सी एस आई आर–भारतीय समवेत औषध संस्थान
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद्)
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File no. 12(288)/2020-P

Dated: 29.05.2020

This is in continuation of our tender inquiry no. 12(288)/2020-P dt 26.05.2020. On the request of various parties during pre-bid conference/ meeting, we are hereby uploading flowchart/executive summary of the project .

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RESTRICTED CIRCULATION

COVID-19/AYUSH-CSIR 2020/Version-MOA Approved dated 13 May 2020

FINAL PROTOCOL(Synopsis)

Ashwagandha for the Prophylaxis against SARS-CoV-2 Infection: A Randomized Hydroxychloroquine Controlled Clinical Trial in Health Care Providers

(Study Code: AYUSH-CSIR-HCP-01)

Ministry of AYUSH and Council for Scientific and Industrial Research

Collaborative Clinical Research Program

with technical support from Indian Council of Medical Research

Prepared Under Supervision of:

Arvind Chopra MD, DNB, FRCP (London), International Fellow (American College of Rheumatology), Director and Chief Rheumatologist,
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Submitted to

Ministry of AYUSH, Government of India

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STUDY SYNOPSIS

a. **Background:** There is an urgent need for effective and safe chemoprophylaxis against novel Corona Virus Disease of 2019 (COVID-19) due to Severe Acute Respiratory Syndrome- Corona Virus-2 (SARS CoV-2). There is no drug or any vaccine available. Based on extrapolation of antiviral effect and down regulation of aberrant immune response demonstrated in laboratory experimental studies (including SARS virus and recently some data on SARS-CoV-2) and very sparse clinical data, Hydroxychloroquine (HCQ) was given to several high risk participants such as health careproviders as per the regimen contained in the ICMR advisory: 400 mg twice daily on day one and to be followed by 400 mg weekly for seven weeks [The entire advisory is enclosed with this protocol (Appendix S, pages 109-111)]. The pandemic is likely to last longer. Over short-term use, drug toxicity may not be much of a concern but long-term use of HCQ will need diligent monitoring of several adverse effects. Several clinical research studies have been initiated globally to investigate the therapeutic role of HCQ in COVID-19. Other options for chemoprophylaxis include Ashwagandha; an Ayurveda 'Rasayana' is popularly used since ancient times to build up the immunity which is central to combat infectious illness like COVID-19. Several experimental studies have also demonstrated convincingly the immune enhancing and modulating properties of Ashwagandha. There are other health benefit also- anabolic, anti-oxidant, tissue protective. A recent Indian experimental study has conclusively demonstrated that Ashwagandha can effectively interfere with the binding of SARS-CoV-2 to the host cell receptor (ACE 2) but requires further validation. Ashwagandha has been clinically evaluated in auto-immune disorders such as rheumatoid arthritis (RA). The investigators (AC, MS, AV, GT, AR, BP) have reported equivalent efficacy of an Ashwagandha formulation and HCQ for management of Rheumatoid Arthritis in a controlled clinically study of RA of 6 months duration (38). Therefore, Ashwagandha is likely to show clinical benefit through its predominant effect on the immune system in case of COVID-19.

b. **Study title:** Ashwagandha for the Prophylaxis against SARS-CoV-2 Infection: A Randomized Hydroxychloroquine Controlled Clinical Trial in Health Care Providers

c. **Objective:** This research project is a randomized control trial (RCT), which aims to study the efficacy; safety and other health benefits of Ashwagandha in the prophylaxis against COVID-19 in High Risk Population (HRP) in comparison with HCQ.

d. **The investigational product:** The investigational product is Ashwagandha (an aqueous extract of *Withania somnifera*) and this will be compared to HCQ.

e. **Study duration:** The study duration will be of 12 weeks.

f. **Study design:** Consenting eligible HCP will be randomized to a prospective, open label, two arms, parallel efficacy multi-centric study with an equivalence design (sample size = 400 participants). The study design is as per Zelen Model wherein the participants are permitted to exercise their choice of the study drug. The HCP will be selected if they are naïve for prior HCQ use and are actively involved in the management of COVID-19 cases. This is an equivalence design study (equivalence margin of difference 15% with HCQ, 80% power, alpha 0.05 or less). Participants in the HCQ arm will take HCQ for 7 weeks only but will be monitored and evaluated up to study completion at week 12. However, participants in the Ashwagandha arm will continue to take the drug for the total duration of 12 weeks but will be monitored at 7th week, similar to those on HCQ.

