Chelsea and Westminster Hospital NHS
NHS Foundation Trust

A Randomised Controlled Trial of Early Intervention in **P**atients Hosp**I**talised with C**O**VID-19: Favipiravir and Sta**N**dard care v**E**rs**E**s Standard Ca**R**e

PIONEER

Protocol Number:	**CW002**
Version and Date:	Version 2.4 dated 21st April 2021
EudraCT:	2020-001449-38
Principal Chief Investigator:	Professor Pallav Shah Chelsea and Westminster Hospital 369 Fulham Road, London SW10 9NH
Lead Sponsor:	Chelsea and Westminster Hospital NHS Foundation Trust 369 Fulham Road London SW10 9NH

Protocol Approval: 

Professor Pallav Shah

21st April 2021
Date

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsors, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

GCP Compliance Statement:

This trial will be conducted in compliance with the protocol, the principles that have their origin in the Declaration of Helsinki and all applicable regulatory requirements

TABLE OF CONTENTS

1. SYNOPSIS

Trial Identifying Numbers	IRAS: 282405 EudraCT: 2020-001449-38
Chief Investigator	Professor Pallav Shah
Lead Sponsor	Chelsea and Westminster Hospital NHS Foundation Trust Research and Development, Unit G02 Harbour Yard, Chelsea Harbour, London SW10 0XD
Co-Sponsor	NEAT ID Foundation Registered address: PL 709 Rue Haute 322, 1000 Brussels, Belgium Administrative office: 27 Old Gloucester Street, London WC1N 3AX, UK
Data Management	Clinical Informatics Team Research Organisation (KC) Ltd. (ROKC) The Stanley Building, 7 Pancras Square, London N1C 4AG
Pharmacovigilance	Pharmacovigilance Team Research Organisation (KC) Ltd. (ROKC) The Stanley Building, 7 Pancras Square, London N1C 4AG
Monitoring	Clinical Risk Based Monitoring Team Research Organisation (KC) Ltd. (ROKC) The Stanley Building, 7 Pancras Square, London N1C 4AG
Lead Sponsor Contact	Damon Foster Research Delivery and Operations Manager Chelsea and Westminster Hospital NHS Foundation Trust Damon.foster2@nhs.net020 3315 6887
Study Contact	Dr Christopher Orton Respiratory Research Fellow Royal Brompton and Harefield NHS Foundation Trust c.orton@rbht.nhs.uk
Study Title	A Randomised Controlled Trial of Early Intervention in **P**atients Hosp**I**talised with C**O**VID-19: Favipiravir and sta**N**dard care v**E**rs**E**s Standard Ca**R**e
Short Title	PIONEER
Name of Active Ingredients	Favipiravir
Primary Objective	To determine whether early intervention with Favipiravir improves the time to significant improvement in clinical status in patients with COVID-19 infection
Secondary Objectives	To assess whether early intervention with Favipiravir improves mortality in patients with COVID-19 infection To determine whether early intervention with Favipiravir

	reduces resource utilisation in patients with COVID-19 infection To explore whether early intervention with Favipiravir attenuates the excessive inflammatory cytokine response in patients with COVID-19 infection
Exploratory Objectives	To identify prognostic markers indicating the need for early intervention with Favipiravir in patients with COVID-19 infection To assess the pharmacokinetics and pharmacodynamics of Favipiravir
Study Type	Interventional Cohort: prospective, open-label, multi-centre randomised control trial Data Cohort: Collection of clinical data on all newly admitted patients with suspected or confirmed COVID-19 infection
Methodology	Eligible participants with suspected or proven COVID-19 infection will be randomised 1:1 to receive Favipiravir or standard of care Data Cohort: Collection of clinical data on all newly admitted patients with suspected or confirmed COVID-19 infection (UK only) Future Research: Blood, urine, nasopharyngeal, sputum samples will be collected from trial participants, with consent for use in future research
Participants	Patients hospitalised with suspected or proven COVID-19 infection
Planned Sample Size	500 globally
Planned Treatment Duration	10 Days
Planned Study Duration	October 2021
First Enrolment Date (actual)	1st May 2020
Treatment Regimen, Dose and Route of Administration	Arm 1: Product: Favipiravir Dose Day 1: 1800mg BD PO Dose Day 2-10: 800mg BD PO + Standard of care Arm 2: Standard of care
Inclusion Criteria	1. Adult participants: Signed informed consent or documented and witnessed oral informed consent 2. New admission to hospital for period expected to last ≥ 1 night 3. Suspected or confirmed COVID-19 infection Patients are suspected of COVID-19 infection if they have the

	following: • Influenza like illness (fever ≥37.8°C or patient reported history of fevers and at least one of the following respiratory symptoms, which must be of acute onset: persistent cough, hoarseness, nasal discharge or congestion, shortness of breath, sore throat, wheezing or sneezing). **And** • Finding from either a chest x-ray or CT suggestive of Covid-19 infection. **And** • Alternative causes are considered unlikely and therefore in view of the investigator, admission of the patients to hospital is primarily attributable to symptoms of COVID-19 disease. 4. For women to be eligible to enter and participate in the study they should be non-child-bearing: • of potential defined as either post-menopausal (12 months of spontaneous amenorrhea and ≥ 45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy or bilateral oophorectomy or, • or if child-bearing potential have a negative pregnancy test at screening and agrees to remain sexually abstinent or use a method of contraception with a failure rate of < 1% per year as indicated in Appendix B during the treatment and for a period of 7 days after the last dose. Hormonal contraceptive methods must be supplemented by a barrier method. 5. Men who are sexually active must use an adequate method of contraception as listed in Appendix B, for a period of at least 7 days after the last dose.
Exclusion Criteria	1. Pregnant or breast feeding, due to potential teratogenicity (Negative pregnancy test if appropriate) 2. Hepatic impairment – (AST or ALT > 3.5 x upper limit of normal) 3. Presently enrolled in an interventional drug study 4. Unable to take medication via the oral or nasogastric route 5. Known sensitivity to Favipiravir

2. ROLES

Protocol Design Contributors & Trial Steering Group

Professor Pallav L Shah, Chief Investigator. Professor of Respiratory Medicine, National Heart & Lung Institute, Imperial College, London. Consultant Physician, Chelsea & Westminster Hospital NHS Foundation Trust and the Royal Brompton Hospital (pallav.shah@imperial.ac.uk)

Dr Christopher Orton, Co-Investigator, Clinical Research Fellow, Royal Brompton Hospital (c.orton@rbht.nhs.uk)

Dr Luke Moore, Co-Investigator, Consultant in Infectious Diseases, Microbiology & Virology Consultant, Chelsea and Westminster Hospital NHS Foundation Trust (luke.moore@nhs.net)

Professor Mark Johnson, Co-Investigator, Director of Research, Chelsea and Westminster Hospital NHS Foundation Trust (mark.johnson@imperial.ac.uk)

Professor Anton Pozniak, Co-Investigator, Consultant Physician, Chelsea and Westminster Hospital NHS Foundation Trust (anton.pozniak@chelwest.nhs.uk)

Dr Michael Pelly, Co-Investigator, Consultant Physician, Chelsea and Westminster Hospital NHS Foundation Trust (michael.pelly@chelwest.nhs.uk)

Professor Gavin Donaldson, Co-Investigator, Professor of Respiratory Studies, Senior Statistician, National Heart & Lung Institute, Imperial College, London. (gavin.donaldson@imperial.ac.uk)

Dr Marta Boffito, Co-Investigator, Consultant Physician, Chelsea and Westminster Hospital NHS Foundation Trust (marta.boffito@nhs.net)

3. STUDY MILESTONES

Milestones	Planned Date
Study Start	1st May 2020 (actual date)
Study End	October 2021
Study Report	October to December 2021

4. ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ADR	Adverse Drug Reaction
BD	Twice daily
CA	Competent Authority
CI	Chief Investigator
COVID-19	Corona virus
CRF	Case Report Form
CWFT	Chelsea and Westminster Hospital Foundation Trust
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECMO	Extracorporeal Membrane Oxygenation
EC50	Concentration of a drug which produces 50% of the maximal possible effect
ECRF	Electronic Clinical Research form
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
IRB	Institutional review board
NEWS2	National Early Warning System 2
NHS	National Health Service
NRES	National Research Ethics Service
OD	Once daily
PI	Principal Investigator

PIS	Participant/ Patient Information Sheet
PVMP	Pharmacovigilance Management Plan
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SERF	Safety Event Reporting Form
SUSAR	Suspected Unexpected Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group
WOCBP	Woman of Child-Bearing Potential

