TRIAL TITLE

A randomised, single blinded study investigating the role of 'Sambucol® Black Elderberry (*Sambucus nigra*) in the treatment, progression and reduction of symptoms in participants with Coronavirus 19

SHORT TRIAL TITLE

BERRY

This protocol has regard for the HRA guidance and order of content

IRAS Number: 282732 **NCT:05489770**

SPONSORS Number: 2020/COVID19/11

Funders Number: N/A

PROTOCOL VERSION NUMBER AND DATE
V6.2 22.07.2021

DOCUMENT CONTROL

V1.0 24.09.2020	New Document
V2.0 10.11.2020	Amendments to text following REC Review Page 12. Section 3.1 - correction of typo Page 13. Section 6.1 -inclusion criterion changed to 'capacity to provide written or electronic consent. Page 14. Section 7 -Trial procedures Summary Table – minor amendments to 'Information about the trial', 'At swabbing station' and Randomisation and collection of trial treatment'. Follow up telephone call now within 24 hours. Reference to written consent added to follow up visits. Note 'c' removed as no longer relevant. Page 15. Sections 7.1 and 7.1.1. now include references to verbal, written and electronic consent. Page 15. Section 7.2 paragraph added for electronic consent and verbal consent. Page 18. Section 7.7. Electronic consent and written consent added to table. Page 20. Section 8.1 - details of manufacturer removed as deemed commercially sensitive. Page 26. Section 9.6 – changed to 'Participants will be asked to report any pregnancy occurring within 28 days of trial treatment'
V3.0 21.01.2021	Changes to The trial Flow Chart, Section 7 trial Procedures and section 7.1.1 Participant ID in include giving out the Participant Information Sheet at the swabbing Station
V4.0 25.01.2021	Changes to Section 7 Trial Procedures and Section 7.6 Baseline data to add the question, Have you been vaccinated against COVID-19 and if so , when?
V5.0 27.01.2021	Changes to sections Trial summary, Trial Setting, Trial procedure, Recruitment and Participant identification to allow recruitment of participants from DoH swabbing sites and patients who have hear about the trial from external sources and who contact the Research Team directly. Change to the exclusion criteria to exclude anyone already taking Sambucol or any other elderberry supplement. Removal of the phrase from section 7.3.1 No out of hours randomization will occur.

V6.0 26.02.2021	Addition of a key Protocol contributor. Clarification of time after a positive swab that a participant is eligible sections 6.1, 7, 7.11 and 7.12. Reminder to participants to stop taking study liquid- section 7 Addition of extra operational definitions for (S)AEs section 9.2
V6.1 21.07.2021	Addition of the option of delivering the liquid to participants by courier
V6.2 22.07.2021	Addition of the questions about vaccination

SPONSOR
East Kent Hospitals University NHS Foundation Trust (EKHUFT)
Site address: Trust Head Quarters
Kent and Canterbury Hospital
Ethelbert Road
Canterbury
CT1 3NG

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) 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
I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:
..../...../.....
Name (please print):
.....
Position:
.....

Chief Investigator:

Signature: Date:
..../...../.....
Name: (please print):
.....

Statistician:

Signature: .....

Name: (please print):
.....

KEY TRIAL CONTACTS

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Funder(s)	N/A
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i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
DSUR	Development Safety Update Report
EKHUFT	East Kent Hospitals University NHS Foundation Trust
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MHRA	Medicines and Healthcare Products Regulatory Agency
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

iii. TRIAL SUMMARY

Trial Title	A randomised, single blinded study investigating the role of 'Sambucol® Black Elderberry (Sambucus nigra) in the treatment, progression and reduction of symptoms in participants with Coronavirus 19	
Internal ref. no. (or short title)	BERRY	
Trial type	Food supplement trial	
Trial Design	Single Centre, placebo controlled, single blinded, two arm, randomised controlled trial.	
Trial Participants	Outpatients over the age of 18 with a positive COVID-19 swab result, after attending an East Kent Hospitals University NHS Foundation Trust site for swabbing, or a swabbing station booked through gov.uk website, or who contact the research team after seeing the approved posters or hearing about the trial through other external sources eg the media. And who have evidence of a positive test for COVID-19 within the last 5 days.	
Planned Sample Size	204	
Treatment duration	14 days	
Follow up duration	28 days	
Planned Trial Period	24 Months	
	Objectives	*Outcome Measures*
Primary Objective	Reduction in the severity of symptoms by 30% at day 10 in people who are symptomatic with the SARS-CoV-2 (COVID-19) virus treated with Sambucol vs. Placebo	Wellness VAS score
Secondary Objective	Reduction in admission to hospital by day 28. Reduction the severity of symptoms at day 3, 7, 14 and 28 days	Admissions to hospital Wellness VAS score
Treatments	Sambucol® Black Elderberry Original (Sambucus nigra) Liquid Placebo for Sambucol® Black Elderberry Original (Sambucus nigra) Liquid	
Formulation, Dose, Route of Administration	Liquid dose of 15ml orally, 4 times a day = Total 60ml per day	

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
Pharmacare Europe Ltd. Unit 3 Dialog, Fleming Way, Crawley, West Sussex, RH10 9NQ.	Non-Financial – free of charge supply of Sambucol and placebo
East Kent Hospitals University NHS Foundation Trust (EKHUFT)	Research support staff to carry out trial as non-funded.

v. ROLE OF TRIAL SPONSOR AND FUNDER

The sponsor is East Kent Hospitals University NHS Foundation Trust and will hold overall responsibility for the initiation and management of the trial.
The required product and placebo will be provided by Pharmacare Europe Ltd.
The sponsor is responsible for trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. The obligation in terms of the final decision regarding any of these aspects of the trial therefore lie with the sponsor.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES

Trial Steering Committee (TSC)

The Trial Steering committee is a multidisciplinary group consisting of a group of members who jointly have responsibility for the design, conduct and evaluation of the clinical research project who will meet every 4 months and report to the sponsor.
The role of the TSC is to provide overall supervision for a trial on behalf of the Trial Sponsor and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

Trial Management Group

The Trial Management Group will meet on a weekly basis due to the rapidly evolving nature of the COVID pandemic to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them.

The trial will be conducted in compliance with the protocol, standard operating procedures, policies, local R&D management guidance, Good Clinical Practice including the Research Governance Framework.

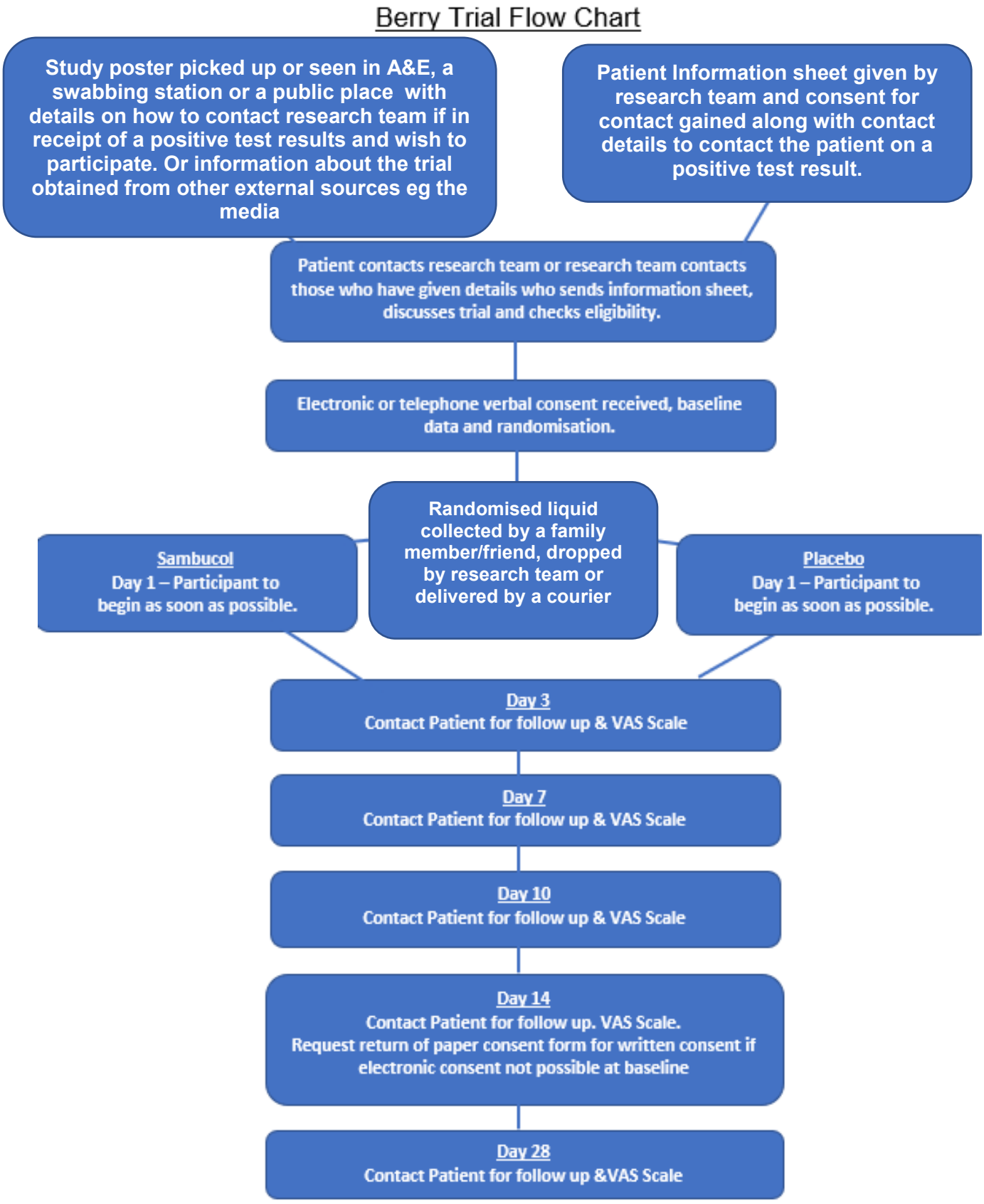
vii. PROTOCOL CONTRIBUTORS

The protocol has been compiled with the input of clinicians, a pharmacist and an independent statistician who are experienced in NHS clinical trials. Overviewed by research delivery teams to ensure practical implementation of the protocol, and reviewed by the research and innovation department to ensure compliance as sponsor. Due to COVID-19 restrictions we have been unable to involve service users in the development of this protocol. However, results will be shared amongst the patient group.

viii. KEY WORDS:

Coronavirus symptoms, COVID-19, Sambucol®, Sambucus nigra, Elderberry, SARS-CoV-2

ix. TRIAL FLOW CHART



1 BACKGROUND

The outbreak of the new coronavirus SARS-CoV-2 (COVID-19) in China has rapidly progressed to pandemic status of global importance. The current lack of a proven anti-viral that is effective has meant the current management of severe respiratory coronaviruses remains supportive. The success achieved in treating bacterial infections is not paralleled in antivirals. The relative paucity lies in a lack of drugs that stop replication within a living cell, and that the peak rate of growth may occur prior to symptoms.

A randomised controlled trial of lopinavir/ritonavir (an antiviral treatment commonly used to treat HIV) compared to standard of care in patients with severe COVID-19 demonstrated no clinical benefit and in 13.8% treatment had to be stopped early due to adverse events (1). Prophylactic use of hydroxychloroquine continues worldwide both within and outside of clinical trials but concern remains with prescribing an unproven drug with well-known adverse neurological and cardiac effects (2).

'RECOVERY' is a large UK randomised controlled trial established to test a range of potential treatments for COVID-19 in hospitalised patients, including lopinavir/ritonavir and hydroxychloroquine. Over 12,000 patients have been enrolled from 176 NHS hospitals. It showed no benefit of hydroxychloroquine nor lopinavir/ritonavir in this population, and by contrast, that low-dose dexamethasone reduces the risk of death by about one-third among patients receiving ventilation and by one-fifth in those requiring oxygen alone. However, no benefit was demonstrated amongst those not requiring respiratory support. (3)

Pharmacognosy is the study of medicines derived from natural sources. Plant extracts have been widely used to treat a number of medical conditions, with some of the best-known examples including, quinine isolated from *Cinchona pubescens* (cinchona tree) used to treat malaria, *Papaver somniferum* to make morphine and *Digitalis purpurea* for treating atrial fibrillation. A number of plant constituents have demonstrated anti-viral activity. Hippocrates, 'Father of Medicine' referred to Elderberry as 'natures medicine chest'.
In vitro *Sambucus FormosanaNakai* extract showed potent antiviral activity against human coronavirus NL63 in terms of decreased cytopathic effect and sub-G1 arrest in coronavirus infected cells. It produces a significant reduction in viral yield, plaque formation and virus attachment. The authors conclude that like *Sambucus nigra L*., *Sambucus FormosanaNakai* might possess antiviral features against the broad spectrum of human respiratory coronaviruses (4).
This supports the previously published data of *Sambucus spp*., and *Sambucus nigra L*. providing the antiviral properties against influenza A and B viruses and herpes simplex type 1 (5,6). Zakay-Rones et al 1995 demonstrated a significant improvement in symptoms in 93.3% of patients treated with standardised elderberry extract within 2 days compared to within 6 days in the control arm ($p<0.001$). Complete cure occurred in 90% of those receiving the extract in 2 to 3 days (7). In subsequent randomised double -blind studies Zakay-Rones et al demonstrated no adverse events and significant improvement in clinical symptoms and higher antibody titres in those receiving *Sambuci fructus* (8).
Chen at al 2014 demonstrated with in vitro testing of coronavirus Infectious Bronchitis Virus (IBV) with *Sambucus.nigra* a reduction in virus titres by four orders of magnitude, compromised envelopes and membrane vesicles. This virion disruption likely renders it non-infectious (9). Of further interest was that complete inhibition occurred when pre-treatment of virus in combination with post- infection treatment.

SARS-CoV-2 (COVID-19) is a readily transmissible virus that has a wide-ranging incubation period of 2-14 days (US Centers for Disease Control and Prevention). The symptoms are often non-specific and include fever, cough, fatigue, diarrhoea and loss of sense of taste and smell. Clinical features range from mild to severe. Varying transmission patterns and mild symptoms are of concern as they facilitate rapid spread. Pre-existing potential drug therapies are under investigation, and only started once the patient has symptoms, but do have well established side effect profiles. Prophylaxis and prevention are currently dependent on social distancing and isolating with vaccines remaining in development, potentially not for mass use in the near future.

Sambucus extract has well documented anti-viral properties and no known drug interactions were identified in the literature. Hence, *Sambucus* maybe well suited for limited prophylaxis or treatment of mild/ moderate COVID-19. There is clear in Vitro evidence of activity against coronavirus and in human trials of influenza. The aim of this study is to see if Sambucol® Black Elderberry Original Liquid (*Sambucus nigra*) at a dose of 15ml, 4 times a day, reduces the duration or severity of symptoms of COVID-19. Symptomatic patients presenting to drive through testing (i.e. non-hospitalised) who test positive and who consent will be randomised to placebo or Sambucol® and blinded to treatment allocation. Study staff/investigators responsible for assessing outcomes and data analysis will also be blinded to treatment allocation. Data will be collected to determine resolution of symptoms and the two groups compared.

2 RATIONALE

There is a paucity of other pre-existing drug treatments changing the outcomes/symptoms in non-hospitalised patients with COVID-19. Evidence shows that *Sambucus.Nigra* has antiviral action against coronavirus in vitro and has been successful in treating influenza viruses in vivo. It is therefore likely that *Sambucus.nigra* may be effective in the treatment of COVID-19 in terms of reducing duration of symptoms and potentially progression to more severe disease.
Sambucol® Black Elderberry Original Liquid *(Sambucus nigra)* does not require a prescription and has no known side effects, meaning it would be a well-tolerated treatment in early disease in comparison with other postulated medications. The dose and route of administration for the trial is standard. A placebo arm will be used to ensure any reported affect is due to the Sambucol® only.
Currently there is no research looking into symptoms reduction on the wider outpatient community. This trial has the potential to target the disease progression in this outpatient population and thus reduce hospitalisation of COVID-19 patients. This will also have an impact on wider health economics enabling people to return to work sooner.

Aim: To determine whether 'Sambucol® Black Elderberry Original Liquid *(Sambucus nigra)* is effective in reducing the severity of symptoms of COVID-19.

2.1 Assessment and management of risk

We anticipate this to be low risk trial given that Sambucol® Black Elderberry Original Liquid *(Sambucus nigra)* has never had reported adverse events/effects since commencing manufacture in 1991.
A thorough literature review has demonstrated there are no recorded side effects or drug interactions. Due to this it is classified as a food supplement and can be purchased freely without consultation or prescription, in food health shops and supermarkets, without limitation.
Vomiting and diarrhoea has been reported with the consumption of large volumes of raw and unripe fruit.
As with any product there is a potential allergy to the ingredients, hence those with known allergy will be excluded. As with all medicines, patients will be advised to seek urgent medical help if there are any signs of a severe allergy (i.e. difficulty breathing, swelling face/lips/ tongue).
With limited data on the effect in pregnancy and breast feeding this patient group has been excluded.
Poorly controlled diabetics will be excluded due to the high sugar content.
The dose used is constant with no increments.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

Hypothesis - Sambucol reduces the severity of symptoms by at least 30% by day 10 in people who are symptomatic with the SARS-CoV-2 (COVID-19) virus, compared to placebo.

To determine whether Sambucol reduces the severity of symptoms by 30% by day 10 in people who are symptomatic with the SARS-CoV-2 (COVID-19) virus, as determined by VAS score.

3.2 Secondary objectives

To determine whether Sambucol reduces hospital admissions by day 28.
To determine if Sambucol reduces the severity of symptoms at day 3, 7, 14 and 28 days

3.3 Outcome measures

Reduction on symptom severity as per Wellness VAS Score
Reduction in hospital admission as per participant hospital admission rates

3.4 Primary endpoint

Primary endpoint will be the difference in number of patients by day 10 who have an improvement in reported SARS-CoV-2 (COVID-19) symptoms as per wellness VAS scale.

3.5 Secondary endpoints

Reduction in hospital admissions by day 28 as measured by rates of hospital admission
Reduction in the severity of symptoms at day 3, 7, 14 and 28 days as measured by wellness VAS Scale.
Reduction in the number of patients with mild/moderate disease progressing to severe disease (ITU /HDU admission)

3.6 Exploratory endpoints - N/A

3.7 Table of objectives and outcome measures

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective Does Sambucol reduce the severity of symptoms by 30% at day 10 in people who are symptomatic with the SARS-CoV-2 (COVID-19) virus?	Patient Wellness VAS score	Day 10 score
Secondary Objectives Reduction in admission to hospital by day 28. Reduction in the severity of symptoms at day 3, 7, 14 and 28 days To determine of those admitted to hospital the number of patients with mild/moderate disease progressing to severe disease (ITU /HDU admission)	Admissions to hospital Wellness VAS score Number admitted to HDU/ITU	Within 28 days of enrolment Day 3,7, 14 and 28 Day 28 data

4 TRIAL DESIGN

This study is a superiority test of Sambucol to placebo in the treatment of COVID 19 positive patients, with a parallel design.
Single Centre, placebo controlled, single blinded, two arm, randomised controlled trial.

5 TRIAL SETTING

This trial will run as a single centre trial at East Kent Hospitals University Foundation Trust. Secondary care patients will be highlighted from the positive COVID 19 swab lists. These lists include all patients attending swabbing centres or accident and emergency departments in the trust, but who are not admitted. Eligibility, consent and randomisation will be completed by GCP trained research nurses and doctors
: Participants will also be identified at local swabbing sites. Members of the Research Team will be there to approach and discuss the trial with people attending for swabbing.

Participants may also contact the research team after seeing the approved posters or hearing about the trial through other external sources eg the media.

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6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Aged over 18 years
- Symptomatic SARS-CoV2 infection
- Positive SARS-CoV2 swab test result within the last 5 days
- Capacity to provide written or electronic informed consent
- Able to complete follow up visits required via phone/email
- Able to provide a positive swab result

6.2 Exclusion criteria

- Known allergy to Sambucus fructi (Elderberries) or food colourants
- Pregnant or breast feeding
- Poorly controlled diabetes
- Treatment with any immunosuppressive medicines including Prednisolone 10mg daily or equivalent. Oral anti-inflammatory medicines such as Ibuprofen are allowed.
- Participation in any COVID 19 research study involving prophylactic or therapeutic IMPs in the last 30 days.
- Previous participation in this trial.
- Already taking Sambucol or any form of elderberry supplement

7 TRIAL PROCEDURES

	Research team activities
Information about the trial	The approved study posters will be available in A&E and at swabbing stations, to inform patients about the availability of the trial for those who test positive. Participant can express interest in participating when swabbed and details for contact can be taken by the research team, or patients can email the research team later to express interest. Participants may hear about the trial through other external sources eg the approved posters or the media and may contact the research team.
At swabbing station	Patients will be approached by a member of the research team at the swabbing station and asked if they have symptoms. If they do, they will be asked if they have time to talk and the research team member will explain about the study and ask if the patient is interested in taking away any further information about the study. If they say yes, they will be given the Patient Information Sheet. The research team member will ask if they are happy to provide their contact details so that they can be contacted after they receive their test result.
Patients contacting the Research Team Directly	Patients who have heard about the trial through the media or by seeing one of the approved posters may contact the Research Team directly. If they are able to show the positive swab test result that they have had a within the last 5 days, the research team will email them the Patient Information Sheet. The research team will then contact them as below
Telephone Contact	Patients who have given their contact details at a swabbing station or A&E will be telephoned after 24hours to see if they have tested positive for COVID-19, and if they have they are asked if they are interested in taking part in the study. The member of the research team will then check whether they have read the Patient Information Sheet and answer any questions.
Patient Information Sheet (PIS)	PIS will be emailed to patients who test positive and express interest in the study, for them to read and consider taking part.
Follow up telephone call within 5 days of a positive swab; Verbal Consent and Baseline data collection	Opportunity to raise and discuss any questions about the trial or PIS[(a)]. Eligibility criteria will be checked and electronic or verbal consent will be received. An eligible patient can decline to participate without having to give any reason. After consent, the research team will collect baseline demographics, VAS score, patient symptoms. [(a)]
Ineligible patients	If anyone does not meet the eligibility criteria the research team will explain why and ensure that they have time to ask any questions.
Randomisation and collection of trial treatment	Patients will be randomised to active or placebo liquid and a 14 day supply of study liquid dispensed to take home and start straight away. This can either be collected by a family member or friend and dropped to the patient's doorstep – or the research team will drop to the doorstep so that everyone has a chance to take part. If a participant lives further away the liquid will be delivered to their home address by courier.
Follow Up visits on day 3, 7, 10, 14 and 28	All follow up visits will occur either by phone, text or email depending on participant preference at day to collect the following data: • Current symptoms

	• How well are you feeling VAS score 0 -100 (0 will be recorded in the case of death) • What are your current symptoms? • Have you started any new medications? • Have you missed any doses of your study liquid? • Experienced any adverse events? • At day 14 – if a participant verbally consented initially, they will be asked to sign a paper consent form which was sent out with their trial liquid and return it in the research team for filing. At day 14 they will also be reminded that they need to stop taking their study liquid.
Notes	(a) This limits the exposure of the research team to the virus during later collection of written consent

7.1 Recruitment

Once patients notify the research team that they are happy to be contacted after a positive swab, the research team will then call the patients at home to see if they are still interested in taking part and send out the information sheet via email if they did not receive it at the swabbing station. If the patient does not have an email address they can arrange collection of the information sheet from site or it can be read out over the phone to them. Once they have had time to consider all the information and wish to take part, the research team will check all inclusion / exclusion criteria and eligibility. If they are not eligible the research team will explain why and ensure they have time to ask any relevant question they may have. If patients are eligible but decline they can do so without any reason.

For eligible patients wishing to take part, a link for an electronic consent form will be sent via email for e-signing. If this is not possible for any reason, then verbal consent will be taken over the telephone with the patients and two members of the research team. This will be recorded on a telephone consent form which will be read fully by the research team to the patients before consent is received. A copy of the telephone consent form will be sent to the patient's home with their randomised trial liquid. Enclosed will also be a blank copy of the full written consent form to send back via free post envelope supplied.

After consent research team will collect basic demographics, baseline VAS scores and check the patient's symptoms.

Eligible patients will be randomised 1:1, with no stratification, to either active treatment or placebo using REDCap software and be provided with the relevant bottles at full dosage, for 14 days. Dosage instructions will be provided on the labelling and will be discussed by the research team over the telephone prior to randomisation. Participants will have a contact number to contact the research team if they need to ask questions at any time.

7.1.1 Participant identification

Study posters will be left in A&E telling patients how they can take part if they receive a positive swab result. Patients will also be approached at the hospital swabbing tent if symptomatic on presentation for swabbing. Outpatient nurses carrying out the swabbing clinics will notify the research team of the time slots of any patient who might be eligible from their daily lists. No further details will be passed to researchers other than this.

A member of the research team will explain the study and ask if they would be happy to be contacted in the event that their swab comes back positive. If so, they will give the patient the Patient Information Sheet and will ask for their details to contact them after the swab result is returned.

Alternatively, patients can contact the research team later using the details on the poster, available at the swabbing station, in the event of a positive swab within the last 5 days.

At a non-EKHUFT swabbing site, patients will be approached by a member of the research team who will explain the study and ask if they would be happy to be contacted in the event that their swab comes back positive. If so, they will also give the patient the Patient Information sheet and ask for their details to contact them after the swab result is returned.

Alternatively, in the event of a positive swab, patients can contact the research team using the details on the poster displayed at the swabbing station.

Patients who have heard about the trial through the media or by seeing one of the approved posters may contact the Research Team directly. If they are able to show the positive swab test result that they have had a within the last 5 days, the research team will email them the Patient Information Sheet.

7.1.2 Screening

The only diagnostic test required will be the positive COVID result, which has already been taken. Proof of positive swab result will be requested at eligibility check. No other screening tests required.

7.1.3 Payment

There will be no payment for taking part in this trial.

7.2 Consent

For eligible patients wishing to take part, a link for an electronic consent form will be sent via email for e-signing. If this is not possible for any reason, then verbal consent will be taken over the telephone with the patients and two members of the research team. This will be recorded on a telephone consent form which will be read fully by the research team to the patients before consent is received. A copy of the telephone consent form will be sent to the patient's home with their randomised trial liquid.

Consent will be obtained by GCP trained research team members delegated the task by the PI. No trial procedures will occur before consent.

The Chief Investigator (CI) retains overall responsibility for the conduct of research at the site.
The taking of consent will be delegated to research staff and doctors who have been duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. A delegation log will be completed, checked and signed by the CI.
Only participants over the age of 18 years and capable of informed consent will be recruited.
Informed consent will be obtained prior to the participant being randomised and receiving Sambucol or placebo.
The right of a participant to refuse participation without giving reasons will be respected.

The participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing any further treatment and must be provided with a contact point where they may obtain further information about the trial. Data collected up to the point of withdrawal will only be used after withdrawal if the participant has consented for this on withdrawal. If a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.
The CI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence

7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

No ancillary studies, no biological specimens collected.

7.3 The randomisation scheme

The method of randomisation

- Simple randomisation with a 1:1 allocation ratio with no stratification.
- Using REDCap software https://www.project-redcap.org/

7.3.1 Method of implementing the randomisation/allocation sequence

- Following consent, randomisation will be via REDCap using a randomisation list generated by the study statistician and uploaded onto REDCap.
- Team members are provided with login details and randomise patients by simply completing an on-screen form with patient details, inclusion and exclusion criteria. Treatment allocation is immediately available.

  Investigators can view the details of patients they have previously randomised.

7.4 Blinding

The placebo has comparable appearance and taste to Sambucol® Black Elderberry Original Liquid.

Trial participants, trial statistician and outcome assessors will be blinded to which arm the participant has been randomised. Investigators, the research delivery team, clinical trial pharmacist and study staff not involved in assessing outcomes will not be blinded. All research delivery team members will be aware that they are not to divulge the randomised arm to participants at any time point.

Participants will remain blind to their allocated trial arm for the duration of the trial.

7.5 Emergency Unblinding

In case of serious adverse event, when deemed necessary by the investigator or treating health care professional, unblinding may be requested. A designated number will be provided on hospital systems and to patients in case unblinding needs to be performed by the research team. The CI will be contactable by the research team if necessary. It is thought unlikely unblinding will need to occur unless a new allergic reaction occurs to the food colouring in the liquid.

Documentation of the unblinding process including the reason and person who performed the unblinding, will be recorded in the site file. Thereby retaining the blinding of the outcome assessors.

An alert will be placed on the patient administration system (PAS) for the trust to advise clinicians that the participant is on the BERRY trial including contact details of who to contact for unblinding in an emergency. An assessment to unblind should be made in consultation with the clinical and research teams. If the decision is made to unblind the participants randomisation to the health professional, it will be expressed that the participant should not be given this information and that it should be shared only on a need to know basis. The medical team will be advised to document the act of unblinding in the patient notes, but not the randomised arm unless this is deemed essential for the participants ongoing care. This will maintain overall blinding in the trial. The treating health care professional will continue to deal with the participant's medical emergency as appropriate.

In all cases the Investigator will evaluate the causality and expectedness of SAEs as though the participant was receiving the active medication.

Unblinding and the reasons for doing so will be recorded on the CRF/data collection tool, in the site file and medical notes. It will also be documented at the end of the trial in any final trial report and/or statistical report

The CI/Investigating team will notify the Sponsor in writing as soon as possible following the unblinding and CI/PI will also notify the relevant authorities.

SUSARs are required to be reported unblinded.

7.6 Baseline data

- Patient details (e.g. name, NHS number, date of birth, sex)
- COVID-19 symptom onset date
- COVID-19 severity (appendix 2)
- Date positive SARs-CoV2 test
- Major comorbidity/ Medical History (e.g. heart disease, diabetes, chronic lung disease)
- Regular medications
- Duration symptoms and type of symptoms
- Wellbeing VAS Score
- Demographics
- Smoking Status
- Vaccinated against COVID-19? Dates? And which vaccine?

7.7 Trial assessments

Trial Visit Schedule								
	Screening	Day 1	Day 3 (+/-1)	Day 7 (+/-1)	Day 10 (+/-1)	Day 14 (+/-1)	Day 28 (+/-1)	Early Exit
Verbal Consent	X							
Eligibility	X							
Inclusion/Exclusion	X							
Demographics	X							
Medical History	X							
Duration of Symptoms	X							
Symptom Check	X	X	X	X	X	X	X	X
Comorbidities	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Smoking Status	X							
Electronic Consent (telephone consent if electronic not possible)		X						
Written Consent (if electronic consent not possible)						X		
Randomisation		X						
Dispense Trial Liquid		X						
Adverse Events			X	X	X	X	X	X
Telephone/Emails Visit			X	X	X	X	X	X
Trial Liquid Compliance			X	X	X	X	X	X
Wellbeing VAS Score		X	X	X	X	X	X	X

7.8 Long term follow-up assessments

With the exception of any pregnancy outcomes, Data collection will end at day 28 following randomisation. Research team will follow up the outcomes of any notified pregnancies.

This will be to check to see if patients have been admitted to hospital in the 28 days following a positive SARS-CoV2 test.

If admitted:

- Date of hospitalisation

Admission hospital and location (i.e. HDU/ITU) – reason and outcome. Date discharge / death

7.9 Qualitative assessments

N/A

7.10 Withdrawal criteria

Subject withdrawal criteria

- Patient choice (no justification required)
- Responsible physician choice - medical reasons (i.e. individual adverse events or new information gained about a treatment).

Patients may withdraw their consent to participate in the trial at any time without reason. No further trial procedures will be undertaken and no data or samples will be collected from the time of withdrawal.
However, data 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).

Circumstances where the trial may be prematurely stopped include:

- Failure to recruit participants at the required rate to meet target.
- Publication of trial results for an alternative to Sambucol which shows dramatic improvement in symptoms when given pre-admission.
- Identification of a serious safety issue
- Sponsors request

7.11 Storage and analysis of clinical samples

Not applicable – No clinical or biological samples.

7.12 End of trial

The trial end date - 01/11/2022

Last patient last visit date – 01/10/2022

8 TRIAL TREATMENTS

8.1 Name and description of treatments

Sambucol® Black Elderberry Original (Sambucus nigra) Liquid
Constituents: 29.4 % (w/w) Black Elderberry (Sambucus nigra) fruit juice, 70% (w/w) of glucose syrup. The main ingredient is black elderberry juice and it meets the requirements of the Directive

2012/12/EU relating to fruit juices. The product also contains two food additives: citric acid (E330) as acidity regulator and potassium sorbate (E202) as preservative.
Primary packaging: Plastic PET amber bottles 120ml. Caps are PP28 white tamper-proof caps with security seal.
Secondary Packaging: None. Outer Carton: Cardboard 376mm x 191mm x 116mm. 32 bottles per case.

Placebo for Sambucol® Black Elderberry Original (Sambucus nigra)120ml
Constituents: 70% (w/w) of glucose syrup, Flavouring agent: Elderberry Blossom. Colourants: Eurocert Carmoisine (311804) (E-122) and Eurocert Brilliant Black PN (419358) E-151. The product also contains two food additives: citric acid (E330) as acidity regulator and potassium sorbate (E202) as preservative.
Primary packaging: Plastic PET amber bottles 120ml. Caps are PP28 white tamper-proof caps with security seal.
Secondary Packaging: None. Outer Carton: Cardboard 376mm x 191mm x 116mm. 32 bottles per case.

8.2 Regulatory status of the treatment
Sambucol Liquid is marketed within the EU and other countries as a food supplement.

8.3 Product Characteristics
Sambucol® Black Elderberry Original (Sambucus nigra) Liquid has been used as a supplement since 1991 with no reports of adverse effects received by the Manufacturer.

8.4 Treatment storage and supply

8.4.1 Storage: Sambucol/placebo will be stored at ambient temperature, below 25^{o}C there are no temperature monitoring requirements needed.

8.4.2 Shipment: Treatments will be supplied Free of Charge by Pharmacare (Europe) Limited.

8.4.3 Ordering and Re-Ordering: Initial shipment will be shipped to site following site activation. Further supplies – logistics as agreed between site and Pharmacare.

8.4.4 Receipt: Shipments will be received by Pharmacy Clinical Trial Staff and inspected for any damage or defects. In the event of product defect or damage contact Technical@pharmacareeurope.com and cc. Noelia.rodrigo@pharmacareurope.com

8.4.5 Accountability: Pharmacy will keep an inventory log for stock received**.** The Batch number will be recorded in the CRF of product issued to each participant. No other accountability records will be kept.

8.4.6 Dispensing: On confirmation of eligibility, e consent and randomisation will occur. Patients will be randomised to active or placebo liquid and a 14 day supply of study liquid dispensed The Research Nurse will write the Patient's Trial ID No. on the label and record the Batch number in the patient's record The liquid can either be collected by a family member or friend and dropped to the patient's doorstep – or the research team will drop to the doorstep so that everyone has a chance to take part. If a participant lives further away the liquid will be delivered to their home address by courier

8.4.7 Recall Procedure: In the event of a product defect participants will be telephoned and asked to stop taking the product and either to destroy as for household waste or to return any unused product

to site according to the seriousness of the defect. Further investigation will be by Pharmacare's Recall Procedure, as appropriate.

8.4.8 Post-trial access to Sambucol Liquid: Various Sambucol® products are readily available to purchase from Health Food stores, Pharmacies and various on-line retailers. Sambucol will not be supplied to participants after the end of the trial.

Blinding: Active Sambucol and Placebo will be packaged and labelled as THE BERRY TRIAL LIQUID. The active and placebo packs will be differentiated by – Q and Z respectively appended to the Batch Number. Packs will be received and stored by unblinded Pharmacy Staff and personnel distributing treatments to participants will also be unblinded.

8.5 Preparation and labelling of Treatments

Active Sambucol and placebo will be packaged and labelled as 'THE BERRY TRIAL LIQUID' and supplied by the Manufacturer details of dosage and storage conditions, Batch Number and expiry date; PI Name; Trial name; space for Pt Trial ID no and 'For Clinical trial Use only' as shown in Appendix 1.
Sponsor Name, address and contact telephone number will be provided on the Patient Information Leaflet.

8.6 Dosage schedules

All participants will take a fixed dosage of 15ml orally four times a day. Total daily dose 60ml. Missed doses can be taken at any time. If the patient vomits shortly after taking a dose they can repeat the dose.

8.7 Dosage modifications

There are no dose modifications. If a participant feels unwell after taking a dose they should contact the Research Nurse to discuss whether they should continue or stop treatment and withdraw from the trial. Research Nurse will seek advice from the Chief Investigator.

8.8 Known drug reactions and interaction with other therapies

There are no known drug interactions or adverse effects of Sambucol Original Liquid®. Due to the high sugar content of the liquid participants with unstable diabetes are excluded from the trial.

8.9 Concomitant medication

A record of all concomitant medication will be recorded in the CRF by the Research Nurse during the consent process. If the participant is admitted to Hospital they will be instructed to continue trial treatment to complete the 14 day course.

8.10 Trial restrictions

- No contraindications whilst on the active phase of the trial including dietary requirements/restrictions
- Due to lack of clinical data available on the use of Sambucol during pregnancy, contraception needs to be used for the 14 days duration for use and for 7 days after completion. This includes:
    - Intrauterine Device (IUD)
    - Hormonal based contraception (pill, contraceptive injection etc.)
    - Double Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
    - True abstinence

8.11 Assessment of compliance with treatment

Participants will be asked to confirm their compliance during planned telephone interviews with research staff on days 3,7,10 and 14.

9 PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information:

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.

9.2 Operational definitions for (S)AEs

The following adverse events are known manifestations of COVID-19 related disease. They will not be recorded in the medical notes as (S)AEs as part of this COVID-19 intervention trial.

- Chills
- Loss of taste and/or smell
- Cough
- Bloody sputum
- Sore throat
- Nasal symptoms: blocked or runny nose
- Ear pain
- Wheezing
- Chest tightness
- Shortness of breath
- Muscle aches
- Joint pain /heaviness
- Fatigue
- Headache
- Confusion
- Loss of appetite
- Abdominal pain
- Nausea/vomiting
- Diarrhoea
- Sore, red, gritty eyes
- Skin rash / irritation
- Dry/Sore lips
- Mouth Ulcers
- High Temperature

Evaluation of adverse events

The Sponsor expects that adverse events (apart from expected AEs) are recorded in the medical notes 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).

Assessment of seriousness

Seriousness is assessed against the criteria in section 9.1. This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be trial drug related
Definitely, Probable and Possible causalities are considered to be trial drug related

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the CRF as specified in section 9.1 and 9.2

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 subject is unable to carry out usual activities and / or the participant's life is at risk from the event.
Admissions to hospital for COVID-19 disease progression will not be reported as an SAE for the purpose of this trial as this is listed as a trial endpoint.
There are no reported risks of taking Sambucol® Original Liquid. Any adverse reaction or adverse event reported during the trial will be assessed for causality by the Investigator and appropriate reporting undertaken where necessary.

9.3 Recording and reporting of SAEs, SARs AND SUSARs

All **SAEs** occurring from the time of start of trial treatment until 14 days post cessation of trial treatment must be recorded on the Trial data collection form and scanned and emailed to the Sponsor **within 24 hours** of the research staff becoming aware of the event. The original form will be copied and held by the Sponsor.
The Chief Investigator is responsible for ensuring that the assessment of all SAEs for relatedness and expectedness is completed and the onward notification of all SARs to the Sponsor immediately or not more than 24 hours of first notification. The sponsor has to keep detailed records of all SARs reported to them by the trial team.
All SAEs/SARs may be reported by the trial team to Pharmacare UK.
Adverse Reactions will be reported to the REC if they could:

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

For each **SAEs** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered anticipated.

Events will be followed up until the event has resolved or a final outcome has been reached."

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the REC. The sponsor will inform the REC and Manufacturer of SUSARs within the required expedited reporting timescales."

9.4 Responsibilities

Principal Investigator (PI):
Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.
2. Using medical judgement in assigning seriousness and causality and providing an opinion on whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.
3. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning whether and event/reaction was anticipated or expectedness in line with the Reference Safety Information [in Phase I and early Phase II CTIMPs].
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
7. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor: (NB where relevant these can be delegated to CI)

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committee identified for the trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. The unblinding of a participant for the purpose of expedited SUSAR reporting [For double blind trials only].
7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the REC.

Trial Steering Committee (TSC):
In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data.

9.5 Notification of deaths

The procedure for notification of death which does not constitute a SAR or SUSAR will be notification to sponsor by the chief investigator of only deaths that are assessed to be caused by the treatment will be reported to the sponsor. This report will be immediate.

9.6 Pregnancy Reporting Participants will be asked to report any pregnancy occurring within 28 days of trial enrolment. GPs will be asked for their assistance in relaying information regarding any pregnancies to the trial team. Any such pregnancies must be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form. 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.

9.7 Overdose

Participants will be advised in the PIS to contact the research team on for advice if they believe they have taken too much Sambucol/Placebo or an overdose. Participants will also be asked about their compliance with the recommended dosage during telephone consultations with the Research Staff.
Emergency contact for 24hr
Overdose definition: More than 50 % excess dosage (> 90ml) in any 24 hour period. Identified during participant consultations. In the event of a confirmed overdose the participant will be withdrawn from the trial.
Any overdose event will be recorded as a protocol deviation and reported to the Sponsor.

9.8 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the circumstances giving rise to those measures.

9.9 The type and duration of the follow-up of participants after adverse reactions.

Adverse reactions are extremely unlikely, however, after clinical assessment by the Investigator follow up will be advised accordingly as either no follow-up required, follow-up via patient's GP or via a Hospital appointment.
Any SUSAR will be reported to the Sponsor irrespective of how long after treatment administration the reaction has occurred until resolved.

9.10 Development safety update reports (DSURs)

The CI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or as necessary, to the Research Ethics Committee and the sponsor.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The sample size was based on detecting a difference in the primary outcome, VAS symptoms score at 10 days, between groups. The standard deviation of the outcome is estimated to be 20 units, and a difference between groups of 10 units is regarded as being of clinical importance. With a 5%

significance level and 90% power, it is calculated that 86 patients per group, 172 in total, are required. To allow for a 15% dropout, it is proposed that 204 patients are recruited into the study.

10.2 Planned recruitment rate
204 participants over 24 months

10.3 Statistical analysis plan
A full Statistical Analysis Plan (SAP) will be developed and agreed in advance of any data analysis.

10.3.1 Summary of baseline data and flow of patients
Summary statistics of all patient demographics and baseline data will be produced for each of the two study groups separately. Categorical variables will be summarised by the number and percentage of patients in each category. Continuous variables will be summarised by the mean and standard deviation if found to follow a Normal distribution, and the median and inter-quartile range otherwise.

The flow of patients through the trial will be illustrated by a Consort diagram.

10.3.2 Primary outcome analysis
The primary outcome, VAS symptoms score at 10 days, will be analysed using Analysis of Covariance (ANCOVA). The scores at 10 days will be used as the outcome variable, with the symptom scores at baseline included as a covariate.

The primary analysis will be performed on an Intention to Treat (ITT) basis. Participants will be analysed in the arm to which they were randomised, irrespective of whether they received their allocated treatment.

If the population varies for the ITT analysis, a per protocol analysis will be performed, as a sensitivity analysis.

10.3.3 Secondary outcome analysis
Secondary outcomes with a baseline measurement at baseline will be analysed using equivalent methods to the primary outcome. Secondary endpoints measured on a categorical scale will be compared between groups using the Chi-square test.

10.4 Subgroup analyses
None planned.

10.5 Adjusted analysis
No adjustments for baseline or demographic factors are planned

10.6 Interim analysis and criteria for the premature termination of the trial
No interim analyses will be performed. See 7.10 for stopping criteria.

10.7 Participant population
The primary analyses for all analysis (primary, secondary, safety) will be done on an ITT basis, with patients included in the groups to which they were randomised, irrespective of whether they received their allocated treatment.

10.8 Procedure(s) to account for missing or spurious data
Spurious data will be identified and checked with original source documentation. If found to still be spurious, based on clinical values may be excluded from the analysis. Any omissions will be noted and justified.

Patients with missing data for any given variable will be omitted from the analysis. No imputations of missing data will be performed.

10.9 Other statistical considerations

None noted

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

CRF

All data will be transferred into a Case Report Form (CRF) which will be labelled using a participant's unique trial ID. All trial data in the CRF must be extracted from and be consistent with, the relevant source documents. The CRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the CRF pages. The CRF will be accessible to trial coordinators, data managers, the investigators, Clinical Trial Monitors, Auditors and Inspectors as required.
The institution will keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

All CRF pages must be clear, legible and completed in ink. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialled by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used.
The CRF contains the validated VAS scoring system and will be used to record patient wellness.

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

Source data may include but is not limited to:
- Signed informed consent forms
- Patient medical records (electronic or paper)
- Clinical research forms/folders

11.2 Data handling and record keeping - Data Protection & Participant Confidentiality

Paper CRFs will be kept in a securely locked room with restricted access. Data will be uploaded to the REDCap database for analysis. Access is password -protected. All patient data will be collected and stored in accordance with the Data Protection Act 1998 and the General Data Protection Regulation.

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

11.4 Archiving

- archiving will be authorised by the Sponsor following submission of the end of trial report
- if the sponsor and trial site are the same, archiving will occur as per standard procedure.
- the location and duration of record retention for:

- essential documents 5 years
- the trial database 10 years

- destruction of essential documents will require authorisation from the Sponsor

- If a study participant becomes an inpatient, their medical records are source data and must be retained for the same retention period as the essential documents.
- If a study participant becomes an inpatient, their medical records should be clearly marked that the patient has taken part in a clinical trial and they should not be destroyed (this should apply to all volumes of patient's medical records)
- The label must clearly state the retention period
- The hospital notes of patients will not be archived with the TSF, as they may still be important for any on-going medical care. Only certified copies of the patient notes that are directly relevant to the study can be archived with the TSF, if necessary.

12 MONITORING, AUDIT & INSPECTION

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG), TSC and CI based on the trial risk assessment. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. This will be dependent on a documented risk assessment of the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

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

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review& reports

- Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial.
- All correspondence with the REC will be retained in the Trial Master File/Investigator Site File
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended

- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the trial
- If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination
- Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC

13.2 Peer review

No external Peer Review has been undertaken.

13.3 Public and Patient Involvement

Patients have not been involved in the formulation of the study due to constraints of time. Dissemination of results will be publicised for patients to review.

13.4 Regulatory Compliance

- The trial will not commence until Favourable REC and HRA approval is received.
- For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

13.5 Protocol compliance

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 will 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 repeatedly will not be accepted and will require immediate action and could potentially be classified as a serious breach.

13.6 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial
(c) the conditions and principles of GCP in connection with that trial; or the protocol relating to that trial, as amended from time to time.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.
The sponsor of a clinical trial will notify the competent authority in writing of any serious breach of the protocol within 7 days of becoming aware of that breach.

13.7 Data protection and patient confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the General Data Protection Regulation 2018, Data Protection Act 2018 and Trust Policy with regards to

the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act’s core principles.
There will be no transfer of data between organisations as all recruitment will be undertaken at one Trust.

Data will be stored for 5 years in a secured locked room which can only be accessed by the minimum number of required people, to include the Trial team and those undertaking quality control, audit and analysis.

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

There are no ownership interests from any member of the current research team that are related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial.
There are no commercial ties to the research team.
There are no non-commercial potential conflicts relating to the current research team.
When new members of the research team join they will be asked to declare if any competing interest/conflict of interest through the signing of such a form which will be stored in the Investigator Site File.

13.9 Indemnity

East Kent Hospitals University NHS Foundation Trust is an NHS body and is therefore legally liable for the negligent acts and omissions of their employees under the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG 96/48. Anyone harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.
Non-negligent harm is not covered by the NHS indemnity scheme. East Kent Hospitals University NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

13.10 Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the HRA and REC.

The only circumstance in which an amendment may be initiated prior to HRA and REC 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 HRA and REC has been obtained.

13.11 Post trial care

There will be no post trial care. However, all SAEs/AEs will be followed up until resolved or if they are not going to be resolved, monitoring will end at 3 months post the 28 day end of study date and reported accordingly.

13.12 Access to the final trial dataset

The final data set will be accessible to the Chief Investigator, TSC and statistician.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

Ownership of the data arising from this trial resides with the trial team and the sponsor. On completion of the trial the data will be analysed and tabulated and a Final Trial Report prepared. However, given the nature of this international pandemic, preliminary data may be reported prior to the completion the

study, or if interim analyses are adequate for dissemination of critical safety or efficacy data. The sponsor will provide, if practicable, advanced notice of any publications to Pharmacare Europe Ltd. At conclusion of the study a fully anonymised dataset will be placed in the public domain. Data sharing within a federated consortium of UK investigators across the four nations will be adopted.

14.2 Authorship eligibility guidelines and any intended use of professional writers

Final authorship of the final trial report will be authorised by the Chief Investigator.

Anyone listed as an author will approve the final version of the paper and accept responsibility for ensuring that he/ she is familiar with its contents and can identify his/her contribution to it.

The study will be written up by the trial group, professional medical writers will not be hired.

15 REFERENCES

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3) RECOVERY Trial news https://www.recoverytrial.net/news accessed 21.57 on 28.07.2020.

4) Antiviral activity of Sambucus FormosanaNakai ethanol extract and related phenolic acid constituents against human coronavirus NL63. Weng J, Lin C, Lai H et al Virus Res. 2019 Nov;273 197767

5) Inhibitory activity of a standardized elderberry liquid extract against clinically-relevant human respiratory bacterial pathogens and influenza A and B viruses. Krawitz C, Mraheil M, Imirzalioglu C et al. BMC Complement Altern Med. 2011;11:16

6) Antiviral activity of the infusion (SHS-174) from flowers of *Sambucus Nigra L*., aerial parts of *Hypericum Perforatum L.,* and roots of *Saponaria Officinalis L*. Against influenza and herpes simplex viruses. Serkedijeva J, Manolova N, Zgorniak-Nowosielska I et al.Phytother. Res.4, 97-100.

7) Inhibition of several strains of influenza virus *in Vitro* and reduction of symptoms by an Elderberry extract (*Sambucus nigra L*) during an outbreak of Influenza B Panama. Zakay-Rones Z, Varsano N, Zlotnik M et al. J Altern. Complement. Med. 1(4),361-369.

8) Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. Zakay-Rones Z, Thom E, Wollan T et al. J Int Med Res 2004;32:132-40

9) Sambucus nigra extracts inhibit infectious bronchitis virus at an early point during replication. Chen C, Zuckerman D, Brantley S et al. BMC veterinary research; Jan 2014;10:24.

16 APPENDIX 1. Manufacturer's Labels.

Sambucol (Active) BN: 104170Q

THE BERRY TRIAL LIQUID
Directions: 15ml (3 teaspoons) four times daily
Store in a dry place below 25°C
Investigator: Ms J. Evans Trial ID No: ……
Batch No:104170 Q
Best Before End: 05/2023
BERRY TRIAL
For Clinical Trial Use Only

Placebo BN:104170Z

THE BERRY TRIAL LIQUID
Directions: 15ml (3 teaspoons) four times daily
Store in a dry place below 25°C
Investigator: Ms J. Evans Trial ID No: ……
Batch No:104170 Z
Best Before End: 01/2023
BERRY TRIAL
For Clinical Trial Use Only

Appendix 2:

Classification of COVID19 severity

Severity	Symptoms/ signs
MILD	Patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnoea, nasal congestion, or headache. Rarely, patients may also present with diarrhoea, nausea and vomiting. The elderly and immunosuppressed may present with atypical symptoms. Adult with pneumonia but no signs of severe pneumonia and no need for supplemental oxygen.
MODERATE	Fever or suspected respiratory infection, plus one of: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 ≤ 93% on room air. Includes those managed on ward requiring oxygen support via nasal specs or mask
SEVERE/ CRITICAL	Patient requiring HDU/ITU support. Invasive ventilation. Acute Respiratory Distress Syndrome. Sepsis- life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Septic shock defined as persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L