Clinical Trial Protocol

Trial Title:	**PRO**phylaxis for pa**T**i**E**nts at risk of **C**OVID-19 infec**T**ion (PROTECT-V)**.**
Protocol Number:	CCTU0307
EudraCT Number:	2020-004144-28
Investigational Product:	Niclosamide
Protocol Version:	3.1
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Protocol Signatures:

I give my approval for the attached protocol entitled ***"PROphylaxis for paTiEnts at risk of Covid-19 infecTion (PROTECT-V)"*** Dated 22 April 2021 V3.1.

Chief Investigator

Name: Dr Rona Smith

Signature: _____

Date: _____

Site Signatures

I have read the attached protocol entitled **"PROphylaxis for paTiEnts at risk of COVID-19 infecTion. (PROTECT-V)"** dated 22 April 2021 V3.1 and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and 2005/28/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any subsequent amendments of the clinical trial regulations, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

Principal Investigator

Name: _____

Signature: _____

Date: _____

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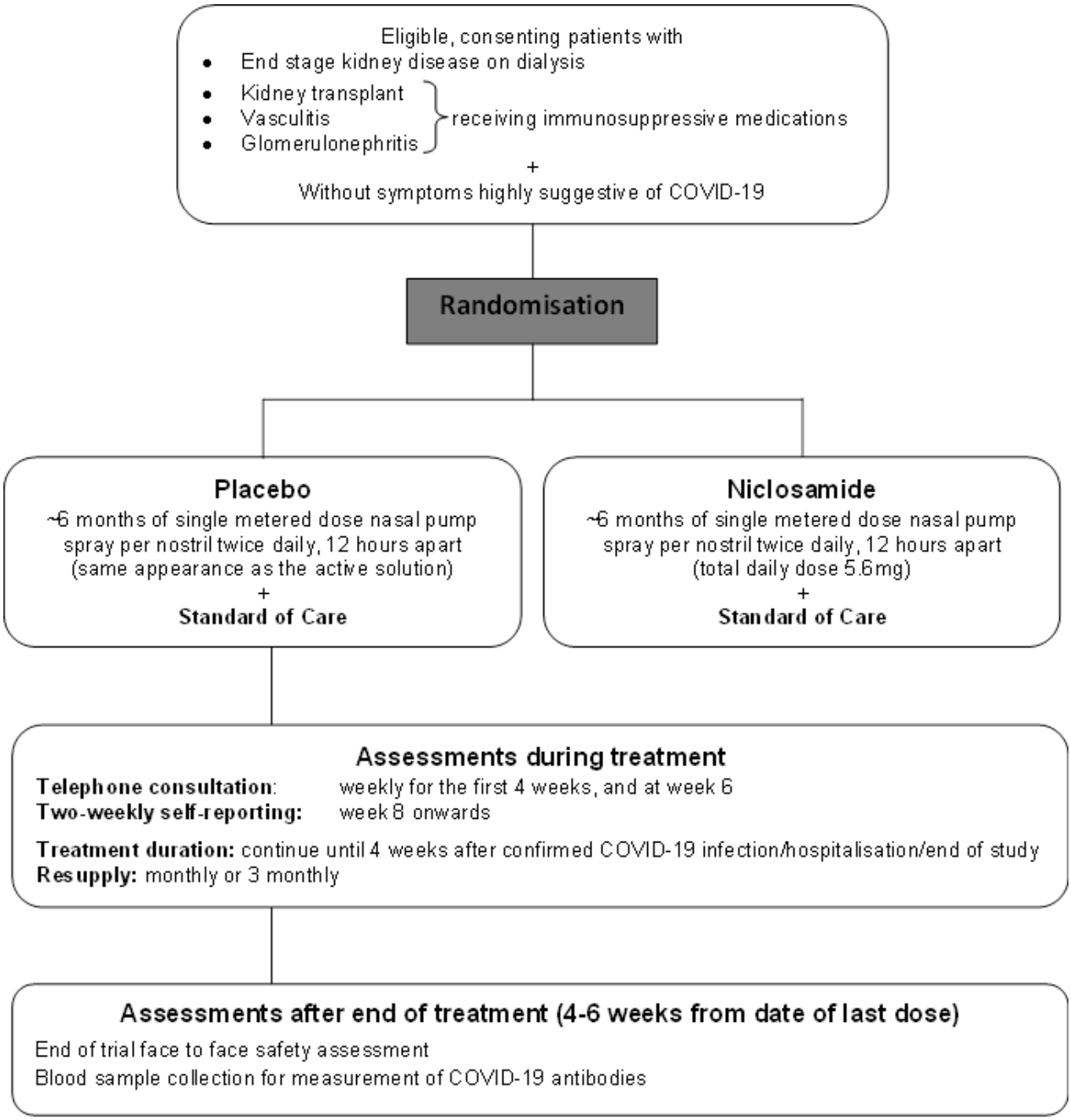
1.ABBREVIATIONS

AE	Adverse Event
AKI	Acute Kidney Injury
ALT	Alanine aminotransferase
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
CA	Competent Authority
CCTU	Cambridge Clinical Trials Unit
CI	Chief Investigator
CI	Confidence Interval
CKD	Chronic Kidney Disease
Con Med	Concomitant Medication
COVID-19	Coronavirus Induced Disease 2019
CRF	Case Report Form (when used for data collection)
CRF	Clinical Research Facility
CTA	Clinical Trial Authorisation
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic Case Report Form
FDA	Federal Drug Agency
FSGS	Focal Segmental Glomerular Sclerosis
GP	General Practitioner
GFR	Glomerular Filtration Rate
GCP	Good Clinical Practice
GN	Glomerulonephritis
HCW	Healthcare workers
HD	Haemodialysis
IB	Investigator Brochure
ICF	Informed Consent Form
ICNARC	Intensive Care National Audit and Research Centre
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IMP	Investigational Medicinal Product
ITT	Intention to Treat
MERS	Middle East Respiratory Syndrome, MERS-coronavirus (MERS-CoV)
MHRA	Medicines and Healthcare products Regulatory Agency
NAFLD	Non alcoholic fatty liver disease
NASH	Non alcoholic steatohepatitis
NIHR	National Institute of Health Research
ONS	Office National Statistics
PCR	Polymerase chain reaction

PHE	Public Health England
PI	Principle Investigator
PID	Patient Identifiable Data
PIS	Patient Information Sheet
PK	Pharmacokinetic
PTO	PROTECT-V Trial Office
R&D	Research and Development
RA	Regulatory Agency
RCT	Randomised Control Trial
REC	Research Ethics Committee
RRT	Renal Replacement Therapy
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SD	Standard Deviation
SKP2	S--Phase Kinase Associated Protein 2
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TNF	Tumour Necrosis Factor
TPM	Trial Procedure Manual
TSC	Trial Steering Committee
WHO	World Health Organisation
WOCBP	Woman of child bearing potential

2.TRIAL FLOW CHART



3.INTRODUCTION

PROTECT-V is a double-blind placebo controlled trial of prophylactic niclosamide against SARS-CoV2 infection in vulnerable populations. The trial will enrol vulnerable patients with kidney or autoimmune diseases, including patients in receipt of dialysis, kidney transplant recipients, individuals with vasculitis and glomerular disease receiving immunosuppression.

4.BACKGROUND AND RATIONALE

4.1.Setting

In December 2019, a respiratory disease causing severe respiratory tract infection a novel coronavirus-induced disease (COVID-19) emerged in Wuhan, China.[1] A month later the Chinese Centre for Disease Control and Prevention identified a new beta-coronavirus (SARS coronavirus 2, or SARS-CoV-2) as the aetiological agent and the disease now called COVID-19. COVID-19 was declared a global pandemic by the WHO on 11th March 2020. To date, there have been > 90 million cases worldwide with 1.94 million deaths.

4.2.Clinical Course and current treatment options

The clinical manifestations of COVID-19 range from asymptomatic infection to mild, upper respiratory tract infections to severe viral pneumonia with associated respiratory failure and death. Some patients will also go on to develop multi-organ failure, with kidney, cardiac and neurological complications of SARS-CoV-2. The frequency of severe disease in hospitalised patients can be as high as 30%. Many potential treatments are being assessed in randomised treatment trials. The UK RECOVERY trial has demonstrated that dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit in patients not requiring ventilatory support. The ACCT-1 trial showed a shorter recovery time 11 days (95%CI, 9 to 12) versus 15 days (95% CI, 13 to 19) in remdesivir-treated patients. A number of other treatment options have demonstrated no benefit, including hydroxychloroquine and lopinavir-ritonavir.

In contrast, there are no drugs proven to *prevent* COVID-19 or to reduce the severity of illness if given as prophylaxis. Although vaccines are now available, there remains a need for other prophylactic agents until vaccine use becomes widespread globally and effectiveness and durability is established, particularly in immunocompromised individuals. Efforts are underway to repurpose established drugs with well understood drug interactions and safety profiles.

