: 3 to 5 nurses, 3 to 5 physiotherapists, 3 to 5 doctors trained in Intensive Care, and 3 to 5 consultant physicians (ITU staff but not trained in anaesthesia).
- To perform statistical and thematic analysis of data.
- To prepare a report for HRA and the RFH Research and Development (R&D) Department, dissemination of study results to participants and appropriate stakeholders, preparing manuscript for publication into an Intensive Care/Anaesthetic journal.

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7.0 TRIAL DESIGN

This is an observational mixed methods study and no additional interventions will be performed.

7.1 METHODS

This project consists of two parallel phases:

Phase 1, a quantitative, observational, cohort study to detect the effect of exposure to anaesthetic machine ventilation of COVID-19 patients in term of adverse events.

The quantitative phase may be also divided in two parts:
1a, a retrospective data collection of patients admitted to RFH ITU (and possibly the Barnet Hospital ITU) and connected to anaesthetic machines between the 1st April and 1st June 2020, and
1b, a prospective data collection of cases that occur between the 1stJune and the 30th October 2020 in order to cover a new period of possible COVID-19 surge.

Phase 2, a survey and an interview stage engaging ITU professionals that managed patients on anaesthetic machines during the COVID-19 surge in an unfamiliar environment (nurses, physiotherapists, and doctors).

Mixed methods were chosen to integrate elements of quantitative and qualitative research in order to achieve a broader understanding of the topic. Also using both methods and integrating results helps determining the interview phase sample and interpreting the findings of the quantitative phase (O'Cathain et al., 2007).

8.0 SELECTION CRITERIA FOR DATA COLLECTION

8.1 DATA SELECTION CRITERIA for phase 1

There will be no exceptions (waivers) to eligibility criteria for data inclusion into the study.

The criteria have been carefully considered and are standards used to ensure the data can be appropriately selected, collected and appropriately analysed. It is therefore vital exceptions are not made to the following detailed selection criteria.

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8.1.1 INCLUSION CRITERIA

Patients to be included in this phase 1 of this study must fulfil all of the following criteria:

- Adult patients >18 years old (indicated from patient details) admitted to RFH ITU from the 1st of April 2020 until the 30th of October 2020;
- Intubated and ventilated (indicated from documentation in notes);
- Ventilated with anaesthetic machine during their admission (as suggested by daily nursing observation charts and daily review sheets in the notes of ICU clinicians and physiotherapists).

8.1.2 EXCLUSION CRITERIA

- Any patient who received treatment in intensive care and was ventilated with an ITU grade ventilator from admission

8.2 PARTICIPANT SELECTION CRITERIA for phase 2

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility should be addressed prior to entering the participant.

The eligibility criteria have been carefully considered and are standards used to ensure the trial results can be appropriately used to make future treatment decisions for other people with similar disease or medical condition. It is therefore vital exceptions are not made to the following detailed selection criteria.

All participants that are screened for inclusion into the study must be entered onto the sponsor screening log RFLRDLOG0001 and will be assigned a sequential number. Participants will be considered eligible for enrolment into this trial if they fulfil all of the inclusion criteria and none of the exclusion criteria as defined below.

Eligible participants will be entered onto the sponsors Subject ID log RFLRDLOG0002 and assigned a Trial specific Identification number in a pre-agreed format in accordance with Site identifier and next sequential numerical value e.g. RF001

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8.1.1 INCLUSION CRITERIA

- ITU professionals (nurses, physiotherapists, ITU consultants trained in intensive care and who that are not accredited anaesthetists) who agree to be interviewed and manifest their consent responding to the survey;
- ITU professionals who managed patients ventilated using anaesthetic machines at the RFH ITU between the 1st April and the 30th of October 2020;

8.1.2 EXCLUSION CRITERIA

- ITU professionals who didn't manage patients on anaesthetic machines

8.1.3 DISCONTINUATION/WITHDRAWL OF PARTICIPANTS

Any study participant is free to withdraw from the study at any time. Collected material pertaining to the participant will be destroyed and their details erased from the database.