Figure 1: Study Design and timelines

Screening of * High Risk Population & Obtain Study Consent
(Exclude SARS-CoV-2 infection/COVID, Verify Eligibility Criteria)
***At Risk : HCP, Contacts of COVID-19 cases, Certain Work Class**

↓

Enrol Study Participants
HCQS naïve, Managing COVID- 19 cases: Randomised, 2 Arm Interventional (HCQS or Ashwagandha) Study

↓

Time Points*	Clinical Assess	Laboratory Assess
Baseline	Clinical Examination including Ayurvedic analysis, Assess QOL with WHO Qs, Assess HR-BHF, Initiate Study documents	Diagnostic (RT-PCR), Serology (IgM, IgG), Routine Body Profile, Selected Cytokine Assay
↓ Week 4	Telephonic Check for COVID Symptoms, Self-Assess Qs, Assess Drug safety	Diagnostic (RT-PCR), Serology (IgM, IgG)
↓ Week 8	Telephonic Check for COVID Symptoms, Self-Assess Qs, Assess Drug Safety	Diagnostic (RT-PCR), Serology (IgM, IgG)
↓ Week 12	Clinical Examine including Ayurvedic, Completion Study Report, Assess QOL with WHO Qs, Assess HR-BHF, Outcomes, Assess Drug Safety	Diagnostic (RT-PCR), Serology (IgM, IgG), Routine Body Profile, Selected Cytokine Assay

*Further Assessment Points : Daily Mobile App based feedback of any COVID-19 Symptoms or drug related side effects; Participants will also be checked any time in case of suspected COVID- 19 symptoms

NOTE: The total study period is 12 weeks; HCQS and Ashwagandha are Study Intervention Drugs; HCQ will be given weekly for only 7 weeks (ICMR Advisory) but participants followed till study completion; Participants will be monitored and followed using a common scheme shown above ; Primary Efficacy Measure: Proportion of participants free from SARS-CoV-2 infection and/or COVID-19 on Study Completion; Participant testing positive for SARS-CoV-2 and/or developing COVID-19 will be withdrawn and referred to COVID- 19 medical facility; Both Ayurvedic and Allopathic Physicians will examine and monitor participants; Cytokine Assay in only selected participants ; HCP :Health Care Provider; HCQ: Hydroxychloroquine; Qs: Questionnaire; HR-HBF: Health Related habits, behaviour and Fitness. (Detailed methodsare described in Appendix A to R)

g. Study Population: Voluntary study participants will be selected from high risk population for COVID-19. This population includes HCP actively participating in the management of COVID-19 cases.

Eligibility Criteria:

Inclusion Criteria:

• Participants of either sex, 20 to 69 years of age
• Participants tested negative for COVID-19 by nose and throat swab using RT PCR technique
• HCQS naïve participants
• Willing to come for regular follow – up visits
• Written Informed Consent

Exclusion Criteria:

1.	Participants with hypersensitivity or Intolerance and contraindications (psoriasis, porphyria and Glucose-6-Phosphate Dehydrogenase deficiency)
2	Pregnant women, lactating women and women of child bearing potential
3.	Participants with known allergy or contraindication to Ashwagandha
4	Have any Chronic, Severe, Unstable, Uncontrolled medical disease such as Diabetes, Hypertension, Cardiac disorders, liver, kidney disorders and lung disorders or other disease of concern which may put the participant at increased risk during the study
5	History of having received any investigational drug in the preceding one month.
6	Prolonged concurrent intake of any drug that is known to prolong QT interval on the ECG as per physician discretion and these drugs include anti-arrhythmic drugs, quinidine, chlorpromazine, haloperidol, olanzapine, thioridazine, fluoxetine, antibiotics belonging to quinolone and macrolide family, antibiotics, fenfluramine and other appetite suppressants, Beta-2 agonists, terfenadine and other anti-histaminic drugs, liquorice and potassium lowering drugs
7	History of taking any kind of Ayurvedic formulation or any other form of CAM (Complimentary Alternative Medicine) therapy in the preceding 2 months
8	Unwilling to come for regular follow-up for the entire duration of the study.
9	Non – co-operative attitude of the participant
10	Any condition that, in the opinion of the investigator, does not justify the participant's inclusion in the study.

h. Sample size: 400 (randomized sample size)

i. Treatment and Follow up Monitoring Schedule:

This will be common to both the study arms

Visit - 1: Baseline Visit
Visit - 2: Week 4 Visit
Visit - 3: Week 8 visit
Visit - 4: Week 12 visit

Participants will be under the combined care of Modern medicine physician and Ayurvedic physician. The details of the procedures and investigations carried out at each visit are as mentioned in the Schedule of Events (Appendix A)

j. Concomitant medication:
Medication prescribed for other co-existent disease will continue under medical supervision which will be recorded in the case record form (CRF).