5. BACKGROUND AND RATIONALE

Coronaviruses are enveloped non-segmented positive-sense RNA family viruses, belonging to the family Coronaviridae and are broadly distributed in humans and other mammals.(1) Whilst the majority of human coronavirus infections are mild, a novel coronavirus first identified in December 2019 and designated SARS-CoV-2, has caused the global outbreak of respiratory illness, termed COVID-19.(2) Pandemic status was attributed in March 2020, with in excess of 900,000 cases and 45,000 deaths reported worldwide.(3) COVID-19 causes a spectrum of respiratory illnesses, ranging from self-limiting respiratory symptoms, pneumonia, respiratory failure and death.(2, 4) Currently there are no licensed treatments for COVID-19 and whist vaccinations are being developed, the re-purposing of existing drugs is an immediate option. High mortality rates in some regions have been related to the saturation of healthcare resources, such as intensive care beds and ventilators, demonstrating the clear and unmet need for an early intervention that reduces the intense utilisation of such facilities.(5)

Favipiravir is a pyrazinecarboxamide derived, nucleic acid analogue which selectively targets the RNA Dependent RNA Polymerase utilised in viral RNA synthesis, without interfering with host RNA and DNA polymerase activity.(6) Favipiravir has demonstrated broad spectrum activity against multiple families of RNA viruses including a wide range of types and subtypes of influenza viruses.(6) A small non-randomised study in China in patients with Covid-19 infection demonstrated increased viral clearance, and an improved time to resolution of symptoms and changes demonstrated on chest imaging. (7) Currently, the therapy is not licensed in the UK but has been in use in Japan since 2014. (8) Favipiravir is currently undergoing FDA approval for uncomplicated influenza in the USA, whereby Phase 3 studies (NCT02008344, NCT02026349) investigated 1800 mg BD on day 1, followed by 800 mg BD days 2-5 vs placebo. As part of these works, 1472 subjects received this dosage and 3160 received at least one dose, with no serious drug related adverse events identified. Subjects in the FDA studies achieved "undetectable virus" status significantly faster than the subjects on placebo.(9)

6. OBJECTIVES AND OUTCOME MEASURES & ENDPOINTS

6.1. Primary Objective

- To determine whether early intervention with Favipiravir improves the time to significant improvement in clinical status in patients with COVID-19 infection

6.2. Secondary Objective

- To assess whether early intervention with Favipiravir improves mortality in patients with COVID-19 infection
- To determine whether early intervention with Favipiravir reduces resource utilisation in patients with COVID-19 infection
- To explore whether early intervention with Favipiravir attenuates the excessive inflammatory cytokine response in patients with COVID-19 infection

6.3. Exploratory Objectives

- To identify prognostic markers indicating the need for early intervention with Favipiravir in patients with COVID-19 infection

6.4. Outcome Measures & Endpoints

Objectives	**Outcome Measures/Endpoints**
Primary Objective To determine whether early intervention with Favipiravir improves the time to significant improvement in clinical status in patients with COVID-19 infection	Time from randomisation to a sustained clinical improvement (maintained for 24 hours) by two points on a seven-category ordinal scale or to discharge, whichever occurs first(10) The seven-category ordinal scale: 1: Not hospitalised with resumption of normal activities 2: Not hospitalised, but unable to resume normal 3: Hospitalised, not requiring supplemental oxygen 4: Hospitalised, requiring supplemental oxygen 5: Hospitalised, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation or both 6: Hospitalised, requiring ECMO (Extra-corporal membrane oxygenation), invasive mechanical ventilation or both 7: Death(10)

Secondary Objectives To assess whether early intervention with Favipiravir improves mortality in patients with COVID-19 infection To determine whether early intervention with Favipiravir reduces resource utilisation in patients with COVID-19 infection To explore whether early intervention with Favipiravir attenuates the excessive inflammatory cytokine response in patients with COVID-19 infection	1. Clinical status as assessed with the seven-category ordinal scale at day 7 and day 14 (post-randomisation)(19) 2. Change in clinical status as assessed with the seven-category ordinal scale at day 7 and day 14 (post-randomisation) relative to baseline(10) 3. All-cause in-hospital mortality 4. Time to clinical response defined as: Time to 2 point reduction (maintained for 24 hours) in total NEWS2 (National Early Warning Score 2) compared to baseline NEWS2 taken at Randomisation(11) 5. Time to 2 point reduction (maintained for 24 hours) in the NEWS2 (National Early Warning Score 2) component compared to baseline NEWS2 taken at Randomisation for each of the following: • Temperature • Heartrate • Respiratory rate • Oxygen saturations(11), 6. Number of participants requiring intensive care admission 7. Duration of intensive care admission 8. Number of participants requiring mechanical ventilation 9. Duration of mechanical ventilation 10. Number of participants requiring non-invasive ventilation, continuous positive airways pressure or high-flow oxygen via (Optiflo®, Airvo system or equivalent) 11. Percentage of progression in supplemental oxygen requirement at day 7 12. Number of participants readmitted to hospital (all-cause) 13. Proportion of patients with culture confirmed bacterial or fungal infection 14. Changes in host inflammatory profiles at post-randomisation time points, relative to baseline
Exploratory Objectives To identify prognostic markers indicating the need for early intervention with Favipiravir in patients with COVID-19 infection. To assess the pharmacokinetics and pharmacodynamics of Favipiravir	• Change in viral PCR titres at post-randomisation time points relative to baseline • Change in host transcriptome profiles at post randomisation time points relative to baseline • Computer tomography quantitative analysis • Favipiravir pharmacokinetics and pharmacodynamics properties at day 5 to 10.

7. TRIAL DESIGN

The study is an open-label, two arm, multi-centre randomised controlled clinical trial, to investigate the clinical effectiveness, safety, and resource utilisation of early treatment intervention in patients admitted to hospital with a suspected or proven COVID-19 infection. Subjects will be randomised 1:1 to one of two arms to receive:

- Arm 1: Favipiravir + standard of care
- Arm 2: Standard of care

The study treatment duration will be 10 days for each participant. If a participant recovers sufficiently to be discharged home before day 10, favipiravir will be supplied and the regimen completed as an outpatient.

Samples will be collected at three timepoints: baseline, between days 5 to 10 and days 14 to 28 (see section 9.4). In such instances where participants recover sufficiently to be discharged home and are not in hospital at the latter sample collection timepoints, they will be invited to return to facilitate this (provided that they are well enough and maximally twice).
For further information on activities at visits and schedule see Section 8.

Participants will exit the study at day 28 or if they become deceased.

7.1. Data Cohort

In order to collect data on a representative sample of the full cohort of participants that could be entered into the study, a data cohort will be included in the study for the patients presenting in UK.

Data will be collected for participants with a diagnosis date within a window agreed by the lead sponsor and UK sites, in order to collect a large enough dataset for conclusions to be drawn. No personal identifiable data will be shared outside the care team, so no consent is required for this activity.

The following data will be collected:
All available baseline demographic and clinical data through to 28 days will be collected including clinical, physiological and blood results. Radiological analysis will be collected and included where available. Outcomes will be recorded.

7.2. Trial Schematic

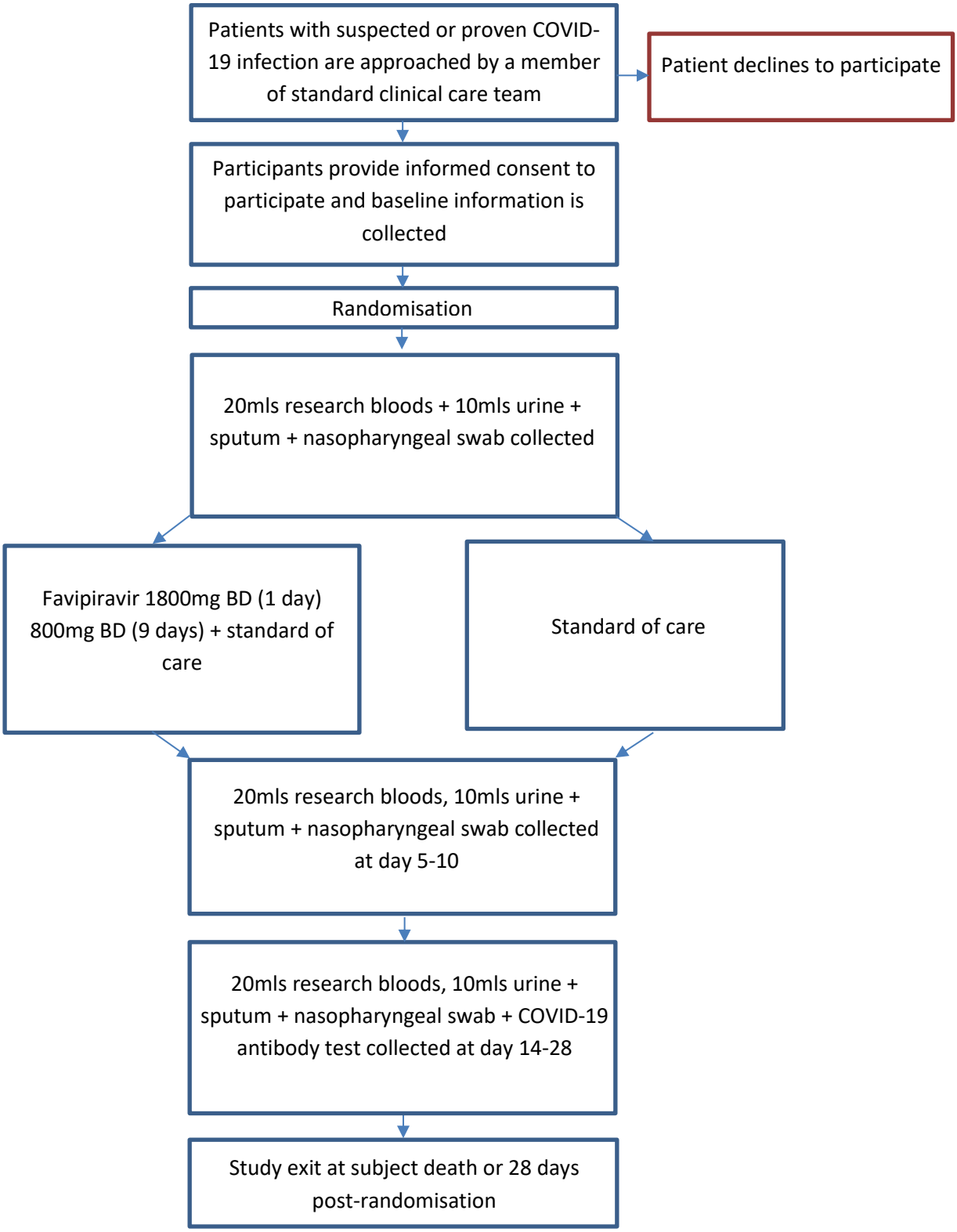

Figure 1TRIAL SCHEMATIC

8. PARTICIPANT IDENTIFICATION, RECRUITMENT & ALLOCATION OF INTERVENTION

8.1. Study Participants

All patients requiring hospitalisation with suspected or confirmed COVID-19 (by SARS-CoV-2 or other National standard), fulfilling all the inclusion criteria and none of exclusion criteria, as defined below, will be considered for participation in this trial.

Globally, five hundred (500) participants will be recruited and randomised into one of two treatment arms in a 1:1 ratio.

Data cohort

Any suspected or proven Covid-19 patient admitted to hospital during a period agreed between the site and lead sponsor is to be included.

8.2. Inclusion Criteria

The participant may enter the study if the following apply:

1. Adult participants: Signed informed consent or documented and witnessed oral informed consent
2. New admission to hospital for period expected to last ≥ 1 night
3. Suspected or confirmed COVID-19 infection

Patients are suspected of COVID-19 infection if they have the following:

- Influenza like illness (fever ≥37.8°C or patient reported history of fevers and at least one of the following respiratory symptoms, which must be of acute onset: persistent cough, hoarseness, nasal discharge or congestion, shortness of breath, sore throat, wheezing or sneezing).

And

- Finding from either a chest x-ray or CT suggestive of Covid-19 infection

And

- Alternative causes are considered unlikely

4. For women to be eligible to enter and participate in the study they should be of non-child-bearing and:
    - potential defined as either post-menopausal (12 months of spontaneous amenorrhea and ≥ 45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy or bilateral oophorectomy or,
    - or of child-bearing potential have a negative pregnancy test at screening and agrees to remain sexually abstinent or use a method of contraception with a failure rate of < 1% per year as indicated in Appendix B during the treatment and for a period of 7 days after the last dose. Hormonal contraceptive methods must be supplemented by a barrier method.
5. Men who are sexually active must use an adequate method of contraception as listed in Appendix B, for a period of at least 7 days after the last dose

8.3. Exclusion Criteria

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

1. Pregnant or breast feeding, due to potential teratogenicity
2. Hepatic impairment – (AST or ALT > 3.5 x upper limit of normal)
3. Presently enrolled in an interventional drug study
4. Unable to take medication via the oral or nasogastric route
5. Known sensitivity Favipiravir

8.4. Recruitment

Potential participants will be identified on admission to hospital by a member of the clinical or research team with either suspected or proven COVID-19 infection. Potential participants (or their acting representative) will be informed about the study and provided a copy of the patient information sheet (PIS) and the informed consent form (ICF), with sufficient time (according to clinical context) provided to consider the information before informed consent is sought.

All patients consented must be assessed as eligible by a clinician. Participation in this trial should be recorded in their patient notes and on the trial database.

Written informed consent must be obtained prior to any study specific procedures, unless participant consent has been given orally due to COVID-19 infection in accordance with local procedures as approved by the local ethics committee.

Sites must keep a record of all screening and enrolled participants using screening and enrolment logs. Subjects will be assigned a subject ID number at the time of randomisation. Once a subject number has been assigned to a subject, it will not be reassigned to any other subject.

8.5. Consent

The informed consent procedure in PIONEER shall be compliant with the trial protocol and GCP, as well as with EU and national regulations.

Where written consent cannot be safely taken due to COVID-19 infection, participant consent can be given orally by the trial participant as per Article 2(j) of Directive 2001/20/EC, in the presence of an impartial witness. Whereby the witness will be required to sign and date the informed consent form and the investigator will provide documented clarification on how the impartial witness was selected.

Alternatively, the trial participant and the person obtaining consent may sign and date separate informed consent forms, which shall ultimately be stored together in the site file as per local policy.

8.6. Participant Withdrawal

Participants may withdraw from the study at any time at their own request, and for any reason or they may be withdrawn at any time at the discretion of the study team or Sponsors for safety, administrative or any other reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal. If the reason for removal of a

participant from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF. Withdrawn participants may be replaced at the discretion of Chief Investigator. The lead sponsor may retain and continue to use any data collected before such withdrawal of consent unless the patient wishes all their data to be removed from the trial.

8.7. Allocation of Intervention

Eligible participants will be randomised 1:1 to one of the two arms using a web-based randomisation portal using blocks of randomly varying length.

An immediate allocation of treatment intervention as well as a participant identification number will be provided by the system to the person entering the data.

8.8. Duration of Involvement

The duration of study treatment is 10 days and participants will remain on the study for 28 days from randomisation.

9. STUDY INTERVENTIONS

A study intervention is defined as any investigational intervention(s) administered to a study participant in accordance study protocol.

For the trial medicinal supplies will be packaged and affixed with a label in accordance with regulatory requirements.

9.1. Study Investigational Medicinal Product

Refer to appendix C for description of study drug.

Participants will be randomised 1:1 to receive:

- Favipiravir 1800mg BD for 1 day, with 800mg BD for 9 days thereafter.
- Standard of care

Favipiravir dosing will consist of 1800mg BD for one day given orally, followed by 800mg BD for 9 days. This was the dose regime that showed that showed a significant time to alleviation of influenza symptoms in a Japanese phase II study on influenza (NCT03394209) and the dose regime studied in the US phase III studies in subjects with influenza (NCT02008344). Favipiravir has demonstrated *in-vitro* activity against SAR-CoV-2 in Vero E6 cells (EC50 = 61.88 µM, (9.7 g/ml) CC50 > 400 µM, SI > 6.46). This is higher than what was found for influenza (1 - 25 µM).(12)

Regime day	1	2	3	4	5	6	7	8	9	10
Favipiravir (Twice daily; mg)	1800	800	800	800	800	800	800	800	800	800

Figure 2 INVESTIGATIONAL MEDICINAL PRODUCT DOSING REGIME

9.2. Nasogastric/ Nasojejunal Administration

Favipiravir tablets can be crushed and dispersed in water for administration in enteral tubes. Crushed tablets should be dispersed in 10-15ml of distilled water in a syringe and allowed to dissolve. Shake well before administration and then the tube should be flushed after administration with 10ml distilled water.

9.3. Treatment Administration

The participants' hospital clinicians are responsible for the administration of the allocated treatment and are free to modify or stop study treatment if clinically necessitated, without the need for the patient to withdraw from the study. Study treatment medication will be subject to the standard local pharmacy reviews, which will guide modifications to both the study treatment (i.e. dose adjustment for renal impairment) and the use of concomitant medication (e.g. in the case of potential drug interactions).

9.4. Drug Monitoring

Full blood count, Liver function tests and Urea & Electrolytes should be performed before a participant is randomised, with routine testing repeated at the 5 to 10 day follow-up visit (or beforehand if clinically indicated). Blood monitoring should be performed more frequently in participants with renal or liver impairment with the necessary dose adjustments implemented as necessary.

Where patients are discharged beforehand, clinical blood monitoring should be repeated at the day 5-10 and day 14-28 visits. This will allow optimal clinical monitoring of the patients through the study given the opportunities available. Inpatients will be receiving repeat testing as clinically indicated and this should be as per local policy given the preceding paragraph.

9.5. Potential Benefits

Steroids have been shown to be effective in treating patients with COVID-19 on oxygen and there is also some evidence that other treatments such as the antiviral medicine called Remdesivir may help patients that are severely affected. Early intervention with Favipiravir, has the potential to improve outcomes in those with COVID-19 infection.