9 STUDY PROCEDURES

9.1 PHASE 1 PROCEDURES: quantitative cohort study

9.1.1a - Retrospective data collection

The quantitative phase of this study aims to broadly examine the impact of using anaesthetic machines for ventilation of COVID-19 positive patients.

Important note: current inability to access the patient notes and observation charts (access to notes is requiring a quarantine period once a patient has been discharged from ITU; this is currently 2 weeks) may lead to partial availability of the data described in the endpoints section. Anecdotal evidence from discussions with nursing staff suggests that it may not be possible to tell from the documentation which patients were ventilated with AnMach versus a conventional ITU ventilator. This issue can only be addressed following accessing some of the observation charts that have been processed and released from quarantine. At this moment we can hypothesise two options:

Option I, we can label the charts as AnMach use: It will be possible to perform a clinical outcomes and adverse events comparison between patients identified as being ventilated by AnMach and those

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identified as being ventilated by conventional ICU ventilators. In this case (less likely) we will request a study amendment after having access to the chart and being sure we can achieve this. We will also request an amendment in case of a second surge of COVID19 for the prospective data collection.

Option II, we cannot distinguish which device was used to ventilate the patients: adverse events possibly linked to AnMach will be recorded from charts of all patients admitted to 2NA and main recovery between the 1st April and the 1st of June 2020. We will also review Datix database for any serious incidents related to the use of AnMach.

The remaining sections refer to this option II = we cannot label charts as AnMach (more likely to be the case).

The Methods for Phase 1 of this study can be broken down into the following sections:

1. Identification of study participants:

This involves applying the inclusion criteria listed above to patients admitted to 2NA and main recovery between the 1st April 2020 and 1st June 2020. The list of these patients will be generated using the records from the Cerner EPR Computer System where all patient locations within the hospital are updated in a 'live' fashion. This will give us an accurate picture of all the patients admitted to 2NA and main recovery during the above period thus providing a population of patients who were exposed to ventilation by AnMach. In order to identify individuals who were ventilated by AnMach while in this location, we will review the nursing charts and the physiotherapy notes which we anticipate will provide evidence for the method ventilating a particular patient in that location of the hospital

2. Review of raw data:

Following identification of study participants using the inclusion criteria (Section 8.1.1), data from their admission will be reviewed and collected. This will involve manual review of the following:

- Observation charts (when released for review). These provide quantitative data and trends can be identified to provide evidence that ventilatory support was being weaned or escalated:
    - These charts will show hour by hour trends in the level of respiratory support being delivered to the patients, including; the mode of ventilation, the delivered oxygen concentration, the pressure settings of ventilation, position of the patient (i.e. whether proned or not).
    - They also show the physiological status of the patient including their hourly observations and regular blood gas sampling, thus providing evidence about

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whether the patient was deteriorating, improving or remaining static in terms of ventilatory support.
    - The chart may also provide qualitative evidence of a patient weaning from ventilation. The back of the chart provides space for the nursing staff to record information regarding the course of the day using 'free-hand'. This will provide evidence of the ventilator being used as well as the clinical direction of the patient i.e. whether weaning or not.

- Daily review sheets filled in by ICU clinicians and physiotherapists.
    - These will provide more information about the progress of patients while being ventilated. There may be documentation that mentions difficulties that have arisen when ventilating or weaning ventilation in these patients as well as providing indications as to why patients have been switched to different modes of ventilation or device.
    - Physiotherapists' notes may help us to identify the AnMach patients.