k. Efficacy criteria:
The primary efficacy measure will be as follows:
(i)Proportion of SARS-CoV-2 infection* free participants on completion of study (ii)Proportion of participants contracting COVID-19 during the study period
The secondary measures of efficacy and safety will include proportion of participants developing COVID-19, drug related adverse event, drug tolerability, General Health Related Questionnaire (behavior, habit and fitness/ HR-BHF), Quality of life (WHO QOL Brief), Ayurveda measures, Immune Status (serology for specific anti SARS-CoV-2 IgM and IgG antibodies)
*The diagnosis of COVID-19 will be confirmed by a real time RT-PCR based diagnostic test on nose/mouth swab

l. Safety criteria: All adverse events occurring during the study will be recorded and monitored as per GCP-ICH guidelines. Safety would also be assessed in case of all withdrawals.

m. Laboratory investigations: These are common to the both the study arms
•Haemogram, Platelet count, Total leukocyte differential count, Hemoglobin and ESR,
•Liver function test - Serum Bilirubin, ALT, AST, Alkaline phosphatase,
•Kidney Function Test (Serum creatinine, Blood Urea Nitrogen)
•Lipid profile (Total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides, VLDL)
•Blood Sugar Level
•Urine Routine
•C-Reactive protein
•Selected Cytokines: Gamma Interferon, tumor necrosis factor (TNF-alpha and beta), Interleukin (IL) IL-6, IL2, IL-10, IL-17, Monocyte Chemotactic Protein-1
•Nasal and throat swab for specific test for COVID-19 based on real time RT-PCR
•Serum for IgG and IgM for COVID-19

n. Statistical statement:
The design considers equivalence between HCQ and the Ashwagandha arm with a-priori margin set at 7.5% two sided. Standard statistical tests, parametric and non-parametric, will be used for analysis (both intention to treat and per protocol); significance $p < 0.05$ two sided.

o. Regulatory clearances:
The protocol will be submitted for all regulatory and other relevant approvals including that of the ethics committee prior to beginning the clinical component of the study.

p. Funding agency:
COVID-19/AYUSH-CSIR 2020/Version MOA-Approved dated 13 May 2020, is an undertaking of AYUSH-CSIR, Government of India, and is being directly funded by Government of India.

q. Guidelines:
The study will be conducted in accordance with the updated principles of Good Clinical Practice (GCP) described by WHO and the current version of the Declaration of Helsinki, Indian Council of Medical Research (ICMR) Ethical Guidelines for Biomedical Research on Human participants -2017, and Ministry of AYUSH/ Central Council for Research in Ayurvedic Sciences (CCRAS) guidelines on the subject (2018) including archiving of essential documents.

STUDY PROCEDURES/TIMELINES AND EVENTS SCHEDULE

The overview is shown in Table 1.

Baseline *Visit: (Visit 1): Exclusion criteria*

Participants who meet the criteria for selection, must have the following procedures completed during this visit prior to study entry.

Visit 1 (Baseline)

o	Providing with Participant Information Fact Sheet (Appendix C) for thorough study.
o	Signing of Informed Consent. (Appendix B)
o	Complete medical examination form: medical history, physical examination, vital signs (BP, Pulse, Respiration rate and Weight), co-morbidity, medication history.
o	Record Baseline Symptoms
o	Ayurvedic evaluation.
o	Quality of life as assessed by WHO-QOL Brief and Health Related-Behavior Habit Fitness questionnaire
o	Laboratory work up- general health and cytokines (anti-TNF, IL 6, gamma interferon, IL 13)
o	Laboratory work up- diagnostic for COVID-19 (nose/throat swab and serology)
o	Dispense study medication and begin medication log entry
o	Schedule return visit in 4 weeks

Visit 2 (Week 4):

o	Complete Follow Up Assessment

o	Laboratory work up-diagnostic for COVID-19 (nose/throat swab and serology)
o	Monitor Adverse Events
o	Check study participant pocket diary
o	Dispense study medication and update medication log
o	Schedule return visit in 4 weeks.

Visit 3 (Week 8):

o	Complete Follow Up Assessment
o	Laboratory work up-diagnostic for COVID-19 (nose/throat swab and serology)
o	Monitor Adverse Events
o	Check study participant pocket diary
o	Dispense study medication and update medication log
o	Schedule return visit in 4 weeks.

Visit 4 (Week 12):

o	Complete Follow Up Assessment
o	Complete medical evaluation
o	Ayurvedic evaluation
o	Complete questionnaire for Quality of life – WHO QOL and Health Related Behaviour Habit and Fitness questionnaire
o	Laboratory work up-general health and cytokines (anti-TNF, IL 6, gamma interferon, IL 13)
o	Laboratory work up-diagnostic for COVID-19 (nose/throat swab and serology)
o	Complete Follow Up Assessment
o	Update medication log (record any unused study medication)
o	Check study participant pocket diary
o	Monitor Adverse Events
o	Record final outcome