9.6. Potential Risks

The following are known side-effects of the investigational medical product:

Favipiravir	
Common	Raised uric acid level (4.8%); diarrhoea (2.3%); reduced neutrophil count (1.8%); raised liver enzymes (1.6%); nausea (2.1%); urinary tract infection (1.5%), headache (1.1%), vomiting (1.0%), blood triglycerides increased (1.9%)
Uncommon or Rare	Confusion; fulminant hepatitis; renal failure; agranulocytosis; Steven-Johnson syndrome (toxic epidermal necrolysis)
Cautions	Participants on theophylline, pyrazinamide, repaglinide, or famiciclovir should be treated with caution due to drug interactions

10. PARTICIPANT ASSESSMENTS

10.1. Baseline Data Collection

The following information will be collected:

- Demographics
- Co-morbidities
- Medication history and allergy
- Date of COVID-19 symptom onset
- Date of confirmatory COVID-19 test (SARS-CoV-2 infection by PCR or other National standard)
- Smoking status
- Travel history for preceding 6 months
- Clinical parameters (Heart rate, Respiratory rate, Oxygen Saturations)
- Baseline bloods (Full blood count, C-reactive protein, procalcitonin (if this is not part of site routine testing it is not required by protocol), ferritin, urea, d-dimer, LDH, troponin, urea & electrolytes, liver function (if available)

10.2. Inpatient Data Collection

Whilst patients are hospitalised all routine data, including laboratory test results, procedures and medication will be collected as necessary, as part of the trial from day 0 to day 28 or until discharge, whichever is sooner. Change in ordinal score lasting >24 hours will be recorded. If patients are re-admitted within the 28-day period, data will also be collected from this second admission until 28 days post-study commencement.

10.3. Follow-Up Data Collection

For participants discharged prior to day 10, a member of the research team will telephone and conduct a short interviews to collect the following information:

- Study drug compliance - Drug accountability data will be collected during the Trial. Any deviation from protocol-directed administration is to be reported.
- AEs and SAEs
- Concomitant medications
- Overall health
- Ordinal score (including at discharge) collected as a snapshot

10.4. Sample Collection

Patients will be required to provide research samples at 3 time points whilst on the trial:

Time (days)	Blood	Viral Swab	Sputum	Urine	Serology SARS-CoV-19
Baseline	20ml	1 x Nasopharyngeal	As able	10ml	

Between Day 5-10	20ml	1 x Nasopharyngeal	As able	10ml	
Between Day 14-28	20ml	1 x Nasopharyngeal	As able	10ml	COVID-19 antibody test

Participants discharged home before day 5 will be requested to return twice (provided they are well enough), for repeat sampling to be collected between days 5 to 10 and days 14 to 28 post-randomisation. Participants discharged home before day 14 will be requested to return once (provided they are well enough), for repeat samples to be collected between days 14 and 28.

If bronchoscopy is performed on any study participant as part of standard of care, an additional bronchoalveolar lavage sample and endobronchial brushings will be collected for research purposes. If this is the case, an additional paired blood sample will be collected by a member of the clinical or research team and used for research purposes.

For exploratory endpoints it is not required to get all exploratory research samples for all participants. Each site will separately agree with the lead sponsor and this will be based on their capabilities and available resources.

A laboratory manual will be provided to all sites detailing collection, processing and handling procedures. Samples will be stored at -80^{o}C or -150^{o}C at site for batch shipment to agreed locations for interim storage. Samples will then be transferred for pathological, inflammatory and genetic analyses to the agreed laboratories, as detailed within the instructions provided in the lab manual. All sites will have tissue transfer agreements in place prior to the transfer of relevant material.

Collected samples will only be labelled with the participants unique study number. Solely the local study team will have the ability to link the patient identifier back to the participant.

Participants are being asked to consent to their samples being stored for up to 10 years for potential future research and to that storage being outside the EU, if necessary.

11. DATA COLLECTION & MANAGEMENT

11.1. Source Documentation

Source documents are an integral part of the trial and evidence the integrity of the data collected. The investigator and institution should maintain adequate, complete and accurate source and study documentation that include all relevant medical information for every participant. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Where changes to source data are made these changes should be traceable, and not obscure the original entry. An explanation for this change should be available.

All data reported on the eCRF should be transcribed from source documents so must match the source document, where discrepancies are identified these discrepancies must be explained. The investigator and institution must ensure that all previous and current source data is available and that not source data is destroyed during the trial.

For the purposes of the trial and in line with GCP confirmation of consent and or assent, including date of consent and or assent should be documented in the participants' medical notes. Once randomised this information should also be entered into the participants' medical notes, along with their Participant entry, intervention and date of administration of intervention.

11.2. Data Collection

All participant data relating to the study will be recorded within participant specific electronic case report forms (eCRF) onto an electronic data capture system unless transmitted electronically (e.g. radiology reports). The investigator is responsible for verifying that the data entered in the eCRF is accurate and correct. The investigator must maintain accurate source data documentation that evidences the information entered in the eCRF. Site staff must not enter any personally identifiable participant information into the eCRF, only the Participant identification number should be used to link the eCRF entry to the participant.

Corrections to eCRF entries can be made, however these will not mask the previous entry and an explanation for the change should be provided. The site should ensure that data is entered into the eCRF within a reasonable timeframe to ensure continual data analysis and safety monitoring. All SAEs are to be reported within 24 hours.

11.3. Access to Data

The investigator and site must allow trial-related enquiries and must make available direct access to source data documents.
Upon Sponsor request the investigator and site will promptly disclose all trial documentation to the Sponsor(s) or regulatory agency for the purposes of monitoring, audits, and regulatory agency inspections.

The investigator and site agree to make reasonable efforts to implement any request that results from the inspection.

11.4. Data Management

The Lead Sponsor is responsible for the data management of the trial, including verification to confirm that:

- eCRF entries are accurate, complete, and verifiable from source documents
- the safety and rights of participants are being protected
- the correct versions of documentation are in use

- all site personnel supporting the trial are authorised and delegated to do so.
- the study is being conducted in accordance with the currently approved protocol study agreements, ICH GCP, and all applicable regulatory requirements

Data from the eCRF will be entered into a study specific database by designated staff on a regular basis. The database will be kept securely by the Lead Sponsor and access will be given to authorised personnel only, a log of which will be stored in the Trial Master File.

11.5. Any data anomalies or values found to be outside normal ranges will be checked with the Investigator. When corrections are required these will be made on CRF and the study database will be amended.Archiving Data

Following completion of the trial, all trial records and documents, including signed informed consent forms, must be retained by the investigator site for a period no less than 15 years after trial completion unless regulations require a longer retention period.

Records are not to be destroyed without written approval from the lead sponsor.

12. SAFETY REPORTING

12.1. Adverse Events: Definitions and Procedures for Evaluating, and Reporting

All Non-COVID-19 associated AEs and SAEs either observed by the research/clinical team, or reported to the research/clinical team, as well as all actions taken to treat the event must be recorded within the participants medical notes and entered into the eCRF along with the information relating to the duration and severity of the event with the Investigator's opinion of the causal relationship to the treatment (unrelated, unlikely to be related, possible related, probable related , and definitively related).

12.2. Adverse Events (AEs) Definition

For the purposes of this study, any non-COVID-19 related untoward medical occurrence, either newly acquired or worsening of a current AE, in a patient or clinical trial participant administered a study intervention whether or not considered related to the study intervention.

An AE can therefore be any unfavourable and unintended non-COVID-19 related sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events meeting the AE definition for this study:

- Any non-COVID-19 associated abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., Electrocardiogram, radiological scans, vital signs measurements), including those that worsen from time of consent
- Any non-COVID-19 associated exacerbation of a pre-existing condition including either an increase in frequency and/or intensity of the condition.

- Any new non-COVID-19 associated conditions detected or diagnosed after the study intervention has been administered to the participant.
- Symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events **NOT** meeting the AE definition

- Any Medical or Surgical procedure that occurs during the Trial (the medical condition resulting in the requirement of the procedure will be documented as an AE)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

Although these events should not be reported to the Lead Sponsor, these should be recorded in the patient's medical notes according to routine practice.

12.3. Adverse Reaction (AR) or Adverse Drug Reaction (ADR)

An AR is any untoward and unintended responses to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered.

12.4. Serious Adverse Events (SAEs) Definition

A serious non-COVID-19 associated adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening - in the context of "serious" life threatening refers to any event where the participant was at risk of death at the time of the event.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation - *Hospitalisation for an elective procedure to treat a pre-existing condition which occurred prior to study intervention that has not worsened is not an SAE*
- Results in persistent or significant disability/ incapacity
- Is a congenital anomaly/ birth defect
- Is another important medical event that may not be immediately life-threatening or result in death or hospitalisation but medical and or scientific judgement has determined the event may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes as listed above. Examples of such events include, invasive or malignant Cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation.)

For this trial, the following events are subjected to the same reporting requirement of SAE:

- Potential drug induced liver injury
- Pregnancy (See pregnancy section below for reporting pregnancies)
- Suspected transmission of an infectious agent via product (where required by the country specific legislation)

12.5. Serious Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an adverse reaction, the nature or severity of which is not consistent with the information on the experiment, and, when a clinical trial is concerned, with the applicable Reference Safety Information (RSI).

12.6. Collecting and Recording AE and SAE

- All non-COVID-19 associated AEs and SAEs, whether or not they are related to the study intervention or protocol defined procedures must be documented in the patients' medical notes and eCRF. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs.
- The site will enter the AEs and SAEs into the eCRF as soon as it is known to the Investigator or sub investigator. The eCRF must be updated as soon as additional information is made available to the investor or sub investigator.If the electronic system is unavailable for more than 24 hours, then the site will use the paper form
- Reportable SAEs as defined above will be reported to the Co-Sponsor within 24 hours of the study team becoming aware of the event. SAE details will be included in the Safety Event Report Form (SERF) and the SERF emailed to **Safety@rokcservices.com** or faxed to +44(0)203 9052575.
- The AEs and SAEs reporting period will be from participant consent until 28 days after randomisation.
- Pregnancy will be also subjected to the same reporting rules of SAE. Pregnancy details will be included in the SERF and the SERF emailed to **Safety@rokcservices.com** or faxed to +44(0)203 9052575 within 24 hours of the study team becoming aware of the pregnancy.
- All AEs and SAEs will be followed up until resolved or the participant's participation in the study ends (i.e. until the final CRF is completed for that participant).
- When an AE/SAE occurs, it is the responsibility of the investigator or sub investigators to review all clinical information relating to the event.
  The investigator or sub investigator will attempt diagnose the event based on direct examination and/or other clinical information.

  The principle investigator must confirm within the SERF the causality assessment with the study drug. If the SAE is assessed as possibly related, probable related or definitely related, the principal investigator must also confirm the event expectedness versus the Reference safety information (refer to section 12.10).

- The Investigator must record follow-up information (related to the reported event) by updating the patient's medical records and the appropriate forms in the (e)CRF. The worst-case severity and seriousness of an event must be kept throughout the trial.

12.7 SAEs after the end of the trial: If the Investigator becomes aware of an SAE with suspected causal relationship to the study drug or experiment after the subject has ended the trial, the Investigator should report this SAE as per the process above, within the same timelines as for SAEs during the trial (however there will be not requirement to report the SAE in the eCRF).**Reporting requirements to Ethics Committee's (EC's) and Competent Authorities (CA's)**

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided.

The Sponsor will promptly evaluate all SAEs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators, EC's and applicable CA's based on applicable legislation.

12.7.1. Sponsor's reporting of SUSARs

After receiving the SAE report form from the Investigator, the Co-Sponsor has to make a causality (relationship) assessment. The term SADR (Serious Adverse Drug Reaction) is to be used whenever either the Investigator or the Co-Sponsor deems the SAE as possibly or probably related to the study drug.

The Co-Sponsor must evaluate (and document the evaluation of) the expectedness for each SADR against the RSI. In case the event is Unexpected (= a SUSAR) it must be reported by the Co-Sponsor to the EC's, CA's or IRB (following the country applicable legislation) and other participating Investigators within the following timelines:

- **7 calendar days** if fatal or life-threatening event (follow-up information within an additional 8 days)
- **15 calendar days** if non-fatal or non-life-threatening event (follow-up information as soon as possible)

CAs will be notified through the appropriate system (such as Eudravigilance portal in Europe, e-SUSAR portal in UK).

12.7.2. Other Reporting

Any other local reporting requirements other than of SUSAR submission will be outlined in the Pharmacovigilance Management Plan (PVMP) along with the respective timelines for submission.

12.8 Grading of Adverse Events

An event is defined as "serious" when it meets at least one of the outcomes as described in the definition of an SAE, not when it is rated as severe.

The severity of all AEs and/or ARs (serious and non-serious) that are reported during the trial should be graded using the toxicity gradings in the Common Terminology Criteria for Adverse Events v5 (CTCAE) November 27, 2017criteria using the following definitions:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL) such as preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.

Grade 3: Severe or medically significant but not immediately life threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL (bathing,

dressing and undressing, feeding self, using the toilet, taking medications and not bed-ridden).

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE

A semi colon indicates 'or' within the description of the grade.

12.9 Assessment of Causality

The determination of causal relationship between the study drug and the AE/SAE must be performed by the investigator or sub investigator (medically qualified doctor/appropriately delegated to do so).

The below criteria will be used by the investigator or sub investigator to assess the causality of the AE/SAE in relation to the study drug:

- **Unrelated** – There is no evidence of any causal relationship (e.g. the event occurs prior to dosing)
- **Unlikely to be related** – There is little indication to suggest that there is a causal relationship. The participant's clinical condition or other concomitant treatment is related to the AE/SAE.
- **Possibly related** – There is some indication to suggest a causal relationship, however, the participant's clinical condition or other concomitant treatment could explain the event.
- **Probably related –** Reasonable indication to suggest a causal relationship such as a likely reaction of the drug or the event cannot be explained by participants clinical condition or other concomitant treatment.
- **Definitely related –** There is clear indication to suggest a causal relationship with the study drug and no other possible explanation available to explain AE/SAE.

12.10 Assessment of Expectedness

The determination of the event expectedness between the study drug and the SAE must be performed by the investigator or sub-investigator (medically qualified doctor).

Only SAEs assessed as Possibly, Probably and Definitely related qualify for expectedness evaluation.

The expectedness evaluation will be performed by using the below indicated Reference Safety Information:

- **Favipiravir**: Investigator Brochure, Favipiravir, dated 20 March 2020. Section: 7.5. Adverse Reactions

12.11 Development Safety Update Report (DSUR)

The Co-Sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report (i.e. DSUR) to the EC's and CA's containing an overview of all SARs occurred during the

reporting period and taking into account all new available safety information received during the reporting period.

12.12 Data Safety Monitoring Board (DSMB)

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study. The Lead Sponsor will be responsible for release a DSMB chart and appoint the DSMB members. Where local specific requirements in regard DSMB are expressed by local authorities, these will be captured in the PVMP.

13. STATISTICS AND ANALYSIS

13.1 Description of Statistical Methods

The two arms (Favipiravir vs Standard of Care) will be compared with time-to-event analysis using a competing-risks survival regression based on Fine and Gray's proportional subhazards model. All analysis will be performed on an intention to treat basis.

Patient improvement will be monitored for 28 days or until death. It is not expected that any patient will be lost to follow-up, even if discharged home. Kaplan-Meier plots will be constructed showing the probability of survival in each treatment group. Schoenfeld Residuals will be plotted and tested over time to examine the assumption of proportional hazards; with a restricted mean survival time analysis (RMST) as an alternative method for analysis for the proportional hazards assumption is not met.

Similarly, patients who discontinued the clinical trial or administration of the study drug due to worsening of symptoms/lack of efficacy (including patients who switched to rescue therapy) but remain alive will be handled as cases right-censored as of day 28, with no clinical improvement.

Additional secondary analysis of the primary outcome will be undertaken that adjust for, or involves a sub-set of patients, and examines the effect of

(a) country of recruitment
(b) time from onset of symptoms (median split)
(c) limited to those patients with confirmed SARS-COV-2 infection
(d) by high or low (median split) viral load.
(e) early or late during recruitment to the study – to examine improves in clinical care and understanding.

Other secondary analysis have been pre-specified in the statistical analysis plan and listed on clinical trials.gov. Differences between the two trial arms will be compared by standard and appropriate statistical tests.

13.2 Sample Size Justification

Primary Objective

To determine whether early intervention with Favipiravir improves the time to significant improvement in clinical status in patients with COVID-19 infection

Primary outcome measure
The primary end-point of this study is the time from randomisation to a sustained clinical improvement (maintained for 24 hours) by two points on a seven-category ordinal scale or to discharge, whichever happens first (recommended by WHO)(10).

The seven-category ordinal scale (23):
1: Not hospitalised with resumption of normal activities
2: Not hospitalised, but unable to resume normal
3: Hospitalised, not requiring supplemental oxygen
4: Hospitalised, requiring supplemental oxygen
5: Hospitalised, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation or both
6: Hospitalised, requiring ECMO (Extra-corporal membrane oxygenation), invasive mechanical ventilation or both
7: Death

This study will recruit 500 participants in total. We have chosen a primary outcome measure, previously used in influenza trials, of a 2-point change in a scale of clinical status (13, 14). No simpler continuous measure was considered appropriate due to the heterogeneous clinical presentation of COVID-19 infection at hospital admission. In a trial investigating influenza, significant difference in time to a 2 point improvement on the 7-point scale scoring system has been found, with a difference between groups of 40 patients on combined Favipiravir and Oseltamivir, compared with 128 patients on Oseltamivir only (p=0.0477)(10). PIONEER will have 250 patients in each group and will thus we will be able to detect similar improvements seen with these anti-viral agents (appreciably used in the treatment of influenza infection), at an alpha of 0.05

13.3 Interim Analysis
In this open-label clinical trial, an interim analysis will be performed when ≥ 90 patients have been recruited to enable the target number of patients to be revised. In the interim analysis, analyses that could lead to a Type-1 error probability will not be performed. For the purposes of the interim analysis the method described by Cui et al will be used to weight the number of patients before and after the interim analysis for the Log-rank test, test statistics or with the Cox proportional hazard regression model to allow for adjustment and sub-group analysis(15). Furthermore, the revised target number of patients shall be at least larger than the original one.

14. QUALITY CONTROL & QUALITY ASSURANCE

14.1 Risk Assessment and Quality Assurance
Quality Assurance (QA) will be put in place to ensure the trial is performed and data generated and recorded is compliant with the principles of GCP and applicable regulatory requirements. The Lead Sponsor will put into place quality control measures such as an audit/inspection of an Investigational Site. Quality control measures will assess the quality of trial related activities such as data collection and recording with regard to accuracy, adequacy and consistency, and to assure that studies are in accordance with Good Clinical Practice.

Investigators and research teams will be forewarned of any audits and have enough time to prepare. During the audit any or all study related documentation, medical records, IMP storage and paperwork as

well as SAEs and AES will be reviewed to assess the accuracy of the information recorded within the eCRF including the verification of any adverse events which have occurred.

14.2 Monitoring

A risk-based monitoring plan will be in place for the trial in line with the relevant standard operating procedures of the Lead Sponsor and their delegates. The monitoring plan will detail the frequency, type and intensity of routine and triggered on-site monitoring. Sites will receive a written report of all monitoring visits and outcomes

15. ADMINISTRATIVE PROCEDURES

15.1 Ethics Approval

The study protocol, participant information and consent form, the Investigator Brochure, available safety information, participant recruitment procedures (e.g. advertisements), information about payments and compensation available to the participants and documentation evidencing the investigator's qualifications should be submitted to the Ethics Committee for ethical review and approval according to local regulations, prior to the study start. Any changes, which may need to be made, will be submitted in the form of numbered and dated protocol amendments in accordance with local regulations.

15.2 Regulatory Approval

As required by local regulations, approval of the appropriate regulatory bodies will be obtained, prior to study initiation.

15.3 Declaration of Helsinki

The investigators will ensure that this study is conducted in accordance with the principles of the latest version of the Declaration of Helsinki.

15.4 ICH Guidelines for Good Clinical Practice

The investigators will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice.

15.5 Approvals

All relevant documentation will be submitted to the competent national authorities (see 14.2), relevant ethics committees, and host institution R&D departments and/or clinical trial centres. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents. In accordance with the applicable laws and regulations, the Lead Sponsor may develop a non-substantial amendment at any time during the trial. If a substantial amendment to the protocol or the documents that supported the original application for

the clinical trial authorisation is needed, the Lead Sponsor must submit a valid substantial amendment to the Competent Authority(ies) (CA(s)) for consideration, and to the relevant Ethics Committee(s) for review and approval.

15.6 Reporting

An End of Study notification and final report will be submitted to the same parties. Study will be registered to clinicaltrials.gov by the Lead Sponsor.

15.7 Participant Confidentiality and Secure Record Keeping

All Participant personal data, including participant consent forms will be kept at the host institution within a secure location with limited access.

No participant identifiable data will be collected within the eCRF, and all participants will be issued a unique subject identification number at randomisation. The Participants subject ID is to be used throughout the study and will be the only identifier for the patient.

Only non-identifiable patient data will be collected and stored on the external eCRF system.

The Investigator and his team will enter data into the eCRF and maintain all source documents that support the data collected from each study participant, and will maintain a Investigator Site File (ISF) containing all Trial documents as specified in ICH-GCP E6(R2) Chapter 8 entitled “Essential Documents for the Conduct of a Clinical Trial”, and as specified by applicable regulatory requirement(s).

The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymised data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the GDPR – as defined below). The receiving party will be bound by contractual agreement to keep the transferred data confidential at all times and to only process the data for the purpose of the Study.

Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the applicable personal data protection laws and regulations (and the Data Processing Annex (DPA) in Appendix C). In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR as defined below. (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent).

The Lead Sponsor as data controller shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

15.8 Compliance

The trial will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical Trials in the EU as provided for in Directive 2001/20/EC or EU Regulation 536/2014, as applicable, and any subsequent amendments, as well as in compliance with, the Declaration of Helsinki (version 7, October 2013), the principles of Good Clinical Practice (GCP), the approved protocol, the Human Tissue Act (England and Wales), the European General Data Protection Regulation EU 2016/679 (GDPR), the Data Protection Act 2018 (UK), the National Health Service (NHS) UK Policy Framework for Health and Social Care Research, the Mental Capacity Act 2005 and other national and local applicable regulations, including but not limited with respect to Belgian sites to the Belgian Law relating to experiments on human persons dated May 7th, 2004.

15.9 Indemnity

There will be provision made to process and settle claims by the Lead Sponsor. The Lead Sponsor is an NHS organisation and a member of the Clinical Negligence Scheme for Trusts.

15.10 Publication Policy

The Lead Sponsor is responsible for registering the study and to will fulfil the ethical obligation to disseminate and make the research results publicly available. As such the Lead Sponsor is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, Lead Sponsor, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

A whole or part of the study results will be communicated, orally presented, and/or published in appropriate scientific journals. Full anonymity of participant's details will be maintained throughout. Participants wanting to see the results of the trial can request a copy of the article from the investigators once it has been published.

Publications will be coordinated by the Lead Sponsor. The Lead Sponsor will delegate as appropriate to meet this responsibility. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal. For multi-centre studies, it is anticipated that the primary results of the overall study shall be published in a multi-centre publication.
Participating sites are not allowed to publish any subset data or results from the study prior to such multicentre publication.

Any publication by a participating site must be submitted to the Lead Sponsor for review at least thirty (30) calendar days prior to submission or disclosure. Lead Sponsor shall have the right to make reasonable objections to publications or to request a delay of the projected publication for a period of up to three (3) months from the date of first submission to the sponsor in order to enable the sponsor to take steps to protect its intellectual property rights and know-how (if any).

15.11 Joint Commission International (JCI) standard

The participating organisations include some that are accredited to JCI standards. The Lead Sponsor is not accredited and it is not a requirement that participating organisations are accredited. It has been agreed that the principals in the following paragraph will apply to this study:

The Sponsors and their delegates shall comply with the following obligations: (a) the Sponsors and their delegates will use trained and qualified employees or contractors to manage and coordinate the study; (b) the Sponsors and their delegates will ensure that multi-centre study reporting is reliable and valid, statistically accurate, ethical, and unbiased. (c) the Sponsors and their delegates will not grant incentives, other than standard compensations and reimbursement of costs, to study participants or to participating site's staff that would compromise the integrity of the research; (d) the Sponsors and their delegates are responsible for monitoring and evaluating the quality, safety, and ethics of the study and will respect the participating site's policies and processes when performing such monitoring and evaluation activities; (e) the Sponsors and their delegates will protect the privacy and confidentiality of the study participants in accordance with all applicable laws.

16. TRIAL OVERSIGHT

The Lead Sponsor and Co-Sponsor will ensure independent trial oversight in order to uphold the integrity of the trial through verification and corrective action where required.

Sponsors will verify site procedure in relation to:

- participant eligibility, consent and enrolment,
- allocation to trial groups
- administration of trial interventions
- data collection, accuracy and reporting
- AE/SAE collection and reporting
- Protocol adherence

16.1 Independent Data & Data Safety Monitoring Board (DSMB)

In addition to routine monitoring and trial oversight an Independent Data Monitoring Committee (IDMC) will monitor and analyse interim data from the first 90 participants entered into the study.

The members of the DSMB must not be involved in the study or have any competing roles which may interfere with their ability to ensure both participant safety and the continued ethical integrity of this trial.

DSMB will make recommendations to the TSC (Trial Steering Committee) on whether analyses of interim data shows no overall impact on patient safety and whether the study should continue in accordance with the current protocol.

The DSMB may make recommendations for discontinuation of the trial or for the TSC to make modifications to the protocol. In such circumstances the TSC will be made aware of the results of the interim data in order to implement these recommendations.

The DSMB will determine if, in their view, the randomised comparisons in the study have provided evidence on mortality that is strong enough to affect national and global treatment strategies. Unless this happens, the Chief Investigator, study staff, investigators, study participants, funders and other partners will remain unaware of the interim results until 28 days after the last patient has been randomised.

16.2 Trial Steering Committee (TSC)

The TSC will be set up to develop the design, management and overall supervision of the trial to ensure that he study is conducted in accordance with best international practice. . The TSC terms of reference will outline the membership, activity and frequency of meetings.

16.3 Trial Sponsors

The trial Sponsors will take on overall responsibility of the study including the financing and management. A division of responsibilities will be recorded and clear instructions will be given to sites about responsibilities. The sponsors may each delegate some of the sponsor's activities to designated parties.

17. FINANCE AND INSURANCE

17.1 Funding

The study will be funded by various parties including CW+. Favipirivir supplied by Fujifilm, 1 Broadway, Cambridge, MA 02142, United States.

17.2 Insurance

Appropriate insurance will be put in place by the responsible organisations.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the International Committee of Medical Journal Editors guidelines and other contributors will be acknowledged.

19. REFERENCES

1. Richman DD, Whitley RJ, Hayden FG. Clinical virology: John Wiley & Sons; 2016.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020;395(10223):497-506.
3. WHO COIVD-19 Situation Dashboard https://experience.arcgis.com/experience/685d0ace521648f8a5beeeee1b9125cd Accessed 02.04.2020.
4. Gao W, Li L, Wang Y, Zhang S, Adcock IM, Barnes PJ, et al. Bronchial epithelial cells: The key effector cells in the pathogenesis of chronic obstructive pulmonary disease? Respirology (Carlton, Vic). 2015;20(5):722-9.
5. Ji Y, Ma Z, Peppelenbosch MP, Pan Q. Potential association between COVID-19 mortality and health-care resource availability. The Lancet Global Health. 2020;8(4):e480.
6. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proceedings of the Japan Academy Series B, Physical and biological sciences. 2017;93(7):449-63.
7. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering. 2020.
8. Hayden FG, Shindo N. Influenza virus polymerase inhibitors in clinical development. Current opinion in infectious diseases. 2019;32(2):176.
9. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral research. 2018;153:85-94.
10. Wang Y, Fan G, Salam A, Horby P, Hayden FG, Chen C, et al. Comparative effectiveness of combined favipiravir and oseltamivir therapy versus oseltamivir monotherapy in critically ill patients with influenza virus infection. The Journal of Infectious Diseases. 2019.
11. Royal College of Physicians National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. Updated report of a working party, London: RCP, 2017.
12. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell research. 2020;30(3):269-71.
13. Peterson RL, Vock DM, Powers JH, Emery S, Cruz EF, Hunsberger S, et al. Analysis of an ordinal endpoint for use in evaluating treatments for severe influenza requiring hospitalization. Clinical Trials. 2017;14(3):264-76.
14. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama. 2020.
15. Cui L, Hung HJ, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999;55(3):853-7.

20. APPENDIX A: NEWS2

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Figure 3 The NEWS2 Scoring system(11)

21. APPENDIX B: CONTRACEPTION

21.1 Women of Childbearing Potential (WOCBP)

A woman is fertile following menarche and until she becomes postmenopausal unless permanently sterile as per the below:

- Premenarchal female
- Postmenopausal female
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For women with permanent infertility of a medical cause other than the above, the investigator should determine study entry requirements.

Where fertility status is unclear additional evaluation should be considered.

21.2 Contraception Requirement

Male Participants

Male participants are eligible to participate if they agree to one of the following during the study and for 7 days following the last dose of any trial medication

- Be abstinent from intercourse and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method during intercourse with a WOCBP who is not currently pregnant.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to one of the following forms of contraception that has a failure rate of < 1% per year:

- Combined (oestrogen- and progestogen- containing) hormonal contraception
    - Oral
    - Intravaginal
    - Transdermal
    - Injectable
- Progestogen only hormonal contraception
    - Oral
    - Injectable
- Progestogen- only contraceptive implant
- Intrauterine hormone-releasing system
- Intrauterine device
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

22. APPENDIX C STUDY INVESTIGTION OF MEDICINAL PRODUCT

22.1 Favipiravir

Refer to the Investigator Brochure or equivalent for full details of the medicinal product

Mechanism of action

Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamide; T-705) is a selective nucleic acid (pyrazine molecule) analogue that interferes with viral RNA replication. Preclinical data has shown that host cellular kinases convert favipiravir to T-705 ribosyl triphosphate (T-705RTP) which is mistaken by the influenza viral RNA polymerase for natural nucleotide triphosphates resulting the selective inhibition of viral RNA synthesis and thus interfering with viral replication.

Composition

Each tablet contains 200mg of the active ingredient Favipiravir and the following inactive ingredients; colloidal silicon dioxide (diluent), povidone K30 (binder), low-substituted hydroxypropyl cellulose (disintegrant), crospovidone (disintegrant) and sodium stearyl fumarate (lubricant) and film coated with OPADRY, which includes hypromellose (2910, 6mPa·s), titanium dioxide, talc and yellow ferric oxide.

Route of Administration

Orally

Therapeutic Indications

Influenza

Contraindications

- Known hypersensitivity to either the active or inactive ingredients

Warnings and Precautions

Based on nonclinical and clinical studies, the following events may occur. Patients or subjects should be advised of these potential events and how to avoid them.

Preclinical

Studies in the mammalian chromosomal aberration test and mouse lymphoma assay at high concentrations showed the Favipiravir proved mildly mutagenic. Although the potential for genotoxicity at high exposures cannot be ruled out, evidence indicates that this risk is minimal at the exposures planned in the study.

Clinical

Nonclinical studies have shown mild phototoxicity. One study subject experienced mild photosensitivity (rash) following a tanning bed session. All subjects should avoid excessive exposure to sunlight or artificial ultraviolet light.

Clinical studies of subjects with renal impairment have shown higher exposure levels and reduced urinary excretion compared to subjects with normal renal function. No alternative dosing is recommended. No data are available in patients with end stage renal disease or renal failure.

Mild to moderate, asymptomatic elevations in serum uric acid have been observed in healthy volunteers and subjects with influenza treated with Favipiravir in clinical studies. The changes have been reversible upon Favipiravir discontinuation. Laboratory values and potential AEs related to increases in uric acid levels should be monitored.

In two proof-of-concept studies of orally administered Favipiravir against lethal Ebola virus infection in cynomolgus macaques, GI tract lesions were observed that were not consistent with the known natural history of Ebola nor with previous animal and clinical studies of Favipiravir. The contributing factors responsible for these lesions cannot be determined with certainty. However, evidence suggests that bacterial infections and pre-existing enterocolitis in the treated macaques may have been responsible for the confounding results, and an ongoing risk to patients may not exist.

Drug Interaction

A series of healthy volunteer studies have been completed to investigate possible favipiravir interactions with drugs that are either frequently administered to influenza patients or are eliminated by pathways common to favipiravir

- Acetaminophen: Favipiravir in combination with acetaminophen increased acetaminophen blood levels 14 to 17% based on plasma AUC comparisons.
- Hydralazine: Co-administration of favipiravir and hydralazine resulted in a 13% reduction in hydralazine AUC. No changes in favipiravir PK were observed.
- Ortho Novum® 1/35 (norethindrone and ethinyl estradiol): Favipiravir co-administration increased both norethindrone and ethinyl estradiol blood levels. Norethindrone plasma AUC increased 47% and ethinyl estradiol plasma AUC increased 43%. One subject discontinued the study due to transient, mildly elevated ALT (2.8 × normal) and AST (1.7 × normal).
- Oseltamivir: Favipiravir did not alter the PK of oseltamivir nor did oseltamivir alter favipiravir PK.
- Raloxifene: Co-administration of favipiravir with raloxifene, a potent aldehyde oxidase inhibitor, did not appreciably alter favipiravir PK. Favipiravir plasma AUC was reduced 15% when administered in combination with raloxifene.

- Repaglinide: Favipiravir administration with repaglinide, an anti-diabetic agent that is extensively metabolized by CYP2C8 and CYP3A4, increased repaglinide plasma AUC 30 to 50% due to inhibition of CYP2C8.
- Pyrazinamide: Pyrazinamide administration with favipiravir examined possible renal urate transporter interactions. Pyrazinamide increased blood uric acid levels 2 to 9 mg/dL over baseline. The addition of favipiravir increased blood uric acid levels 4 to 11 mg/dL over baseline, indicating a moderate additive effect. One subject developed headache and fever in association with elevated liver function tests (AST, ALT, gamma-glutamyl transferase, and lactate dehydrogenase) following pyrazinamide and favipiravir co-administration, which was determined to be an serious adverse event (SAE) and resolved upon discontinuation.

Adverse Reactions

Data from three clinical studies in suspected or confirmed influenza treated on a 5 day regimen of favipiravir at the proposed dose (or a broadly similar exposure given TID).
The majority of all TEAEs in these studies have been mild in severity and assessed as unrelated to study drug and resolved without sequelae.

Table 1 **Number of Subjects with TEAE by System Organ Class (SOC) and PT with at Least 0.5% Occurrence (US213b, US316, US317)**

Safety Population **SOC PT**	**Pooled Placebo** **(N = 894)** **n (%)**	**Pooled Favipiravir** **(N =1653)** **n (%)**
Number of Subjects With Adverse Event(s)	227 (25.4)	419 (25.3)
Gastrointestinal disorders	75 (8.4)	122 (7.4)
Diarrhoea	39 (4.4)	38 (2.3)
Nausea	16 (1.8)	34 (2.1)
Vomiting	8 (0.9)	16 (1.0)
Abdominal pain upper	5 (0.6)	8 (0.5)
Dyspepsia	5 (0.6)	6 (0.4)
Abdominal pain	7 (0.8)	4 (0.2)
Infections and infestations	59 (6.6)	82 (5.0)
Urinary tract infection	16 (1.8)	24 (1.5)
Sinusitis	6 (0.7)	6 (0.4)
Oral herpes	5 (0.6)	2 (0.1)
Pneumonia	5 (0.6)	2 (0.1)
	39 (4.4)	86 (5.2)
Investigations		
Blood triglycerides increased	11 (1.2)	32 (1.9)
Alanine aminotransferase increased	11 (1.2)	31 (1.9)
Aspartate aminotransferase increased	11 (1.2)	21 (1.3)

Blood cholesterol increased	6 (0.7)	5 (0.3)
	23 (2.6)	39 (2.4)
Nervous system disorders		
Headache	8 (0.9)	18 (1.1)
Dizziness	5 (0.6)	8 (0.5)
	48 (5.4)	55 (3.3)
Respiratory, thoracic and mediastinal disorders		
Bronchitis	11 (1.2)	6 (0.4)
Epistaxis	8 (0.9)	8 (0.5)
Vascular disorders	5 (0.6)	23 (1.4)
Dizziness	2 (0.2)	14 (0.8)

Note: AEs are classified according to SOC and PT of MedDRA Version 15.0. Subjects are counted once within each SOC or PT.
Note: US213b BID and TID, US316 and US317 are pooled for analysis. In US213b, TEAE if an AE started within 15 days of first dose. In US316 and US317, TEAE if an AE occurred within 22 days of first dose.

Table 2: Expected Adverse Drug Reactions by PT (US213b, US316, US317)

PT	**Pooled Favipiravir N = 1653 n (%)**
Diarrhoea	38 (2.3)
Nausea	34 (2.1)
Blood triglycerides increased	32 (1.9)
ALT increased	31 (1.9)
Urinary tract infection	24 (1.5)
AST increased	21 (1.3)
Headache	18 (1.1)
Vomiting	16 (1.0)

Note: AEs are classified according to PT of MedDRA Version 15.0. Subjects are counted once within PT.
Note: US213b BID and TID, US316 and US317 are pooled for analysis. In US213b, TEAE if an AE started within 15 days of first dose. In US316 and US317, TEAE if an AE occurred within 22 days of first dose.

23. APPENDIX D: Data Processing Agreement

Definitions:

- "Protocol" means the document entitled "A Randomised Controlled Trial of Early Intervention in Patients HospItalised with COVID-19: Favipiravir vErsEs Standard CaRe - PIONEER" containing the details of the study as developed by the Lead Sponsor and approved by the relevant Ethics Committee(s).
- "Lead Sponsor" means Chelsea and Westminster Hospital NHS Foundation Trust.
- Participating site acts as a data processor as defined under article 4, 8) of the Regulation (EU) 2016/679 ("Data Processor") for the Lead Sponsor who acts as data controller as defined under article 4, 7) of the Regulation (EU) 2016/679 ("Data Controller").
- "Applicable Law" means any applicable data protection or privacy laws, including:
    a) the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR");
    b) other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition;
- "Personal Data" means any information relating to an identified or identifiable natural person ("Data Participant"), including without limitation pseudonymised information, as defined in Applicable Law and described in the Protocol.

Rights and obligations:

1. The Data Processor is instructed to process the Personal Data for the term of the Trial and only for the purposes of providing the data processing tasks set out in the Protocol. The Data Processor may not process or use Personal Data for any purpose other than a Data Participant's medical records, or other than provided in the instructions of the Trial protocol, including with regard to transfers of personal data to a third country or an international organization, unless the Data Processor is required to do so according to Union or Member State law.
2. Data Processor shall at all times maintain a record of processing of Personal Data in accordance with Applicable Law and if the Data Processor considers an instruction from the Data Controller to be in violation of the Applicable Law, the Data Processor shall promptly inform the Data Controller in writing about this.
3. The Data Processor must ensure that persons authorized to process the Personal Data have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality.
4. The Data Processor shall implement appropriate technical and organizational measures to prevent that the Personal Data processed is:
    (i) accidentally or unlawfully destroyed, lost or altered,
    (ii) disclosed or made available without authorization, or
    (iii) otherwise processed in violation of Applicable Law.
5. The appropriate technical and organizational security measures must be determined with due regard for:

(i) the current state of the art,

(ii) the cost of their implementation, and

(iii) the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons.

6. Taking into account the nature of the processing, the Data Processor shall assist the Data Controller, by means of appropriate technical and organizational measures, insofar as this is possible, in fulfilling its obligation to respond to requests from Data Participants pursuant to laws and regulations in the area of privacy and data protection (such as, the right of access, the right to rectification, the right to erasure, the right to restrict the processing, the right to data portability and the right to object)

7. The Data Processor shall upon request provide the Data Controller with sufficient information to enable the Data Controller to ensure that the Data Processor's obligations under this DPA are complied with, including ensuring that the appropriate technical and organizational security measures have been implemented.

8. The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to the Data Processor, who shall have access to the Data Processor's data processing facilities and receive the necessary information for the sole purpose of auditing whether the Data Processor has implemented and maintained said technical and organizational security measures. The expert shall upon the Data Processor's request sign a non-disclosure agreement provided by the Data Processor, and treat all information obtained or received from the Data Processor confidentially, and may only pass on, after conferral with the Data Processor, the findings as described under 10) (ii) below to the Data Controller.

9. The Data Processor must give authorities who by Union or Member State law have a right to enter the Data Controller's or the Data Controller's processors' facilities, or representatives of the authorities, access to the Data Processor's physical facilities against proper proof of identity and mandate, during normal business hours and upon reasonable prior written notice.

10. The Data Processor must without undue delay in writing notify the Data Controller about:

(i) any request for disclosure of Personal Data processed under the Protocol by authorities, unless expressly prohibited under Union or Member State law,

(ii) any finding of (a) breach of security that results in accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, Personal Data transmitted, stored or otherwise processed by the Data Processor under the Protocol, or (b) other failure to comply with the Data Processor's obligations, or

(iii) any request for access to the Personal Data (with the exception of medical records for which the Data Processor is considered data controller) received directly from the Data Participants or from third parties.

11. Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 10) (ii)(a) above will contain at least the following information:

(i) the nature of the Personal Data breach, stating the categories and (by approximation) the number of Data Participants concerned, and stating the categories and (by approximation) the number of the personal data registers affected (datasets);

(ii) the likely consequences of the Personal Data breach;

(iii) a proposal for measures to be taken to address the Personal Data breach, including (where appropriate) measures to mitigate any possible adverse effects of such breach.

12. The Data Processor shall document (and shall keep such documentation available for the Data Controller) any Personal Data breaches, including the facts related to the Personal Data breach, its effects and the corrective measures taken. After consulting with the Data Controller, the Data Processor shall take any measures needed to limit the (possible) adverse effects of Personal Data breaches (unless such consultation cannot be awaited due to the nature of the Personal Data breach).
13. The Data Processor must promptly and reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 10) (ii) above and (b) any requests from Data Participants under Chapter III of the GDPR, including requests for access, rectification, blocking or deletion. The Data Processor must also reasonably assist the Data Controller by implementing appropriate technical and organizational measures for the fulfilment of the Data Controller's obligation to respond to such requests.
14. The Data Processor must reasonably assist the Data Controller with meeting the other obligations that may be incumbent on the Data Controller according to Union or Member State law where the assistance of the Data Processor is implied, and where the assistance of the Data Processor is necessary for the Data Controller to comply with its obligations. This includes, but is not limited to, at the request to provide the Data Controller with all necessary information about an incident under 10) (ii), and all necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

Subprocessor:

15. The Data Processor may only engage a subprocessor, with prior specific or general written consent from the Data Controller. The Data Processor undertakes to inform the Data Controller of any intended changes concerning the addition or replacement of a subprocessor by providing a reasonable prior written notice to the Data Controller. The Data Controller may reasonably and in a duly substantiated manner object to the use of a subprocessor. The Data Processor must inform the Data Controller in writing of the discontinued use of a subprocessor.
16. Prior to the engagement of a subprocessor, the Data Processor shall conclude a written agreement with the subprocessor, in which at least the same data protection obligations as set out in this DPA shall be imposed on the subprocessor, including obligations to implement appropriate technical and organizational measures and to ensure that the transfer of Personal Data is done in such a manner that the processing will meet the requirements of the Applicable Law.
17. The Data Controller has the right to receive a copy of the relevant provisions of Data Processor's agreement with the subprocessor related to data protection obligations. The Data Processor shall remain fully liable to the Data Controller for the performance of the subprocessor obligations under this DPA. The fact that the Data Controller has given consent to the Data Processor's use of a subprocessor is without prejudice for the Data Processor's duty to comply with this DPA.