3. Data recording and translation to Outcomes/Endpoints

The data for each patient will be recorded and anonymised in an encrypted Excel spread sheet and will include:

- Age, gender
- Reason for admission
- APACHE II score
- SOFA score
- Date of admission to ICU
- Date of intubation
- Was patient ventilated using AnMach?
- Number of days of ventilatory support before weaning ventilation
- Number of days spent weaning from ventilation to being successfully weaned from ventilator (extubation)
- Was patient transferred from AnMach onto conventional ICU ventilator?
- How many days following ventilation with the AnMach did the transfer happen?
- What was the indication for transferring a patient from an AnMach to the conventional ICU ventilator?
- Did the patient receive a tracheostomy?
- Adverse events possibly correlated with the use of AnMach: soda lime issues, gas flow issues, hypoxia, elevate pressure of ventilation, water need to be cleaned out of tubes, sudden respiratory rate increase, need for manual ventilation
- Organ support - number of days of
    - Use of one or more inotropic drugs or anti arrhythmic

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- Renal - a need for renal replacement therapy
- Liver - correction of coagulopathy (plasma use), hypoglycaemia (glucose use), presence of hyperlactataemia (high lactate levels) related to liver failure
- Neuro - delirium

- Date of discharge from ICU or date of death
- Length of ITU stay

The above data will be used to identify quantitative values for the primary and secondary endpoints discussed in section 13.1. This will then be analysed as discussed in Section 13.0

9.1.1b - a prospective data collection

Prospective data may be suitable for collection depending on the course of the COVID-19 crisis. At present there are no patients at the Royal Free Hospital being ventilated on anaesthetic machines. However, if there is a 'second surge' in cases and the department is forced to re-expand and use anaesthetic machines for ventilation then there may be scope to develop a prospective element to data collection. Should there be patients being ventilated with anaesthetic machines in the future, we would consider a prospective cohort study to examine outcomes for patients ventilated by anaesthetic machines and request an amendment of the study protocol to HRA.

9.2 PHASE 2 PROCEDURES: qualitative study, survey and interviews

9.2.1 PARTICIPANT RECRUITMENT PROCESS

All participants who wish to enter the study will be fully screened and consented by the Chief Investigator, or one of the qualified clinicians involved in the study as Clinical Co-investigator.

The Survey

A structured questionnaire will be developed by the study team. The questionnaire will be hosted by the Qualtrics platform (https://www.qualtrics.com/uk/), a service provided to academics with a stricter privacy policy compared to more frequently used survey platforms. The survey will be a mean of screening ITU professionals. The participants will be asked to answer the following questions:

Qualification: nurse, physiotherapist, intensivist not anaesthetist, anaesthetist
Years of ITU experience

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Did you look after a patient ventilated on anaesthetic machine during your time on 2NA/main recovery?
Have you ever ventilated a patient on an anaesthetic machine before this event?
Were you aware of any guidance for ventilating patients using anaesthetic machines?
Have you experienced any problems with ventilating patients on anaesthetic machine? - if yes please describe
Would you consent to be interviewed about your experience using anaesthetic machines?

The first page of the survey will include information accompanying the questionnaire fully explaining the purpose of the research and what the data collected would be used for.

The in-depth interviews

In the second phase of the study, in-depth interviews with 12 (minimum) to 20 (maximum) ITU professionals will be performed. Study participants who volunteer to be interviewed will be contacted on the phone or via a video call platform (e.g. Zoom or Microsoft Teams) and asked for their availability for a thirty minutes interview. The interview will be recorded and later transcripted. Interviewees will be asked to record their consent before beginning the interview. The topic guide for interviews and the answers to the survey will guide the interviews. The main topic will be the professionals experience of managing a patient on anaesthetic machines: easiness, adverse events, solutions, recording of events, impact on their mental health.

9.2.2 INFORMED CONSENT

The Investigator or designee will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

The first page of the survey will contain the PIS and consent statements, participants will be asked to sign proof the reading of the PIS.

The return of the completed questionnaire filled in the survey platform will be assessed also as ‘implied consent’. No separate documented study consent will be sought. The consent to interview will be also recorded using a tape recorder.

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10 STUDY COMMENCEMENT

The study will only commence once evidence of the following approval/essential documents are in place:

1. HRA approval,
2. Final sponsorship and host site confirmation of capacity and capability.

Phase 1 and phase 2 will start in parallel. The recruitment process for **phase 2** will happen in the RFH ITU. The CI and her delegate will approach ITU professionals and ask them to do the survey on a computer or a tablet or a mobile phone. An email will be circulated to the ITU staff containing the survey link.