Prophylactic study sites

1. RRAP Central Ayurveda Research Institute for Cancer (CCRAS), Podar Medical Campus, Dr. A. B. Road, Worli, Mumbai.
2. Dept. of Pharmacology and Therapeutics, , GS Medical College & KEM Hospital, Parel, Mumbai.
3. TN Medical College and Nair Hospital , Mumbai Central, Mumbai.
4. Post graduate Institute of Medical Education & Research, Chandigarh.
5. ESI Hospital, Central Road, Andheri, Mumbai
6. King George Medical University, Lucknow.
7. Banaras Hindu University, Varanasi

Adjunct Treatment study sites

1. Symbiosis University Hospital & Research Centre, Symbiosis Inter
2. All India Institute of Ayurveda (AIIA), Gautam Puri, Tagore road, New Delhi.
3. RRAP Central Ayurveda Research Institute for Cancer (CCRAS), Podar Medical Campus, Dr. A. B. Road, Worli, Mumbai
4. D Y Patil University school of Medicine & Hospital, Nerul, Navi Mumbai.
5. Medanta Institute of Education and Research, Gurgaon.
6. Jehangir Hospital, Pune.
7. Datta Meghe Institute of Medical Sciences, Nagpur.
8. Bhausaheb Deshmukh Medical College, Amravati. (Maharashtra)

RESTRICTED CIRCULATION

COVID 19/AYUSH-ICMR 2020/Adjunct Protocol/Version 3.3-F dated 11 May 2020

FINAL PROTOCOL (Synopsis)

A Randomized, Open Label, Parallel Efficacy, Active Control, Multi-Centre Exploratory Drug Trial to Evaluate Efficacy and Safety of an Ayurvedic Formulation as Adjunct Treatment to Standard of Care for the management of Mild to Moderate COVID-19 Patients

Ministry of AYUSH and Council for Scientific and Industrial Research

Collaborative Clinical Research Program

With technical support from Indian Council of Medical Research

Prepared Under Supervision of

Arvind Chopra MD, DNB, FRCP (London), International Fellow (American College of Rheumatology), Director and Chief Rheumatologist,
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STUDY SYNOPSIS

a. Background:

Coronavirus Disease-19 (COVID-19) pandemic has unleashed an unprecedented damage to life and livelihood. Over four Million people have contracted the disease globally and almost 2.7 lakh have died by the end of April 2020. There is no specific therapy and the vaccine is likely to be ready by early 2021 if not earlier. All the global strategies are focussed on stringent measures to contain the virus and mitigate the suffering of the people. India is under lockdown since early March 2020 and the situation though grim is fairly stable. There is an upward trend in number of cases but the health care system is suitably meeting the challenge. Clinical research is a vital part of such epidemics. There is a dire need to find newer more effective drugs or at least improve the current standard of care.

India has a rich tradition of Ayurveda since ancient times and several 'Rasayana' drugs are well known to enhance the immunity status. Though COVID 19 is an acute infectious disease with a predominant affliction for lungs and airways, the clinical experience so far has shown a rapidly progressive inflammation triggered by several exuberant immunological events. Therefore, there may be a potent role of immunity enhancing and or immunomodulators drugs in the medical management of COVID 19. It is against this perspective that the Ministry of AYUSH and Council of Scientific & Industrial Research (CSIR) have initiated an ambitious and comprehensive research program to discover Ayurveda formulations with proven value in the chemoprophylaxis and treatment of COVID 19.

In this protocol, the focus is on medical treatment.

Three Ayurveda herbal formulations are selected – AYUSH-64 (a proprietary multi plant formulation of CCRAS), Yashtimadhu (*Glycyrrhiza glabra extract* extensively researched by IIIM, Jammu) and 'Samshamani Vati Plus' a classical formulation (*Tinospora cordifolia* plus *Piper longum*).

This protocol is common to study all the three formulations; however, any one of them at a time will be individually evaluated for efficacy in a separate randomized two-arm controlled study.

b. Study title:

A Randomized, Open Label, Parallel Efficacy, Active Control, Multi-Centre Exploratory Drug Trial to Evaluate Efficacy and Safety of an Ayurvedic Formulation as Adjunct Treatment to Standard of Care for the Management of Mild to Moderate COVID-19 Patients.

c. Objective:

Primary: To compare the efficacy and safety of a combination regimen of standard of care (SOC) plus a selected standardized Ayurvedic drug (as adjuvant) in the management of mild to moderate cases of COVID-19 with that of standalone SOC control (active control).

Secondary: The secondary objectives are (i) To determine the effect of combined standard of care plus Ayurveda drug on the surrogate markers of disease severity and progression, and recovery (ii) To identify predictors of drug response (iii) To describe the clinical phenotype (with reference to characteristics, timelines of occurrence of complications and course of illness)

d. The investigational products:

Three formulations will be used in the study; those will be separately used as adjunct treatment. These formulations are –Samshamani Vati Plus, AYUSH 64 and Yashtimadhu.

e. Study duration:

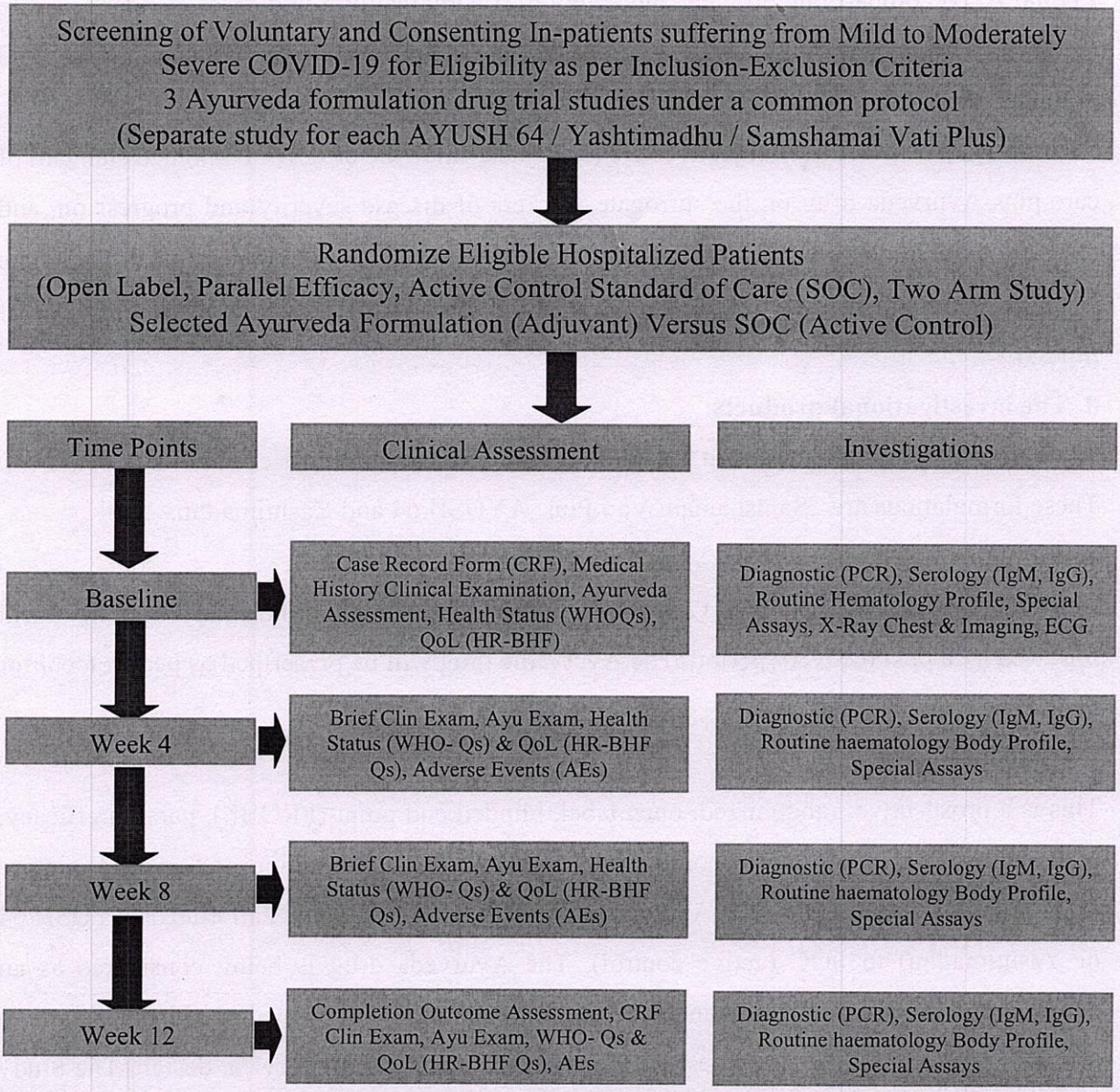
The total duration of the study is 12 weeks – this includes a period of hospital based treatment followed by a post recovery period. The Ayurvedic drug will be prescribed as per protocol for a total duration of 12 weeks.

f. Study design:

This is a prospective, randomized, open label, blinded end point (PROBE), parallel efficacy, multicentric, two arm study to compare the efficacy of a combination of Standard of Care (SOC) plus a selected individual Ayurveda herbal drug (Samshamani Vati Plus or AYUSH 64 or Yashtimadhu) to SOC (active control). The Ayurveda drug is being considered as an adjunctive or an add-on therapy and each of the three drugs will be evaluated in separate two arm trial with a common study design. The drug trials are 'exploratory' in design. The Study Flow diagram summarizes the study design and schedule of events (Fig 1) (Appendix A).

g. Sample size: The total sample size is 140 patients per drug trial- 70 patients in each arm.

h. Study Population: All adult patients with laboratory-confirmed SARS-CoV2 infection with mild to moderate category will be selected from the outpatient or inpatient facility in COVID-19 medical centers/hospitals. Voluntary patients will be explained about the study and if willing will sign the informed consent and be screened for eligibility.



***Further Assessment Time Points**: (i) During Hospitalization: Daily monitored vital parameters, disease symptoms, disease progression and recovery, and investigations carried out as per protocol till DISCHARGE; Laboratory and Imaging investigations as per protocol but the study investigator and treating physician can do any additional test as per their judgment (ii)Post DISCHARGE: Daily Telephonic Contact using a special mobile phone application for any relapse or any other symptoms or complications or any other Issue (iii) Discharge: Complete all formalities as required for study completion (iv) Skip week 4 or week 8 end point evaluation within 2 weeks of DISCHARGE

The total study period is 12 weeks; Primary Efficacy is 'Clinical Recovery' as described in the protocol; Study participant developing severe COVID 19 or severe complication and requiring special critical support/ ICU/ ventilator support will be withdrawn from the study but followed up to record outcome;
Both Ayurvedic and Allopathic Physicians will jointly examine and monitor study participants in addition to the hospital treating physician

Fig 1: Study Flow Diagram with Schedule of Important Study Events

i. Eligibility:

A) Inclusion Criteria:

i. Typical clinical presentation of acute onset febrile illness with cough and a RT_PCR based laboratory confirmation test for COVID-19
ii. Patients with either sex, 18 to 75 years age
iii. Patients with mild to moderate patients
iv. All patients must agree not to share medication
v. Patients willing to participate and sign an informed consent

B) Exclusion Criteria:

i. Patients suffering from severe COVID-19 Disease as judged by a physician and fulfilling at least two of the following three criteria* (i) Respiratory distress at room ambience (≥30 breaths per min) (ii) Oxygen saturation at rest ≤93% (peripheral digital arterial oxymetry) and requiring oxygen support for over one hour to normalize (iii) Any of the known COVID-19 complications and emergency procedures which may require shift/admission in intensive care unit such as respiratory failure, adult respiratory distress syndrome, requirement of oxygen support for over 1 hour, requirement of mechanical ventilation, septic shock, or severe non-respiratory organ dysfunction or failure. (Adapted and modified from the reference: Yang Liu et al. Lancet Infect Dis 2020, 2020 https://doi.org/10.1016/ S1473-3099(20)30232-2)
ii. Chronic, Severe, Unstable, Uncontrolled co-existent medical illness such as Diabetes, Hypertension, Cardiac disorders, liver, kidney disorders and lung disorders or other disease of concern which may put the patient at increased risk during the study
iii. History of immunosuppression: solid organ or bone marrow transplant, use of immunosuppressive antimetabolic and biologic agents, intrinsic immunodeficiencies, HIV infection.
iv. Active cancer diagnosis, on palliative treatment or requiring current therapy with antimetabolic agents, immunotherapy or radiotherapy.
v. Patients on parenteral nutrition
vi. Patients with known sensitivity or contraindication to any of the ingredients of study medication
vii. History of bleeding haemorrhoids, haemoptysis, acid peptic diseases, ulcers and pulmonary diseases (tuberculosis, asthma, etc.)
viii. Patients who are likely to worsen or planed ICU admission or ventilator support due to any reason

ix. Pregnancy and lactation

x. Participation in a drug interventional clinical drug trial of any nature in the three month period preceding onset of COVID-19

xi. Participation in any other clinical trial of an experimental agent treatment for COVID-19

xii. Patients on any kind of Ayurveda treatment or any other alternative and complementary medicinal systems such as Homeopathy, Unani, Siddha and in particular requiring oral therapy of any kind.

xiii. Physician decision that involvement in the study is not in the patient's best interest

j. Efficacy:

A) Primary Outcomes:

a) Mean time (days) for clinical recovery [Day of randomization to the day of clinical recovery (see criteria below)]

b) Proportion of patients showing 'clinical recovery'

Criteria of 'Clinical Recovery':

i. Normal body temperature (≤36.6°C axilla or ≤37.2 °C oral)

ii. Absence of cough or mild cough (infrequent, short episodic, non-wheezy, relieved by minimal or no medication, not interfering with routine speech and not related to lying in bed, mild sore throat or nasal congestion)

iii. Absence of breathlessness on routine daily self-care chore or respiratory rate less than 30 breaths per minute without supplemental oxygen

iv. Absence of any other symptom/sign attributed to COVID-19 illness

v. Normalization of SpO2 by standard peripheral oximetry device (above 95 percent)

vi. Recovery should be sustained for at least 48 hours under physician observation

vii. Assessed by physician blinded to treatment allocation (blinded end-point assessment)

viii. All of the above criteria ought to be fulfilled

Note: Clinical recovery would be deemed from the first day of satisfying the above criteria

B) Secondary Outcomes:

1) Rate of patients with negative SARS-CoV-2 on nasal or throat swab in a 2 day continuous real time RT-PCR test beginning from 'first day of clinical recovery' or 'Day 10 after onset of symptoms depending on whichever of the two time points is first achieved

2) Timelines (days counted from onset of illness)- normal body temperature, absence or minimal cough (see 'clinical recovery' for the definition), absence of dyspnoea, onset of clinical pneumonia, pneumonia diagnosed on chest X-Ray or CT scan, time to supplemental

oxygen, admit in intensive care unit, mechanical ventilation (non-invasive), mechanical ventilation (invasive), steroid use, respiratory failure, adult respiratory distress syndrome, cytokine storm syndrome, secondary infection, shock, septicaemia shock, hospital discharge, negative nose or throat swab confirmatory test, and all-cause mortality.

3) Proportion of patients developing an event that reflects clinical or otherwise improvement of worsening (the events are similar to those listed under Timelines, see above)

4) Improvement on pulmonary function tests using simple 'home expiratory spirometer' device and peripheral pulse oximetry

5) Improvement in selected laboratory parameters: blood haemoglobin, differential and total leukocyte counts, liver enzymes, renal functions, acute phase reactants, serum IL-6 and other selected cytokines, serum muscle enzymes (CK, CPK), serum ferritin, serum d-Dimer, anti-oxidant markers, serum BNP (cardiac function)

6) Serological Protective Antibody Assay (IgM and IgG)

7) Radiological Improvement on digital chest X - ray and HRCT chest

8) Drug related: side effects and toxicity, and tolerability (Safety criteria: All adverse events occurring during the study will be recorded and monitored as per GCP-ICH guidelines. Safety would also be assessed in case of all withdrawals.)

9) Health status: WHO QOL brief, health related behaviour habit and fitness questionnaire based on visual analogue scale

10) Ayurvedic Measures:

BASELINE:

a) Prakriti

b) Clinical Features

c) Ayurvedic Disease Subsets / Stages

FOLLOW UP / MONITORING:

a) Clinical Features

b) Ayurveda examination

c) Ayurvedic Disease Subsets / Stages

k. Medication*:

Interventional Experimental:

i)AYUSH-64: 500 mg tablet, 2 tablets bid (twice daily)

ii)Yashtimadhu: 300 mg tablet, 2 tablets bid (twice daily)

iii)Sanshamani Vati Plus: Each tablet to contain 300 mg Guduchi plus 75 mg Pippali, 2 tablets bid (twice daily) (*Considering the *Dosha* status Ayurveda physician may change the dose.)

Concomitant:

Medication prescribed for other co-existent disease and permitted as per inclusion criteria will continue under medical supervision of the primary care physician and this will be recorded in the CRF.

l. Laboratory investigations:

These are common to the each of the three Ayurveda formulation drug trials:

i. Haemogram, Platelet count, Total leukocyte differential count, Hemoglobin and ESR,
ii. Liver function test - Serum Bilirubin, ALT, AST, Alkaline phosphatase,
iii. Kidney Function Test (Serum creatinine, Blood Urea Nitrogen)
iv. Lipid profile (Total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides, VLDL)
v. Blood Sugar Level
vi. Urine Routine
vii. C-Reactive protein titer
viii. LDH, Ferritin
ix. Pro-Cal
x. CK, B-type natriuretic peptide (BNP), Troponin, D-Dimer
xi. Serum Electrolytes (Sodium, Potassium, Chloride, Iron, Zinc, Manganese) Vitamin D, B12
xii. Oxidation Biomarkers-Superoxide Dismutase (SOD), Glutathoine (GSH)
xiii. Cytokine Panel (Interleukin-2, Interleukin 1 - 4, Interleukin-6, Interleukin-10, TNF-α, Interleukin-1β, Interleukin-13), Monocyte Chemotactic Protein (MCP), Gamma Interferon. RATIONALE FOR CYTOKINE ASSAY: Cytokine assay can be used to study important anti-viral effects (gamma interferon), immune mediated inflammation (IL-6, anti-TNF, IL-17), TH 1 and TH 2 immune response and antibody producing B cell activity (IL4, IL13), activation of immune cells such as macrophage activation (MCP). Intense up regulation and elevation of IL 6 and several other cytokines has been reported by several clinical case series and research in COVID-19 and can guide specific therapy (as in case of use of monoclonal antibody to IL-6 receptor being used to treat Cytokine storm in COVID 19)
xiv. Serum Immune Response tests (IgG and IgM) for COVID-19
xv. Urine Pregnancy Test for women of child bearing potential

Other Investigations:

i. USG Abdomen and Pelvis
ii. Color Doppler and 12 Lead ECG
iii. Chest X-ray
iv. HRCT Chest

m. Withdrawal Criteria

The patient can withdraw at any time during the study without assigning any reason. The investigator may also withdraw the patient due to reasons connected with the severity of disease, interventional drug (adverse event) or some protocol deviation. Detailed description is provided in the protocol.

n. Statistical statement:

The design of the drug trial is exploratory in nature. Though a randomized selection of patients will be done to either of the two arms, the sample size is that of convenience (expert opinion) and the same is not statistically powered however, sample size (70 patients in each arm) sufficient to draw meaningful conclusions. The statistical significance $p<0.05$(two sided) is predefined for analysis. Statistical analysis will be performed using standard tests to compare the two interventional arms for primary and secondary efficacy measures. Safety events will be also analyzed. Both intent-to-treat and per protocol completer analysis will be performed. Regression analysis will be done to identify predictors of response.

o. Regulatory clearances:

The protocol will be submitted for all regulatory and other relevant approvals including that of the ethics committee prior to beginning the clinical component of the study. The trial protocol will be registered under Clinical Trial Registry of India before enrolling the first patient.

p. Funding agency:

COVID 19/AYUSH-CSIR 2020/Adjunct Protocol/Version 3.3-F dated 10 May 2020 is being funded by Ministry of AYUSH and CSIR Government of India.

q. Guidelines:

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP) of the WHO and the current version of the Declaration of Helsinki, ICMR (Indian Council of Medical Research) Ethical Guidelines for Biomedical Research on Human patients (2017), and AYUSH/CCRAS Guidelines for clinical research in Ayurveda and GCP (2018).

STUDY PROCEDURES: TIMELINES AND EVENTS SCHEDULE

The overview is shown in Table 1.

Baseline Visit: (Visit 1)

Patients who meet the criteria for selection, must have the following procedures completed during this visit prior to study entry.

Visit 1 (Baseline)

o	Providing with Patient Information Fact Sheet for thorough study.
o	Signing of Informed Consent.
o	Complete medical examination form: medical history, comprehensive physical examination, co-morbidity, medication history.
o	Symptom Assessment, Vital Parameters
o	Record Baseline Symptoms
o	Comprehensive Ayurvedic evaluation.
o	Laboratory work up- general health and advanced test and cytokines as in Appendix O
o	Chest X-ray
o	12 Lead ECG
o	Pulse Oximetry
o	Health Related-Behaviour Fitness (HR-BHF) VAS questionnaire, Self-Reported Questionnaire (Mobile app)
o	Dispense study medication and begin medication log entry

Visit 2 (Day 4):

o	Symptom Assessment, Vital Parameters
o	Brief Ayurvedic Evaluation

o	Health Related-Behaviour Fitness (HR-BHF) VAS questionnaire, Self-Reported Questionnaire (Mobile app)
o	Laboratory work up
o	Chest X-ray
o	Pulse Oximetry
o	Monitor Adverse Events

Visit 3 (Day5 up to - Discharge) (Daily Assessment):

o	Symptom Assessment, Vital Parameters
o	Brief Ayurvedic Evaluation
o	Laboratory work up
o	Pulse Oximetry
o	Monitor Adverse Events
o	ECG
o	Chest X-ray
o	Health Related-Behaviour Fitness (HR-BHF) VAS questionnaire, Self-Reported Questionnaire (Mobile app)
o	Completion and Outcome Report

DISCHARGE

o	Symptom Assessment, Vital Parameters
o	Brief Ayurvedic Evaluation
o	Laboratory work up
o	Pulse Oximetry
o	Monitor Adverse Events
o	ECG
o	Chest X-ray
o	Health Related-Behavior Fitness (HR-BHF) VAS questionnaire, Self-Reported Questionnaire (Mobile app)
o	Completion and Outcome Report

Visit 4 (week 4)

o	Symptom Assessment, Vital Parameters
o	Brief Ayurvedic Evaluation
o	Laboratory work up
o	Pulse Oximetry
o	Monitor Adverse Events
o	Health Related-Behaviour Fitness (HR-BHF) VAS questionnaire, Self-Reported Questionnaire (Mobile app)
o	Drug Compliance, Dispense study medication

Visit 5 (week 8)

o	Symptom Assessment, Vital Parameters
o	Comprehensive Ayurvedic Evaluation
o	Medical History, Comprehensive Physical examination
o	Laboratory work up
o	Pulse Oximetry
o	Monitor Adverse Events
o	Health Related-Behaviour Fitness (HR-BHF) VAS questionnaire, Self-Reported Questionnaire (Mobile app)
o	Drug Compliance, Dispense study medication

Visit 6 (Week 12)

o	Symptom Assessment, Vital Parameters
o	Comprehensive Ayurvedic Evaluation
o	Medical History, Comprehensive Physical examination
o	Laboratory work up
o	Pulse Oximetry
o	Monitor Adverse Events

o	Health Related-Behaviour Fitness (HR-BHF) VAS questionnaire, Self-Reported Questionnaire (Mobile app)
o	Drug Compliance
o	Completion Report