4.3.Rationale for a trial

A considerable number of trials have been established at great speed in the wake of the global SARS-CoV-2 outbreak. However, most assess treatments for established COVID-19. To date, only hydroxychloroquine has been evaluated as prophylaxis. Boulware and colleagues evaluated hydroxychloroquine versus placebo after known exposure to a confirmed case of COVID-19.[2] This trial failed to show benefit from hydroxychloroquine, but the trial had serious methodological limitations, provided prophylaxis post-exposure and for a short duration, and excluded patients with significant kidney disease. A proposal to conduct a pre-exposure prophylaxis trial with hydroxychloroquine in patients with chronic kidney disease (CKD) receiving dialysis was rejected by the UK MHRA on safety grounds.

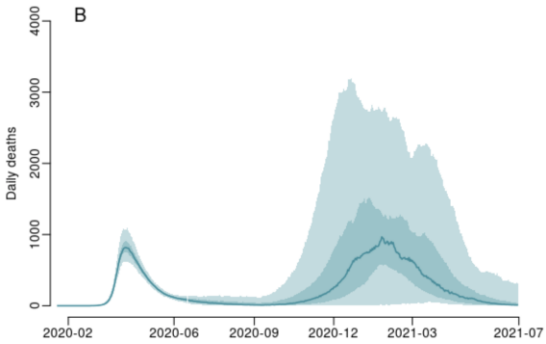
Several patient groups appear to be vulnerable to COVID-19 and at exceptionally high risk of adverse outcomes, including those with kidney disease requiring dialysis, in receipt of a kidney transplant, or with auto-immune diseases that might affect kidney function and require immunosuppression (e.g. vasculitis and glomerular diseases). These patient groups are also known to mount a suboptimal response to vaccination against viruses.

Dialysis patients typically need to attend their dialysis centre 3 times per week for at least 4 hours at a time and travel to dialysis centres by ambulance, car or taxi. It is impossible for them to self-isolate. Further, patients receiving dialysis may be less likely to benefit from admission to intensive care due to their comorbidity and the perceived prognostically deleterious impact of end-stage kidney disease. Those dialysis patients contracting COVID-19 have a 26% risk of death from the disease. To date, 11% of the UK's in-centre dialysis population has contracted COVID-19.

Kidney transplant recipients are immunosuppressed and are at increased risk of infections (including viruses) with attendant morbidity.[3] Chronic Kidney Disease is itself recognised as a risk factor for severe infections. The combination of immunosuppression and reduced GFR render kidney transplant recipients at particular risk of COVID-19 since regular healthcare contact is imperative for most patients. Most kidney transplant recipients have been shielding during the pandemic to date, but the need for monitoring and easing of shielding advice make exposure to COVID-19 a real risk. There have already been 442 confirmed cases among transplant patients despite shielding (UK Renal Registry report 1 July 2020) with 118 deaths (27% case fatality rate).

Vasculitis patients suffer with serious relapsing remitting auto-immune disease that results in the requirement for a considerable burden of immunosuppression. The disease itself often results in organ damage, particularly renal and pulmonary damage, and individuals have significant comorbidity. Whilst individual vasculitis syndromes remain generally rare, the pool of vasculitides represent a considerable patient population thought to be at high risk of contracting COVID-19 leading to severe disease, and even death. There is a paucity of data on the occurrence of COVID-19 in this patient population to date, but of the 64 cases reported by mid June, 17 have died, equating to a 27% case fatality rate.

The urgent need for interventions that provide effective prophylaxis against SARS-CoV2 is emphasised by a recent report commissioned by the UK Government projected 119,000 in-hospital deaths from COVID19 between September 2020 and June 2021 (95%CI 24,500 - 251,000).[4] This suggests a 'second wave' could be considerably worse than the first. Outside the United Kingdom the pandemic is still accelerating. An effective prophylactic treatment could save thousands of lives.



4.4. A pre-exposure prophylaxis trial in vulnerable populations

PROTECT-V aims to enrol patients at particularly high risk of COVID-19 and its complications, seeking to test whether intranasal niclosamide might prevent the disease from occurring. Participants will be randomised 1:1 to niclosamide or matching placebo. Additional treatment arms may be added if further promising treatments become available.

4.5. Niclosamide

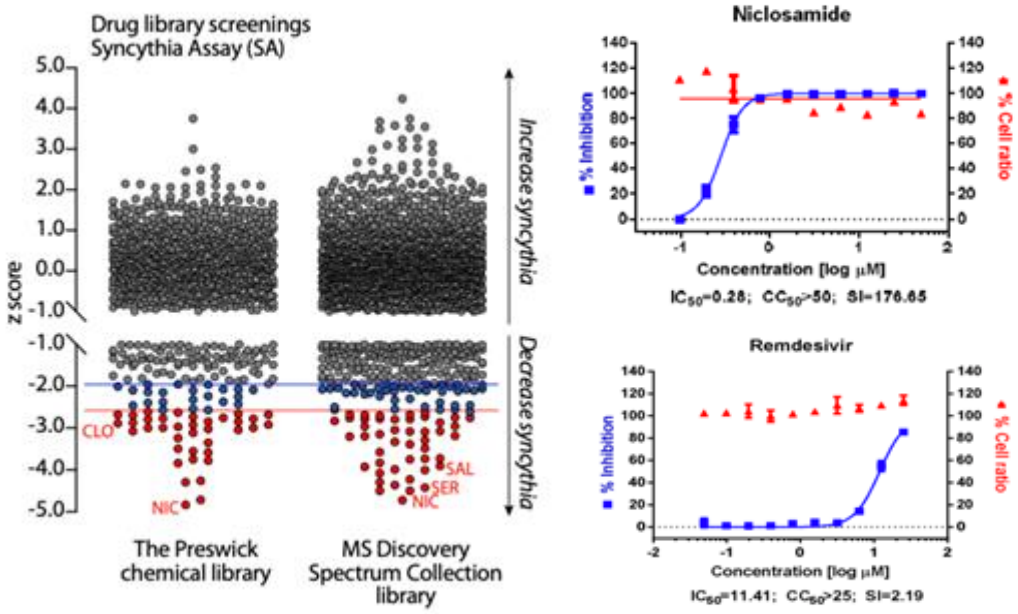
Rationale for niclosamide as a prophylactic measure

Niclosamide is a derivative of salicylic acid. It is a cheap, safe drug that has been used for tapeworm infestations for decades and is on the WHO's List of Essential Medicines. Although the exact target and mechanism of action is uncertain, niclosamide has pleiotropic activities and in vitro activity against a range of viruses and bacteria has been reported, including inhibition of SARS-CoV-1 replication, totally abolishing viral antigen synthesis.[5] Potential mechanisms of action for niclosamide on SARS-CoV-2 include modulation of the pH gradient across endosomal membranes inhibiting viral escape, as well as autophagy related mechanisms[6] In the case of MERS, it is thought that niclosamide acts via SKP2 inhibition to reinstate autophagy.[7]

Prior to the emergence of COVID-19, studies had suggested that niclosamide may have broader clinical applications aside from treatment of parasitic disease, such as a role in malignancy, bacterial and viral infections, metabolic diseases (including Type II diabetes, NASH and NAFLD), and inflammatory conditions (rheumatoid arthritis, systemic sclerosis and atopic dermatitis).[8]

In the context of COVID-19, niclosamide has been identified as the leading candidate for activity against SARS CoV-2 in two separate library screens of existing approved drugs (Giacca et al; 2020. Unpublished data).

Furthermore, researchers at Institut Pasteur Korea have reported niclosamide as one of the most potent FDA approved inhibitors of SARS-Cov-2 in in vitro assays using vero cells, with IC_{50} of 0.28µM >25x higher than that of chloroquine and >40x higher than that of remdesivir.[9]



Left panel: drug library screens using syncythia assay showing that niclosamide is the most potent inhibitor of SARS-CoV2. NIC - niclosamide. CLO - chloroquine. Right panel: Dose-response of SARS-CoV-2 inhibition by niclosamide and remdesivor in vitro. The blue squares represent inhibition of virus infection (%) and the red triangles represent cell viability (%). Institut Pasteur Korea March 20, 2020.

However, oral niclosamide is poorly absorbed from the gut with low bioavailability, thus meaning that re-purposing as a therapy for COVID-19 is tricky, since the dose required to achieve sufficient exposure in target tissues is unknown. However, there are currently five clinical trials registered for testing oral niclosamide in COVID-19 infection, using doses used to treat parasitic infection.

Niclosamide primarily undergoes hepatic clearance after oral administration with the majority eliminated via the feces. When used to treat tapeworm infection, the dose of niclosamide is not adjusted in renal impairment. In humans, following a single oral dose of 2 grams of carbonyl ^{14}C-niclosamide, only 2% to 25% is excreted in the urine over a 4-day period with the remainder eliminated in faeces.[10] Excretion was essentially complete within 1-2 days. In urine, the glucuronides of 1) niclosamide, 2) 4'-nitro-reduced metabolite (2',5-dichloro-4'-amino-salicylanilide), and 3) the N- acetylated metabolite (2',5-dichloro-4'-acetamino-salicylanilide) were reported by Andrews et al., 1982.[10] The glucuronide metabolites found in urine are similar to those found in rats after oral administration of radiolabeled niclosamide (Griffiths and Facchini 1979), a species where oral doses up to 5000 mg/kg/day have been administered for 4 weeks without adverse findings.[11]

Since aqueous solubility and oral bioavailability of niclosamide is so poor there is reason to believe that other formulations, such as an inhaled preparation, would be advantageous for treating COVID-19. Union Therapeutics have developed a new stable liquid formulation (UNI911) of niclosamide. Related formulations have been tested topically in clinical trials for atopic dermatitis in over 600 subjects. These preparations have been re-purposed into an intranasal and nebulised formulation. A phase I escalating dose study in healthy volunteers using these formulations has recently been completed, with a favourable safety profile.

In-vitro data indicating potent inhibition of SARS-CoV2 replication and cellular penetration, together with evidence that SARS-CoV2 initially replicates predominantly in the nasal epithelium, suggests nasal niclosamide is best placed as a prophylactic agent or for treatment of early stage COVID-19 disease when the viral load is a main issue.

The PROTECT-V trial will administer 1% niclosamide ethanolamine solution via a nasal spray pump twice daily (140µL of a 1% niclosamide ethanolamine solution, equivalent to 1.4mg of niclosamide ethanolamine salt per nostril twice daily; total daily dose 5.6mg niclosamide ethanolamine salt (4.7mg free niclosamide acid). Even in a highly conservative approach, where 100% of the administered dose would be assumed to permeate and reach blood circulation, the maximal systemic exposure would still be approx. 40 times lower than the one reported with oral niclosamide at the approved dose (Yomesan chewable tablets) of 2g/day (based on the reported 10% bioavailability of oral niclosamide by Chang et al. 2006,[12] i.e. 200 mg day^{-1} / 5.0 mg day^{-1} = 40).

Based on 1) hepatic clearance as the primary mechanism for elimination of niclosamide, 2) the low human intranasal dose, 3) anticipated low bioavailability, 4) the lack of reported toxicity at high doses in animals, and 5) a reported half-life of niclosamide of 1.3 to 5.6 hours, which suggests that steady state levels are reached within a few days, the proposed nasal application of UNI911 to renally impaired patients will not lead to appreciably high levels of niclosamide or its metabolites outside of those previously evaluated in animals following a single or short-term human dosing regimen and thus no dose adjustments are recommended for patients with renal impairment.

UNI911 has been developed to maximise delivery of niclosamide to local tissues. In a non-clinical PK study UNI911 was administered by nebulisation to the lungs of sheep and sequential bronchoalveolar lavages were performed over a period of 8 hours after dosing. The study demonstrated a local exposure in the epithelial lining fluid in the deep lung above the SARS-CoV-2 IC50 value of niclosamide for the full 8 hour duration supporting a twice daily regimen. On this basis, the proposed twice daily intranasal administration of UNI911 to the nasal cavity should deliver a therapeutically active dose, considering that the dose delivered per surface area to the nasal cavity by intranasal spray pump exceeds that delivered to the lungs in the sheep PK study by nebulisation. The PK findings from the non-clinical study in sheep is also in agreement with PK findings in a recently completed Phase 1 study using UNI911 administered both by nebulisation to the lungs and intranasal spray pump to the nasal cavity.

5.DESIGN AND PROCEDURES

PROTECT-V is a randomised, double blind, placebo controlled event driven trial evaluating the use of nasal niclosamide as a prophylactic agent against COVID-19 infection.

5.1.Trial Population

Approximately 1500 participants will be enrolled from three vulnerable patient populations:dialysis patients, kidney transplant recipients and those with vasculitis or other auto-immune kidney disease/glomerulonephritis (GN).

The provisional distribution between trial populations will be 1:1:1 (dialysis:transplant:vasculitis/GN). No capping for a specific subgroup will be implemented but it is expected to have a minimum of 300 patients in each subgroup approximately. However, the proportion of the total trial population represented by each subgroup may be adjusted depending on the event rate of the primary outcome measure within each patient group. The subgroup-specific event rate will be monitored monthly.

5.2. Eligibility

5.2.1. Inclusion Criteria

To be included in the trial the participant must:

- Be aged 18 years or older
- Have given written informed consent
- Be a member of one of the following vulnerable patients populations
  - ***Dialysis*** – including in centre haemodialysis, home haemodialysis and peritoneal dialysis
  - ***Kidney transplant*** receiving at least one of the immunosuppressive medications listed in the table below
  - ***Vasculitis*** (according to Chapel Hill Consensus Conference 2012 definitions) receiving at least one of the immunosuppressive medications listed in the table below
  - ***Glomerulonephritis**** receiving at least one of the immunosuppressive medications listed in the table below

* Glomerulonephritis includes prior histological confirmation of any of the following conditions - minimal change nephropathy, focal segmental glomerulosclerosis (FSGS), IgA nephropathy, primary membranous nephropathy, membranoproliferative glomerulonephritis or lupus nephritis.

Inclusion criteria	**Dialysis**	**Kidney Transplant OR Vasculitis OR Glomerulonephritis** *receiving **at least one** of the following immunosuppressive medications*
Aged 18 years or older	✓	✓
Written Consent	✓	✓
In-centre haemodialysis or home haemodialysis or peritoneal dialysis	✓	-
Ciclosporin	-	✓
Tacrolimus	-	✓
Azathioprine	-	✓
Mycophenolate Mofetil or Mycophenolic Acid	-	✓
Belatacept	-	✓
Methotrexate	-	✓
Tocilizumab	-	✓
Abatacept	-	✓
Leflunomide	-	✓

Prednisolone (current dose) > 20mg daily for 8 weeks	-	✓
Anti-TNF (infliximab, adalimumab, etanercept)		✓
Belimumab		✓
Cyclophosphamide (within the last 6 months)	-	✓
Rituximab (in the last 12 months)	-	✓
Alemtuzumab (in the last 12 months)	-	✓

5.2.2. Exclusion Criteria

The presence of any of the following will preclude participant inclusion:

- Inability to provide informed consent or to comply with trial procedures
- COVID-19 at time of enrolment – either positive SARS CoV-2 swab (PCR) or symptoms highly suggestive of COVID-19 infection
- Known chronic liver disease or hepatic dysfunction as evidenced by ALT or AST > 3x upper limit of the normal range
- Allergy to niclosamide or history of significant adverse reaction to niclosamide or related compounds, or to any of the excipients used
- Significant structural nasal disease in the opinion of the investigator
- Pregnant, trying to conceive, unwilling to use contraception or breastfeeding
- Participation in another interventional prophylactic or vaccine trial* against COVID-19.

***Patients remain eligible for enrolment if they have received SARS-COV-2 vaccination as part of routine care.**

5.3. Participant Identification and Consent

Potential participants can be identified via a number of avenues including advertisements, word of mouth, trial specific invitation letter, face to face and existing cohort studies.

- The PROTECT-V website will contain a video where one of the central trial physicians explains the study.
- Additional information, including the detailed Participant Information Sheets will be available from the local site study team and on the study website.

Consent will be obtained by the Principal Investigator at each trial site or by a suitably qualified and delegated health professional and member of the research team at each site.

- Potential participants will be given a copy of the Patient Information Sheet to read through thoroughly, including the opportunity to take it home and discuss the trial with relatives/friends and other medical professional eg GP.
- The Principal investigator or a medically qualified and delegated health professional will explain the aims, methods, anticipated benefits, potential hazards and risk benefit balance of the intervention.
- The participant will be allowed as much time as they need to consider all the information.
- The Investigator will explain that participants 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.
- No trial specific procedures will be conducted prior to the participant giving consent by signing the Consent form.
- Participants will be given a copy of their signed PIS and Informed Consent form to retain at home for future reference. Contact details for the local study team are included in the PIS should the participant have any further questions.

If further safety information becomes available, the PIS and Informed Consent Form (ICF) will be reviewed and updated and submitted to the REC for approval. All participants that are actively enrolled in the study will be informed of the updated information and will be required to sign the revised copy of the PIS/ICF in order to confirm their wish to continue on the study.

The Informed Consent form must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator or designee must ensure that each trial participant is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

5.4. Screening

5.4.1. Screening Assessment – in person consultation

The screening and baseline visits may be readily combined in those patients who agree to participation in the trial. Screening will be conducted at participating sites. Participants attending the screening visit will be given a unique ID number to be used in all CRFs.

All eligible participants who proceed to randomisation will be provided with the trial specific Patient ID Card which includes details of the trial IMP and contact details of the local study team and Sponsor.

5.5. Randomisation

The PI or suitably qualified and delegated member of the study team will confirm the eligibility of a participant by entering their screening data into the PROTECT-V eCRF web portal. Once the full screening details have been entered and eligibility confirmed, the participant will be randomised.

Randomisation 1:1 to niclosamide or placebo nasal spray will be carried out using a web-based randomisation system (Sealed Envelope) accessible via password-protected access. Randomisation will be stratified by PROTECT-V disease sub-group, age and site using a stratified block randomisation method.

Immediate allocation of treatment will be performed, with documentation of the decision in a blinded confirmatory email. The system will allocate the participant treatment pack code(s) which will relate uniquely to the first supply of IMP. Different treatment pack code(s) for every subsequent order of IMP supply will be allocated by the randomisation system.

Participants and site teams will remain blinded to treatment allocation. The allocated blinded IMP supply will be collected by participants when possible or sent at least 3-monthly to their home by courier.

5.6. Blinding

PROTECT-V will be a double blind placebo controlled study where neither the participant nor clinician will be aware of treatment allocation.

5.7. Trial Treatments

The IMPs in this study are niclosamide and placebo to match.

5.7.1. Trial Treatment - Niclosamide (UNI911)

5.7.1.1. Niclosamide Name and description

INN:	Niclosamide Ethanolamine
Chemical name (IUPAC):	5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide.2 aminoethanol
CAS registry number:	1420-04-8
Lab code:	UNI911

The IMPs niclosamide Nasal Spray 1% and matching Nasal Spray Placebo will be provided in 10 mL amber glass vials with nasal spray pumps, containing 8.5 mL of the respective solution, delivering 140 µL per spray shot. It is an isotonic and euhydric aqueous solution with red color.

5.7.1.2. Niclosamide Legal status

Niclosamide is currently approved and marketed for the oral treatment of tapeworm infections in several European and developing countries but not the UK. Niclosamide ethanolamine has not previously been approved as a pharmaceutical drug and is used in this trial as an unlicensed product.

5.7.1.3. Niclosamide Supply, dispensing and accountability

Niclosamide Nasal Spray 1% and matching Nasal Spray Placebo will be provided by UNION therapeutics A/S, DK-Hellerup. Supply of the finished product to participating site pharmacies will be overseen by the trial co-ordinator and distributed by a sponsor-appointed third party. Upon initial authorisation by the sponsor, an initial supply will be sent to sites; supplies thereafter will be distributed as detailed in the pharmacy manual.

IMP will be dispensed at appropriate intervals, supplying the bottles labelled with kit numbers allocated. Full accountability records will be completed to document receipt, dispensing and destruction of expired and unused IMP at the end of the study. Further details of dispensing are detailed in the pharmacy manual.

IMP will be collected by the participant during dialysis sessions or sent by courier to the participant.

IMP for the trial will be provided free-of-charge for participating sites.

5.7.1.4. Niclosamide Packaging and Labelling

The IMPs niclosamide Nasal Spray 1% and matching Nasal Spray Placebo are packaged and labelled in single packs with one unit each. The outer carton and bottle label are blinded and complies with regulatory requirements. Each unit is labelled with an individual unique treatment pack number. The same number will appear on the bottle and carton label.

5.7.1.5. Niclosamide Storage

The IMPs niclosamide Nasal Spray 1% and matching Nasal Spray Placebo must be stored as per labelled storage conditions. Participants must only use each spray for a total of 14 days, even if there remains liquid in the bottle.

5.7.1.6. Niclosamide Treatment Duration

PROTECT-V will be an event driven trial, and continue until the required number of events are accrued. It is anticipated that the median treatment duration will be 6 months for each participant with a maximum treatment period of 9 months.

5.7.1.7. Niclosamide Dose

140µL of a 1% niclosamide ethanolamine solution in each nostril twice daily, equivalent to 1.4mg of niclosamide ethanolamine salt per nostril twice daily, approximately 12 hours apart. Total daily dose 5.6mg niclosamide ethanolamine salt (4.7mg free niclosamide acid).

No dose modifications are permitted.

5.7.1.8. Niclosamide Administration

Single metered dose nasal pump spray per nostril twice daily.

5.7.1.9. Niclosamide Missed or Replacement Doses

Missed doses will not be replaced. A dose will be considered missed after 6 hours of usual administration time.

5.7.1.10. Niclosamide Contraindications

Niclosamide and placebo to match are contraindicated in subjects allergic or hypersensitive to niclosamide, its derivatives or any formulation excipients.

5.7.1.11. Niclosamide side effects and concomitant medications

Preliminary results from the Phase I study using both nebulised and intranasal niclosamide, have identified only mild symptoms after administration including irritation in the throat, cough before and/or after inhalation, sneeze, loss of taste or a tingling feeling on the tongue and hoarseness. All of these symptoms were transient and ceased within 60 to 75 minutes. Two subjects experienced mild shortness of breath during inhalation which lasted for 10 minutes. It is likely that the majority of these symptoms could be related to inhalation of niclosamide via the mouth rather than spraying in the nostrils. In addition, the relatedness of symptoms to niclosamide cannot yet be ascertained since 2 out of every 9 subjects were given placebo and the study has not yet been unblinded.

No formal drug-drug interaction studies with inhaled or intranasal niclosamide have been conducted. Given the expected low systemic exposure the risk for drug interactions is considered low. As a matter of precaution, administration of niclosamide should be made separately from any other drug administration.

All standard of care medicines are to continue as per standard practice and will be recorded by the study team as described.

5.7.2. Placebo to match niclosamide

Placebo to match niclosamide will be supplied, stored, labelled, dispensed and dosed as for the active formulation. The placebo product is formulated to have the same appearance as the active solution.

5.7.3. Emergency unblinding

Treatment code break and unblinding must only occur in exceptional circumstances when knowledge of the actual treatment is essential for further management of a participant and their safety. If the investigator or treating clinician deems unblinding to be necessary, the web-based randomisation system can be used by designated local investigators to unblind. The unblinder will not be shown the treatment allocation on-screen. Instead the allocation will be sent by email to the treating clinician and the unblinding notification without allocation should be printed and retained within the Investigator Site File. An email stating that an unblinding has taken place will be automatically sent to the coordination team and CI for oversight purposes.

Unless it is necessary for the safety of the participant, the actual allocation must not be disclosed to the participant or other site personnel, either verbally or by any written correspondence. The CI/PI will also notify the Sponsor and the relevant authorities as necessary.

5.8. Trial assessments

The following sections describe the schedule of assessments that will be completed by participants. The Schedule of Assessments is shown in the table below. Further details are available in the trial procedures manual (TPM).

Research-specific face-to-face visits as part of their trial participation will be kept to a minimum and aligned with routine clinical follow up whenever possible, as healthcare contact needs to be minimised during the COVID-19 pandemic. Therefore, telephone follow-up and self-reporting of symptoms will be utilised.

The first 70 dialysis participants will be included in a Population PK cohort. These participants will have additional assessments as described in section 4.8.1.4.

Data on the primary endpoint (COVID-19 infection) will be captured on a monthly basis via linkage with PHE and by direct reporting by sites or by participants. All subsequent assessments will consist of self-completed questionnaires online or through telephone calls from the local trial team. Data will be collected in real time through linkage with NHS Digital or equivalent, ONS, ICNARC or other routine data sources as necessary. Data on death will be reported by sites or obtained via linkage.

5.8.1. Timing of assessments

5.8.1.1. Screening/Baseline ‘visit’ 1 (face to face)

- Eligibility
- Randomisation
- Baseline data collection
  - Medical history
  - Current medications
  - Symptom checker self-assessment questionnaires
  - Research serum sample collection to detect anti SARS-COV-2 antibodies
- IMP courier delivery arrangements (if necessary) and instruction on IMP administration, storage dose recording.

5.8.1.2. Telephone consultations - weeks 1,2,3, 4 and 6 (±3 days)

Participants will be telephoned by the local PI or research nurse and asked about the treatment received and symptoms suggestive of potential side effects of niclosamide/placebo or of COVID-19 infection, once every week for the first 4 weeks and then again on the sixth week of the trial. If concerns are raised about potential side effects of niclosamide/placebo, the information will be reviewed by the PI and a decision made whether to continue IMP. Participants will be asked to keep a diary of IMP administration with reasons for any missed doses.

5.8.1.3. Two-Weekly self-reporting - week 8 onwards

Participants will be asked to complete a short questionnaire regarding COVID-19 self-assessment/reporting and potential side effects of niclosamide/placebo, once every two weeks during trial conduct via email, in paper form via mail, or via telephone interview. Participants receiving in centre haemodialysis may be assessed during their dialysis sessions. The intention of two-weekly self-reporting is to provide participants with the opportunity to

- indicate any symptoms suggestive of COVID-19 infection,
- adverse effects of IMP administration,
- report new concomitant medications,
- report vaccination against COVID-19.

If a participant has not submitted data electronically for a period of 6 weeks, they will be contacted by the local study team for a telephone interview to minimise loss to follow up.

5.8.1.4. Pharmacokinetic Assessment

Population Pharmacokinetic (PK) assessment will be conducted in the first 30 participants receiving niclosamide for safety purposes, to exclude the unlikely possibility of accumulation of niclosamide during the course of the trial in patients receiving dialysis only. Given that participants and investigators will be blinded to treatment allocation, PK samples will maintain blinding by including the first 70 dialysis patients in the PK sampling cohort. Including 70 participants is necessary to exclude the scenario where a chance imbalance in treatment allocation early in the study results in fewer than 30 participants allocated to niclosamide. These participants will be identified as the 'PK Cohort'.

The PK Cohort will have a blood sample taken at the start of dialysis, before taking the IMP. PK Cohort participants receiving dialysis in the afternoon or evening may take the morning dose of IMP, but should omit the evening dose until the PK sample has been obtained. The procedure for obtaining PK samples is described in the trial procedures manual.

PK samples will be obtained 7 (±3) days after the date of first IMP dose (or coincident with the 3rd dialysis session post-dating randomisation), 14 (±3) days and 21 (±3) days after date of first dose.

5.8.1.5. Unscheduled assessment – "suspected Covid-19 infection"

Should an individual develop symptoms suggestive of Covid-19 infection, which are listed in the Participant Information Sheet, they must arrange a Covid-19 test via the NHS Test and Trace system, booking online or calling 119 to organise an appointment at their nearest testing facility. Alternatively participants will be able to provide a saliva sample using a remote saliva sampling kit (provided by Optigene). Saliva samples can be returned by courier for testing, arranged by contacting the PROTECT-V trial office. Participants will also be required to notify their trial physician. Notification can be made by phone or by logging the occurrence of suspected COVID-19 via the trial website participant portal.

At the same time, the individual should be swabbed for influenza. If this is not done routinely with the Covid-19 test in their area, participants may be provided with a swab, labels and request form for the influenza test

at enrolment by their local study site. The participant can self-swab, or ask a relative, or the individual performing the COVID-19 swab or dialysis nurse to perform the test according to the instructions provided. The swab should be placed in the stamped addressed envelope and placed in a post box immediately to return to local site laboratories for testing.

The individual should contact their local site to

- Inform the site team of their symptoms so that these can be followed up and recorded in the CRF pages
- Get assistance should they be having difficulty organising a swab test themselves. Swabs (or saliva tests) for COVID-19 and swabs for influenza should be performed as soon after onset of symptoms as possible.
- Inform the site team of the result of the COVID-19 swab, and receive the result of the influenza swab.

Participants should continue taking trial medication until advised to stop by a member of the trial team or admitted to hospital

Participants must follow the public health guidance for “suspected COVID-19 infection” current at that time

5.8.1.6. Final safety assessment

PROTECT-V is an event driven trial. The anticipated median treatment duration per participant is 6-9 months. However, the trial may conclude while some participants are in the trial for less than 6 months if the required number of events are observed. Upon completion of the trial, participants will be notified by email or by telephone depending on participant preference. Participants will be asked to stop taking IMP and acknowledge receipt of end-of-trial notification.

A final safety assessment will be conducted in person, 4-6 weeks after the final treatment (defined as the day of notification of end of trial or date of last dose administered). Participants will be asked to return all completed medication diaries and IMP bottles for compliance assessment at this visit. Participants will be asked a series of questions to identify any additional adverse events or adverse reactions experienced since their last follow up assessment and a blood sample will be taken for a SARS-CoV2 total antibody assay, to detect asymptomatic cases of COVID-19 infection.

5.8.2.Schedule of Assessments

Assessment schedule	Screen/ Baseline visit	7 (±3) days PK *	Weekly (±3 days) %	2-weekly (±3 days) %	14 (±3) days PK *	21 (±3) days PK *	As required	data linkage	Final assessment&
Eligibility check	X								
Medical history	X								
Concomitant Medications	X		X	X					
Symptom checker questionnaire$	X		X	X					
SARS-CoV2 PCR	X						X		
Serum sample for SARS-CoV2 Total Ab assay	X								X
Influenza PCR							X		
ALT/AST	X								
Pregnancy test#	X								
SAR/SUSAR reporting							X		X
Randomisation	X								
IMP supplied							X€		
COVID-19 infection								X	
PK		X			X	X			

*PK Cohort only

#A pregnancy test is required for WOCBP within 14 days prior to starting trial treatment. Women are considered WOCBP following menarche and until becoming post-menopausal unless permanently sterile (previous hysterectomy, previous bilateral salpingectomy and or oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A serum pregnancy test is required for all WOCBP participants.

% Weekly for one month and 2-weekly thereafter. Any participant testing positive for SARS-CoV-2 without symptom will be required to complete a CoVid-19 symptom assessment weekly for 4 weeks after diagnosis, unless hospitalised.

$ Telephone consultation will occur for the first 6 weeks.

& Final assessment visit will occur 4-6 weeks after end of treatment

€ IMP will be supplied at least 3-monthly, either at the dialysis centre or by courier.

5.9. Duration of study

PROTECT-V is an event driven trial. The median anticipated treatment period is 6 months with a maximum treatment period of 9 months. Last follow-up visit will be scheduled 4-6 weeks after last dose.

5.10. Treatment withdrawal

Participants will be withdrawn at the discretion of the PI/CI if continuation in the trial is deemed to be against the participant's best interest.

Treatment will be withdrawn if:

- Participants become pregnant
- Participant is hospitalized for COVID-19
- Participant experiences unacceptable drug reaction such as:
    - Moderate or severe pain in the nose
    - Severe itch or burning sensation in the nose
    - Spontaneous nose bleeding as result of nasal ulceration
    - Oedema that prevents breathing through the nose

Participants who have been withdrawn from the trial treatment and are experiencing ongoing toxicity will be followed up until the adverse reaction comes to its conclusion. In the event of a Participant being withdrawn from the trial treatment, they will continue to receive the most appropriate standard of care treatment available under the guidance of their treating clinician.

5.10.1. Treatment period

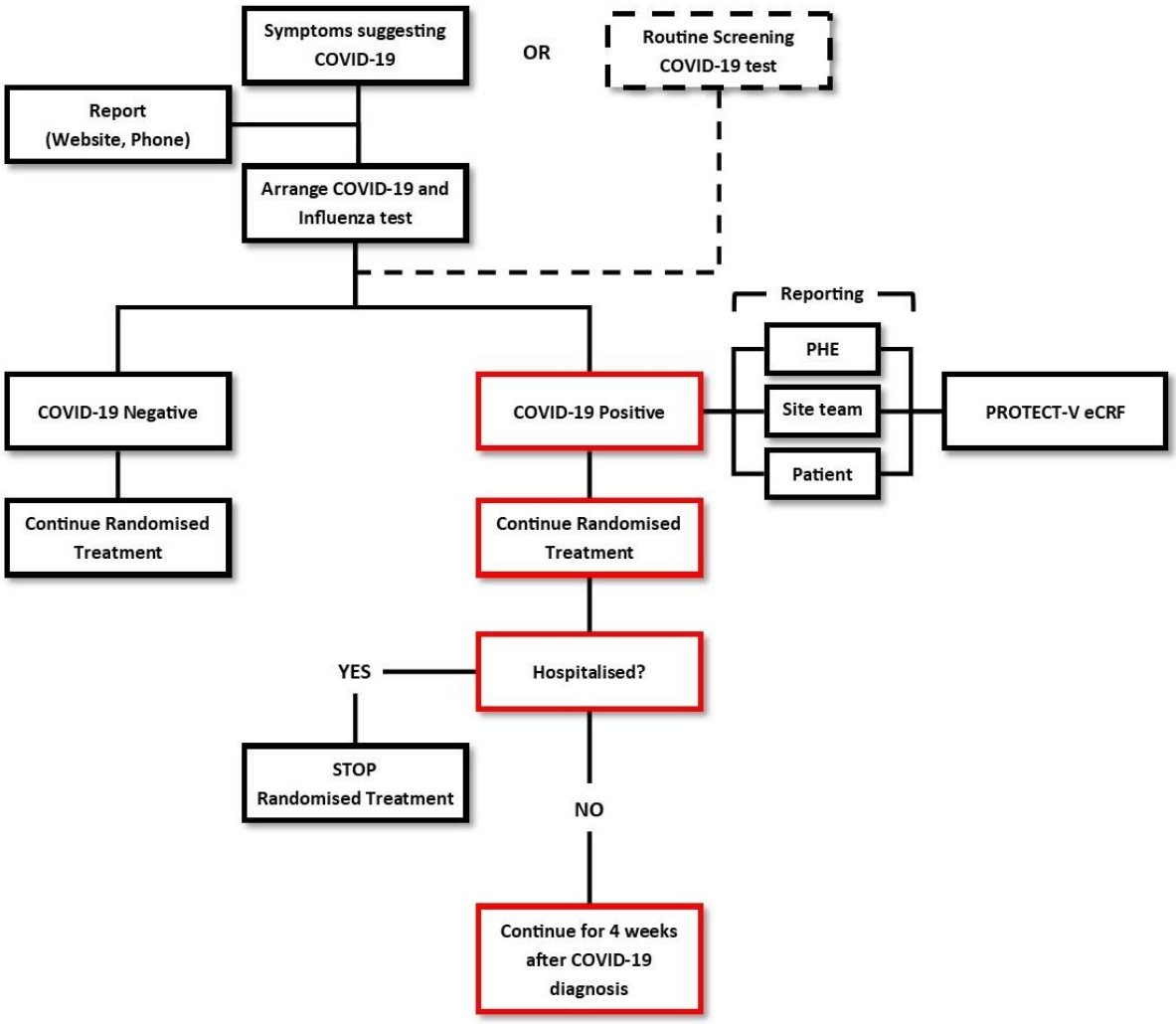
Participants will continue allocated treatment until one of the following occurs:

a. The required number of the primary outcome events have occurred
b. The participant is hospitalised with COVID-19 (see 4.10.2.)
c. 28 Days after a diagnosis of COVID-19 if hospitalisation is not required

After the end of the trial, Union Therapeutics will endeavour to make available to trial participants further supplies of the IMP in the event that the trial demonstrates benefit but this cannot be guaranteed.

5.10.2. Diagnosis of COVID-19

Participants may receive a diagnosis of COVID-19 during the course of participation in the trial, either as a result of routine testing or prompted by suggestive symptoms. Any participant diagnosed with COVID-19 should continue with their randomised treatment for 28 days after the date of diagnosis, unless hospitalised. Participants hospitalised with a diagnosis of COVID-19 should stop the randomised treatment immediately.



Participants receiving a diagnosis of SARS-CoV-2 infection who are asymptomatic (most likely after routine screening) will be required to follow the above algorithm, continuing with treatment for 4 weeks unless hospitalised. If such participants remain asymptomatic, they will be judged not to have reached the primary endpoint for the trial. If they become symptomatic after diagnosis, they will be judged to have reached the primary endpoint of the trial. Under these circumstances, the primary endpoint date will remain the date of confirmed SARS-CoV-2 (the date of the test).

Any participant testing positive for SARS-CoV-2 will be required to complete a COVID-19 symptom assessment weekly for 4 weeks after diagnosis, unless hospitalised.

5.11. Withdrawal of consent

Participants may withdraw consent for continuation in the trial at any point. Participants may choose to withdraw only from active trial participation (trial treatment and self-reporting questionnaires), allowing continuation of data collection through data linkage, or may choose to withdraw both from the trial and all further data linkage.

No further trial procedures will be undertaken and no data or samples will be collected from the time of consent withdrawal, in line with the participant's wishes. However, data and samples collected up to the time of consent

withdrawal will be included in the data reported for the trial. The Investigator should inform the coordination team as soon as possible and complete the consent withdrawal Case Report Form (CRF).

5.12. Objectives

5.12.1. Primary objective

The primary aim of the trial is to determine if nasal niclosamide reduces the risk of confirmed symptomatic COVID-19 infection in vulnerable renal and immunosuppressed patients participating in the study.

5.12.2. Secondary objectives

The trial also aims to:

1) Determine if nasal niclosamide increases the time to confirmed SARS-Cov-2 infection from the date of randomisation including incidental asymptomatic cases in the vulnerable populations taking part in the study.

2) Determine the safety of nasal niclosamide in this patient population

3) Determine if nasal niclosamide reduces mortality and severity of COVID-19 infection in the vulnerable populations taking part in the study.

5.12.3 Exploratory objectives

1) Determine if nasal niclosamide reduces the occurrence of other influenza infections in the vulnerable populations taking part in the study.

2) Determine if nasal niclosamide increases the proportion of individuals with antibodies to SARS-Cov-2 at the end of the trial in the vulnerable populations taking part in the study.

5.13. Outcomes

5.13.1. Primary Outcome

The primary outcome for PROTECT-V is confirmed symptomatic COVID-19 infection during treatment.

5.13.1.1. Definition of the primary outcome event

The primary outcome event is defined as the presence of both

- PCR confirmed SARS-CoV2 and
- One or more symptoms in keeping with COVID-19, including:
  - Respiratory (Cough +/- sputum and shortness of breath)
  - Constitutional (Pyrexia/chills, myalgia/arthralgia, fatigue, rash, headache, confusion)
  - Gastrointestinal (nausea/vomiting, diarrhoea, abdominal pain, loss of appetite)

The date (time) of the primary outcome event is defined as the date of the confirmed COVID-19 test.

5.13.2. Secondary Outcomes

Secondary outcomes include

a. Time to confirmed SARS-Cov-2 infection from the date of randomisation including asymptomatic cases
b. Safety and All-cause mortality
c. Severity of COVID-19 disease (assessed by PI 28 days after date of positive test)
    i. Adapted WHO ordinal scale (defined as the **worst category** 28 days from date of positive test or until date of discharge from hospital, whichever occurred later)
        1. Healthy carriers - confirmed SARS-CoV2 infection, no symptoms
        2. Very mild symptoms, no limitations
        3. Mild, limitations on activities
        4. Mild, hospitalised, no oxygen requirement
        5. Moderate, hospitalised, oxygen via mask or nasal cannulae
        6. Severe, non-invasive ventilation or high flow oxygen
        7. Very severe, intubation and mechanical ventilation
        8. Critical, ventilation and additional organ support (RRT/ECMO)
        9. Death
    ii. Length of inpatient stay
    iii. Common COVID-19 complications (including ARDS, viral pneumonitis, myocarditis/myocardial injury, AKI)

Additional information on longer term outcomes may be collected through review of medical records or linkage to medical databases such as those managed by NHS Digital, ICNARC and Public Health England.

5.13.3. Exploratory Outcomes

Exploratory outcomes will include

1. Occurrence of antibodies to SAR-CoV-2 at the end of the trial
2. Occurrence of other influenza infection (swab confirmed)
3. Occurrence of other respiratory viral infections (aside from COVID-19 and influenza)
4. Staphlococcus aureus infections (dialysis population only)

5.14. Sample management

Only authorised staff will have access to the trial samples. Full instructions for the collection, labelling and storage of samples are provided in the Trial Procedure Manual.

5.14.1. SARS-Cov-2 antibody testing

Serum samples will be taken at baseline and final assessment visits to test presence of antibodies against SARS-Cov-2. Samples will be stored and analysed in batch. Refer to laboratory section of trial procedure manual for full details of sample processing...

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5.14.2. PK analysis samples

The first 70 in centre dialysis participants enrolled in the trial will have blood samples taken 7, 14 and 21 (±3) days after commencing trial treatment for PK analysis to assess for accumulation of the IMP.

Samples will be taken during dialysis sessions before IMP administration by the local staff, labelled with the participant trial ID and sent to Cambridge University Hospitals NHS Foundation Trust laboratory for storage.

Once all 70 sample sets have been collected, the samples will be sent to a subcontracted European Union laboratory for analysis. Once samples have been analysed they will be disposed of according to EU law.

5.15. Methods of analysis

5.15.1. Analysis populations

The following populations will be defined for efficacy and safety analyses:

- Intent-to-treat population (ITT)

The ITT population is defined as all participants randomised in the trial, regardless of whether they actually received trial treatment. The treatment group will be analysed as randomised.

- Safety population

The safety population comprises all participants randomised and having received as least one dose of trial treatment. The treatment group will be analysed as treated.

5.15.2. Efficacy Analysis

The primary outcome measure, symptomatic Covid-19 infection, will be compared between the two treatment groups in the ITT population using a Cox proportional hazards model, adjusting with fixed effects for

- Age
- Sex
- Ethnicity
- Patient population (dialysis, vasculitis/glomerulonephritis, transplant)
- Known high-risk pre-existing conditions (e.g. cardiovascular disease, hypertension, diabetes mellitus), vs not.
- Detectable anti SARS-COV-2 antibodies at baseline
- Receipt of Covid-19 vaccination (a time-dependent covariate)

The hazard ratio will be determined and statistical significance will be declared using a 2-sided alpha-level of 0.045. A 95% confidence interval for the hazard ratio from the Cox modelwill be provided. The estimand properties of the primary and sensitivity analyses of the primary endpoint will be detailed in the Statistical Analysis Plan

Participants who did not develop symptomatic COVID-19, withdrew from the study, are lost to follow-up or died prior to developing symptomatic COVID-19 will be censored at the date of last treatment administered. Asymptomatic PCR confirmed COVID-19 participants will be followed up for a maximum of 4 weeks (this is consistent with the maximum of 4 week treatment after positive COVID-19). If any protocol specified symptoms have occurred, the date of the positive COVID-19 test is the date of primary endpoint event; otherwise, the participant will be censored at the date of last treatment administered.

For the secondary outcome measure of time-to-PCR-confirmed SAR-Cov-2 infection in the ITT population, the analysis will use a Cox proportional hazards model as described for the primary outcome measure. The median, 25th and 75th percentile and 95% Cis for time to PCR confirmed SARS-CoV-2 infection will be provided. The severity scale of COVID-19 disease will be compared using a proportional odds model for all COVID-19 infected participants. Length of inpatient stay will be compared using Fine and Gray approach with discharge alive as event of interest and hospital death as competing event for all hospitalised participants. Common COVID-19 complications for all COVID-19 infected participants and occurrence of influenza

infection in the ITT population will be analysed using the standard chi-square test. The comparisons on the secondary outcome measures will be compared according to a pre-specified hierarchal order. Details will be included in the statistical analysis plan.

5.15.3. Safety Evaluation

The safety analyses will be based on the safety population. All safety parameters will be summarised. Summary tables will be presented for incidence rates of AEs, ARs, SAEs and SARs.

A full statistical analysis plan will be written before any analyses are undertaken.

5.16. Sample size

It is planned to randomise (1:1 ratio) a total of 1500 participants approximately during a period of 3-6 months.

It is estimated the 6-month rate of the confirmed symptomatic COVID-19 infection is around 15% in the placebo group, and 10% in the niclosamide group; this would correspond to a hazard ratio of 0.648. With a 0.045 significance level (for an overall significance level of 0.05 with two interim analyses using a Lan-DeMets error-spending approach corresponding to symmetric 2-sided O'Brien-Fleming boundaries (https://doi.org/10.1002/sim.4780131308) and 90% power, the maximum total number events required is 235. With a 3 month recruitment and a further continuation of 8 months (a total of 11 months), the number of events required will be observed with a total of 1275 subjects, allowing for a 15% noncompliance, a total of 1500 subjects. With a 6 month recruitment and a further continuation of 7 months (a total of 13 months), the number of events required will be observed with a total of 1278 subjects, allowing for a 15% noncompliance, a total of 1500 subjects. The assumption used in the sample size estimation will be monitored by the DMC. Sample size re-estimation might be considered.

5.17. Criteria for the premature termination of the trial

The study will be reviewed every 2 months by the Independent Data Monitoring Committee (DMC) for safety, combined primary outcome measure event rate and making a recommendation for performing efficacy analyses. Should there be sufficient evidence of a difference in the primary outcome measure between the niclosamide arm and the placebo arm at one planned interim analyses, the DMC may consider recommending early termination of the study. As a guide to the DMC, considering the total duration of study is around 1 year, a maximum of two formal interim analyses, based the number of primary endpoint events, are to be performed using a Lan-DeMets error-spending approach corresponding to symmetric 2-sided O'Brien-Fleming boundaries (https://doi.org/10.1002/sim.4780131308). The study will only be stopped earlier if there is sufficient evidence of benefit using the O'Brien-Fleming boundaries, that is, the value of the test statistic crosses the O'Brien-Fleming boundary of beneficial effect of niclosamide.

As a potential pivotal study, it is not planned to stop the study for futility. The study will be stopped early if there are any safety concerns based on the recommendation of the independent Data Monitoring Committee and the approval from the Trial Steering Committee. As guidance, the study might be stopped early for safety concerns

- if the rate of unacceptable toxicity in the niclosamide arm is over 20%, that is, the estimated lower limit of a 95% confidence interval is greater than 20%
- if the incidence of moderate/severe adverse events/symptoms is 15% more in the niclosamide arm with a minimum of 200 participants in each arm at a significance level of 0.05.

5.18. Trial restrictions

Women of childbearing potential are required to use effective contraception for the duration of the trial and for 28 days after the completion of the last treatment. This includes:

- Intrauterine Device (IUD)
- Hormonal based contraception (pill, contraceptive injection or implant etc.)
- Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
- True abstinence (where this is in accordance with the participant's preferred and usual lifestyle)

6. SAFETY MONITORING AND REPORTING

All Adverse Events (AEs) and Adverse Reactions (ARs) will be recorded in the medical notes and in the appropriate section of the CRF. SAEs and SARs should be reported to the sponsor as detailed in section 5.3.

6.1. Adverse Event Definitions

TABLE 1	
Term	**Definition**
Adverse event	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which is not necessarily caused by or related to this treatment.
Adverse Reaction	All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.
Unexpected Adverse Reaction	An adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety information (RSI). When the outcome of the adverse reaction is not consistent with the applicable RSI this adverse reaction should be considered as unexpected.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any untoward medical occurrence that at any dose: - results in **death**, - is **life-threatening** - requires **hospitalisation** or **prolongation** of existing inpatient hospitalisation - results in persistent or significant **disability or incapacity**, - is a congenital anomaly or birth defect. - is another important medical event Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the RSI.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

6.2. Expected AEs or ARs

The Sponsor expects that adverse events are recorded from the point of Informed Consent regardless of whether a participant has yet received a medicinal product. Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event (causality). All expected Adverse Reactions are listed in the latest MHRA approved version of the RSI as specified in section 5.4.2. This must be used when making a determination as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as per section 5.3.

All AEs and ARs, which are new or significantly worse since commencing the trial, should be recorded on the symptom checker questionnaire in the CRF and sent to the trial coordination centre within one month of the investigator becoming aware of the event.

6.3. Recording and Evaluating Serious Adverse Events / Reporting SARs

The Chief Investigator or PI is responsible for ensuring that the assessment of all SAEs for expectedness and relatedness is undertaken, (except for elective overnight admissions for pre-existing medical conditions), and the onward notification of all SAEs and SARs to the Sponsor immediately but not more than 24 hours of first notification. A further review of expectedness will be undertaken by the Chief Investigator. The sponsor has to keep detailed records of all SAEs and SARs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all Serious Adverse Reactions to the competent authority (MHRA) if they could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC

Details of where to report SAEs and SARs can be found in the PROTECT-V trial manual and on the front cover of the protocol.

The Chief Investigator will ensure that all safety information is reported to Union Therapeutics at the same time as notification to the Sponsor.

6.3.1. Assessment of Seriousness

Seriousness is assessed against the criteria in the table 1 above.

6.3.2. Assessment of Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Unrelated – where an event is not considered to be related to the IMP

Possibly – although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP.

Definitely – the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause.

6.3.3. Clinical Assessment of Severity

Mild	The participant is aware of the event or symptom, but the event or symptom is easily tolerated
Moderate:	The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity
Severe:	Significant impairment of functioning; the participant is unable to carry out usual activities and / or the participant's life is at risk from the event.

6.4. Assessment and onward reporting of SUSARs

All suspected adverse reactions related to study IMP which occur in the PROTECT-V trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

6.4.1.Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the:

- Sponsor
- Competent authorities in the concerned member states (e.g. MHRA)
- Ethics Committee in the concerned member states

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

6.4.2.Reference Safety Information (RSI)

RSI is a list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which Serious Adverse Reactions (SARs) require expedited reporting.

For this trial the Reference Safety Information is: Union Therapeutics Investigator Brochure for UNI911 (Niclosamide nasal spray), Version 1.0, 26th August 2020 section 6.1.

6.4.3.When to report SUSARs

6.4.3.1.Fatal or life-threatening SUSARs

The CI must inform the Sponsor of any fatal SUSAR immediately but within 24 hours of the site investigator awareness of the event. The MHRA and Ethics Committee must be notified as soon as possible but no later than 7 calendar days after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting. In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional 8 calendar days.

6.4.3.2.Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to the Sponsor immediately but within 24 hours of the site investigator awareness of the event. The MHRA and Ethics Committee must be notified as soon as possible but no later than 15 calendar days after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

6.4.4.How to report SUSARs?

6.4.4.1.Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

a) a suspected investigational medicinal product
b) an identifiable participant (e.g. trial participant code number)
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
d) an identifiable reporting source
and, when available and applicable:
- a unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
- a unique case identification (i.e. sponsor's case identification number)

6.4.4.2. Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

6.4.4.3. Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

6.5. Pregnancy Reporting

All participant pregnancies within the trial or up to 1 month after the last dose should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification. The Chief Investigator will then report the pregnancy to UNION within 24 hours.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

7. TRIAL COMMITTEES

7.1. Trial Management Group (TMG)

The TMG will meet on a weekly basis during initial set up, and then two weekly face to face or by teleconference to oversee the running of the trial. TMG members will review SAEs which have occurred in the trial. If there are specific safety concerns these may be raised with the TSC and IDMC. TMG members will include co-investigators, trial statistician, trial pharmacist, the trial co-ordinator and data manager at the Cambridge Clinical Trials Unit (CCTU), a representative from Union Therapeutics.

7.2. Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) is responsible for the review of the trial and related activities at regular intervals. The TSC also provides overall supervision for the trial, to ensure that it is conducted in accordance with the protocol and GCP and to provide advice through its independent chairman. The committee will aim to convene at regular intervals to review the data and discuss if the trial is on course to meet the sample size requirements. The details of the TSC are set out in the PROTECT-V Trial Steering Committee Charter.

7.3. Independent Data Monitoring Committee (IDMC)

The DMC will comprise an unblinded independent group, as defined in the PROTECT-V Data Monitoring Committee Charter document, which will define the role of the DMC. The DMC will be responsible for the review of all safety (but not exploratory) data and will meet regularly whilst the trial is ongoing, from opening to recruitment until the final visit of the last participant.

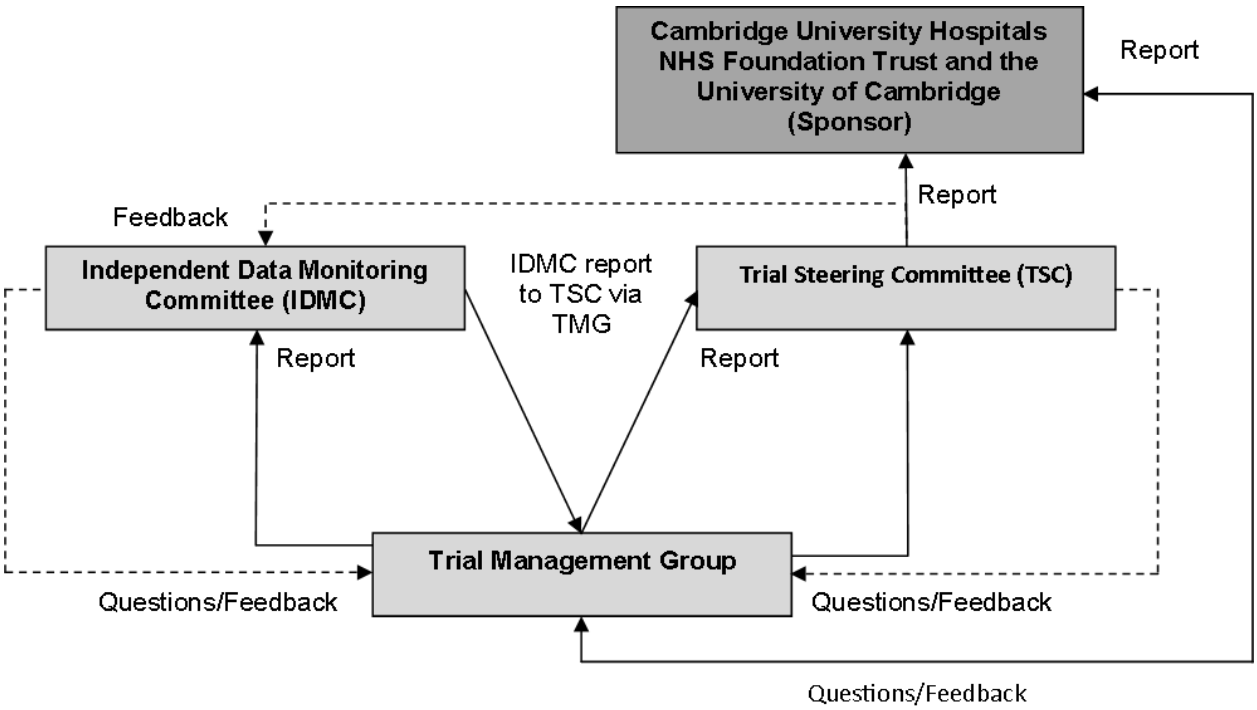

Diagram of Relationships between Trial Committees and Group

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8.DATA HANDLING AND RECORD KEEPING

All data will be transferred into an electronic Case Report Form (eCRF) which will be anonymised. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The eCRFs must be completed in a timely manner. Completeness and accuracy of the eCRF is the responsibility of the investigator. The eCRF will be accessible to trial coordinators, data managers, the Investigators, Clinical Trial Monitors, Auditors and Inspectors as required.

If 2-weekly follow-up questionnaires are completed in paper form (e.g. for in-centre dialysis patients), CRFs should be emailed to the trial coordination centre (using nhs.net email; add-tr.protect@nhs.net). Investigators must ensure that trial related documentation sent to the trial coordination centre contains no participant identifiable data. A trial specific data management plan will describe in detail the data management processes using the eCRF and the trial database.

All trial assessments, including the questionnaires and the medication diary, will be emailed securely (using nhs.net email) to the local PI to enable records to be stored at participating sites.

A copy of the data associated with a trial participant will be provided to the local PI at the end of the trial.

All data entries will be made in the eCRF. It will not be possible to edit any data fields already marked as complete. Requests for corrections or additions will need to be made using the data change request form or logging a data change request in the eCRF.

Study participants will provide explicit consent to the use of identifiable data for the purposes of the conduct of the study. The PROTECT-V trial management team will hold identifiable data on all participants including name, date of birth, gender, NHS number or equivalent, home address and postcode, telephone number and email address where applicable.

Personal identifiable data (PID) will be stored separately from anonymised study data on a secure server hosted within University of Cambridge School of Clinical Medicine Secure Data Hosting Service. PID will be accessible to the PROTECT-V trial team within the Cambridge Clinical Trials Unit, monitors, auditors and inspectors as required. It is necessary to 1) perform validation of NHS numbers and linkage to routinely collected datasets (NHS Digital, ONS), and 2) to generate datasets with participant details for mail merge creation of questionnaires, and is therefore imperative to the conduct of the study.

8.1. Source Data

To enable peer review, monitoring, audit and/or inspection, the investigator must agree to keep records of all participants (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

Source data may include but is not limited to:

- Informed Consent Form
- Relevant sections of the Case Report Form (written or electronic), as defined by the TPM
- Medical Records (written or electronic)
- On-line laboratory test results systems
- Participant Questionnaires (written or electronic)

8.2. Data Protection & Participant Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 2018 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

9. ETHICAL & REGULATORY CONSIDERATIONS

The consent information and consenting procedure is described under section 2.2, and will be approved by the REC.

9.1. Ethical committee review

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

9.2. Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments. Development Safety Update Reports (DSURs) will be submitted to the MHRA in accordance with national requirements. It is the Chief Investigator's responsibility to produce these reports as required.

9.3. Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC and/or MHRA. The only circumstance in which an amendment may be initiated prior to REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the REC and/or MHRA approval has been obtained.

9.4. Peer Review

The PROTECT-V trial protocol has been peer-reviewed by the CUH COVID-19 Trials Prioritisation Group, and independently peer reviewed by the COVID19 Research Committee of the UK Kidney Research Consortium.

9.5. Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of good clinical practice, the protocol and applicable local regulatory requirements and laws.

9.6. GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with local Trust policies.

10. SPONSORSHIP, FINANCIAL AND INSURANCE

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The study will be funded by LifeArc, Addenbrooke's Kidney Patient Association, The April Trust, Kidney Research UK. Trial medications and financial contributions are provided by UNION Therapeutics.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently. The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

11.MONITORING, AUDIT AND INSPECTION

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All participant data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

On-site or remote monitoring will be conducted for all participating sites. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the trial.

12.PROTOCOL COMPLIANCE AND BREACHES OF GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used. Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach. Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

13.PUBLICATIONS POLICY

On completion of the trial the data will be analysed and tabulated and a Final Trial Report prepared. The results of this trial may be published or presented at scientific meetings. All manuscripts or abstracts must be made available for review by Union Therapeutics before submission. This is to protect proprietary information and to provide comments.

Authorship of final trial outputs will be assigned and funding acknowledged in accordance with guidelines set out by the International Committee of Medical Journal Editors.

The statistician will also provide the Chief Investigator with the full summary of the trial results. The investigator is encouraged to share the summary results with the trial participants, as appropriate. The Trial team will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

Trial information from this protocol will be posted on publicly available clinical trial registers before enrolment of participants begins. A results summary will also be posted to publicly available clinical trial registers and a manuscript developed for publication in a peer reviewed journal after completion of the trial.

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