11 DATA MANAGEMENT AND QUALITY ASSURANCE

Data collection points:

- Retrospective data collection: 1st of July – 30th of October 2020
- Survey: 1st of July – 31st of July 2020
- Interviews: 15 July – 31st of Sept 2020

11.1 CONFIDENTIALITY

All data will be handled in accordance with the Data Protection Act 1998.

The data collection forms will not bear the subject's name or other directly identifiable data. The subject's trial Identification Number (ID) only, will be used for identification. The sponsor Subject ID log RFLRD0002 should be used to cross reference subject's identifiable information.

11.2 DATA COLLECTION TOOL

Data Collection Forms will be designed by the CI and collaborators. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly

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inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the forms. The Staff Delegation of Responsibilities Log RFLRDLOG0004 will identify all trial personnel responsible for data collection, entry, handling and managing the database. The data custodian for this study is Agnieszka Walecka.

For phase 1, data is to be recorded directly onto the CRF by the CI and the study management team. The data collected is listed in section 9. For phase 2, survey data will be exported in an excel file and kept in a password coded computer. The interview transcriptions will be kept anonymised in word files and saved in a password coded computer for the thematic analysis while the recording destroyed soon after being transcribed.

11.3 INCIDENTAL FINDINGS

Establish the capacity for inadvertent/incidental data that are of potential relevance for participants or their families.

In case of the accidental finding of mental health issue related to managing patients in an unfamiliar environment, the participants will be advised to seek help via their line managers.

11.4 DATA HANDLING AND ANALYSIS

Quality Control should be applied at each stage of data handling to ensure that all data are reliable and have been processed correctly.

Data will be kept in Microsoft office files, the quantitative data in excel files, the qualitative data in word files. After collecting quantitative data in the CRF, data will be exported in the files in an encrypted computer.

11.5 TRANSFERRING/TRANSPORTING DATA

Person-identifiable information will not be stored on any portable device. Identifiable information will not be sent outside the Trust. If needed, data will be transferred electronically in accordance with the UK Data Protection Act 2018 and GDPR.

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12 ARCHIVING

During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions.

The trial essential documents along with the trial database will be archived in accordance with the sponsor SOP0044. The agreed archiving period for this trial will be **5 years.** This will include any study databases.

13.0 ANALYSIS DESIGN

Annalisa Casarin will be responsible with the CI for the data analysis.

13. 1 Phase 1 ENDPOINTS

13.1.1 PRIMARY ENDPOINTS

- Proportion of patients who experienced any of the following adverse events possibly correlated with the use of AnMach: soda lime issues, gas flow issues, hypoxia, elevate pressure of ventilation, water need to be cleaned out of tubes, sudden respiratory rate increase, need for manual ventilation (frequency).

- Proportion of ventilation weaning failure while on AnMach (frequency) – This is defined as meeting one of the following criteria:
    - Lack of progress on AnMach – Defined as a failure to reduce ventilatory support for period of > 48 hours
    - Need for ventilation on an ITU grade ventilator – This will be a measured event of the transfer from AnMach to ITU-grade ventilator

13.1.2 SECONDARY ENDPOINTS

- Number of patients ventilated with an AnMach in the period of interest (continuous)
- Age (continuous), gender (categorical)

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- Reason for admission (categorical)
- APACHE II score (continuous)
- SOFA score (continuous)
- Duration of ventilation - a measurement of the time from the start of ventilation until the first period of mechanical ventilation is complete (continuous)
- Length of ICU stay – A measure of the number of days between admission to ICU and discharge from ICU (continuous)
- Number of days of ventilatory support before weaning ventilation (patients on spontaneous breathing) (continuous)
- Number of days spent weaning from ventilation to being successfully weaned from ventilator (extubation) (continuous)
- Number of days following ventilation with the AnMach after which transfer to an ITU grade ventilator happened (continuous)
- Indication for transferring a patient from an AnMach to the conventional ITU ventilator (categorical)
- Proportion of patients receiving a tracheostomy (frequency)
- Organ support - number of days of (continuous)
    - Use of one or more inotropic drugs or anti arrhythmic
    - Renal - a need for renal replacement therapy
    - Liver - correction of coagulopathy (plasma use), hypoglycaemia (glucose use), presence of hyperlactataemia (high lactate levels) related to liver failure
    - Neuro - delirium
- Length of hospital stay - A measure of the number of days between admission to Hospital and subsequent discharge from hospital (continuous)
- Mortality at 28 days – proportion of patients who died in the study period (frequency)
    -

13.2 **STATISTICAL ANALYSIS PLANS**

The retrospective (and prospective, if available) data collection:
This is a cohort study with no sample size calculation. The number of patients managed on AnMach and charts available (identified as AnMach Use) will dictate how many cases we will be able to analyse. The statistical analysis will be descriptive and performed with the Microsoft Office Excel data analysis package in case we will not be able to identify the AnMach charts and we will collect only adverse events data and report them as proportions. The clinical outcomes will be described using absolute and relative frequencies (expressed as a percentage) or position indices (average or median) and relative dispersion indices (standard deviation or interquartile range) suitable for the type of variable analysed. If comparison between AnMach patients and ITU ventilator patients will be possible, mean and standard

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deviation of clinical outcomes for the two groups will be compared (the plan for this analysis will be explained in case of requesting a protocol amendment).

The Survey:
The questionnaire answers will be inserted in an excel spreadsheet and cleaned. Incomplete, inaccurate and missing data will be detected and discussed during interviews. The results will be used to select participants for the second stage and implement the topic guide for interviewing the volunteers. For this aspect of the study the statistical analysis will be descriptive and performed with the Microsoft Office Excel data analysis package. Data will be reported as proportions.

13.2.1 SUMMARY OF BASELINE DATA AND FLOW OF PATIENTS

Not applicable

13.2.2 PRIMARY AND SECONDARY ENDPOINT ANALYSIS

The analysis of Phase 1 of the study will be **descriptive** in nature in case it will be not possible identify patients on AnMach from the charts. There will not be statistical comparison between patients identified as being ventilated by anaesthetic machines and those identified as being ventilated by conventional ITU ventilators. The study will not be sufficiently powered to measure a statistical significance of primary and secondary outcomes between the two cohorts of patients.

13.3 THEMATIC ANALYSIS PLANS

A thematic analysis of the interviews will be conducted in order to identify common themes and patterns among the professionals' responses. Thematic analysis has the advantage to condense data into workable themes and the research topics can be explored and interpreted in a way that is not achievable through quantitative data collection only (Castleberry and Nolen, 2018). This kind of analysis allow to examine the perspective of the participants highlighting similarities and differences and summarising unexpected findings (idem). Following a thematic analysis process, the text of transcribed interviews will be coded (every sentence or part of it is assigned a code that identified its meaning) and codes will be grouped in categories and sub-categories. This process will be repeated with all interviews and codes and categories will be revised when new information made it necessary. The final categories will be merged into themes.

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13.3.1 Phase 2 ENDPOINTS

The interviews phase aims to detect the proportion of interviewees who experienced difficulties of managing patients with an AnMach and feeling stressed or overwhelmed by the situation.

14 DIRECT ACCESS TO SOURCE DATA

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

15 ETHICS AND GOVERNANCE REQUIREMENTS

Before any site can enrol patients into the trial, the Principal Investigator must ensure written permission to proceed has been granted by that Trust Research & Development (R&D). If conducting the study at Royal Free London NHS Foundation Trust, contact the R&D team for any assistance.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, which was given favourable opinion by the Research Ethics Committee (REC) and the Health Research Authority (HRA) where applicable.

The Chief Investigator will be provided (via the Sponsor) with file indexes TMF Index RLFRDDOC0013 and ISF index RFLRDOC0003 for use with SOP019 ‘Preparation and Maintenance of the Site File – and SOP054 ‘Preparation and Maintenance of the Trial Master File’. The CI will be responsible for the maintenance of the TMF and may delegate the responsibility of ISF file maintenance to the PI at each participating site.

It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary approval. Refer to R&D OFFICE SOP0016 ‘Protocol amendments of RFL Sponsored Studies’ and R&D OFFICE SOP003 ‘Reporting amendments’.

Within 90 days after the end of the trial, the CI and Sponsor will ensure that the REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. Refer to R&D OFFICE SOP0030 ‘Study Close Down’

The CI will supply an End of Study report of the clinical trial to the REC within one year after the end of the trial. The sponsor can provide an End of study Report template RFLRDDOC0005.

15.1 DEFINITION OF THE END OF TRIAL

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The end of the data collection will be marked as the Last Data entry point. The end of the study is scheduled as the 30th of November 2020 providing a study commencement date on the 1st of July 2020.

15.2 ANNUAL PROGRESS REPORTS (APRs)

The Chief Investigator will prepare the APR in accordance with the RFL R&D Office's SOP 056 'Annual Progress Reports'. Following review by the sponsor the report will be sent to the REC. The APR is due for submission annually within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, until the trial is declared ended.

15.3 PROTOCOL COMPLIANCE

Any Protocol Deviations, Violations will be documented using the deviation reporting form (RFLRDDOC0006), and entered onto the Sponsor's deviation log (RFLRDLOG0005) and processed according to R&D OFFICE SOP 032

The CI will notify the Sponsor immediately of any case where there exists a possible occurrence of a violation of the protocol or a breach of Data protection.

16 FINANCE

The Royal Free Charity has agreed to finance the study assigning the study team £4500. This will support the CI time, the qualitative component (interviewer time, interviews transcription cost), and possibly a research assistant for data collection.

17 PEER REVIEW

This protocol has been or will be peer reviewed before it is authorised for use in accordance with the Sponsor's SOP on Peer Review (SOP 055)

18 PUBLIC AND PARTICIPANT INVOLVMENT

A member of the public was sought to review the study and its aims. The public representative felt that it would be appropriate to investigate the effects of using anaesthetic machines and patients. She was particularly interested in effects of moral injury on members of the ITU staff multi-disciplinary team. She had anticipated that stress levels would have been very high due to using unfamiliar equipment.

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She fears a second wave and agrees that this study is important as it may inform further practice should a second peak in infections arise.

We will endeavour to identify a member of the public (possibly an ITU professional external to the group of study participants) to join our management team and help us identify opportunities for dissemination of the results to appropriate stakeholders.

19 INDEMNITY

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

20 IP AND DEVELOPMENT POLICY

Unless otherwise specified in agreements, the following guidelines shall apply: All Intellectual Property Rights and Know How (IP) related to the Protocol and the Trial are and shall remain the property of the Sponsor excluding

1) Pre-existing IP related to clinical procedures of any Hospital.

2) Pre-existing IP related to analytical procedures of any external laboratory.

All contributors

shall assign their its rights in relation to all Intellectual Property Rights and in all Know How, not excluded above to the Sponsor and at the request and expense of the Sponsor, shall execute all such documents and do all such other acts as the Sponsor may reasonably require in order to vest fully and effectively all such Intellectual Property Rights and Know How in the Sponsor or its nominee.

shall promptly disclose to the Sponsor any Know How generated pursuant to this Protocol and not excluded above and undertake treat such Know How as confidential information jointly owned between it and the Sponsor

Nothing in this section shall be construed so as to prevent or hinder a medical professional from using Know How gained during the performance of the Trial in the furtherance of its normal business activities, to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Right of the Sponsor.

21 PUBLICATION AND DISSEMINATION POLICY

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Publication: “Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations.”

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

21.2 BEFORE THE OFFICAL COMPLETION OF THE TRIAL

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the **Funder** shall have the final say.

21.3 UP TO 180 DAYS AFTER THE OFFICAL COMPLETION OF THE TRIAL

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
- Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.
- Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
- If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

21.4 BEYOND 180 DAYS AFTER THE OFFICIAL COMPLETION OF THE TRIAL

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After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

21.0 STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by the REC (if applicable) and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC

22.0 REFERENCES

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23.0 APPENDICIES

23.1 APPENDIX 2 – AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee.