MINISTRY OF AYUSH
Government of India

Interdisciplinary AYUSH
Research & Development Task Force

Guidelines for AYUSH Clinical Studies in COVID-19

2nd APRIL to 2nd MAY 2020

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Clinical Trials on AYUSH Interventions for COVID-19: Methodology and Protocol Development

A Publication by
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AYUSH Initiatives for COVID Research

Coronavirus Disease-19 (COVID-19) pandemic is a challenge to public health worldwide. In spite of implementation of prophylactic strategies such as promotion of hygiene, social distancing and global lockdown, the spread of disease remains a challenge. There is no 'Standard of Care' available in view of inadequate evidence on existing medicines and their limitations. This is an opportune time when AYUSH concepts and interventions should be evaluated for developing better arsenals to prevent and treat the disease. With this objective, the Ministry of AYUSH has constituted an Interdisciplinary AYUSH Research and Development Task Force for facilitating research on COVID-19.

The pandemic has however raised complex issues for health systems, communications, research infrastructure, and research governance frameworks. On the background of rapidly evolving scientific and ethical uncertainties, it is a challenge to design research that can yield scientifically valid results. The other challenges are short time available to design a study and lack of resources to conduct the study. Any research which is planned during such period should be based on thorough understanding of the disease and its importance as a public health challenge. The AYUSH Task Force has therefore recommended development of a guidance document for researchers that will discuss methodological components of a protocol for evaluating AYUSH interventions in COVID-19.

Clinical Trial Protocol – Development and Implementation

Protocol is a document that describes how a clinical trial will be conducted (the objective(s), design, methodology, statistical considerations and organization of a clinical trial) and ensures the safety of the trial subjects and integrity of the data collected. It provides a structured framework to individuals conducting the study, serves as the basis for trial registration, and facilitates study appraisal by participants and external reviewers, including Ethics Committees (ECs), funding agencies and journal editors.

This document covers various aspects of clinical trial protocols starting from defining objectives up to dissemination of results along with appropriate examples applicable in AYUSH context. AYUSH interventions are multi-targeted and can prove useful at various for prophylaxis of those not yet affected, treatment of active COVID-19 cases and management of recovery stage. Further the trials can evaluate AYUSH interventions as an add-on to conventional care or as stand-alone treatment. They can be conducted on a single drug or formulation from AYUSH system or using whole system approach (wherein holistic approach of AYUSH system is given due consideration). This document has considered clinical trials with all these broad aims. It is expected that the document will help designing better quality clinical trials for investigating AYUSH interventions.

The document refers related published guidelines on this topic and is based on scientific knowledge and experience of the Task force members. The document also includes reports compiled by various working groups under the Task Force, scientific deliberations and discussions during the meetings of these working groups. It also provides sample protocols and Case Record Forms (CRFs) for various trials that can be planned with AYUSH interventions (Refer Annexures 11), which are developed by the members of the Task Force.

Protocol development

Researchers should refer SPIRIT Statement (Standard Protocol Items: Recommendations for Interventional Trials) to improve the completeness and quality of trial protocols. The incomplete protocol content can impair understanding and implementation of the trial; reduce efficiency of protocol review; and lead to burdensome protocol amendments.

National Ethical Guidelines

The researchers aspiring to conduct research during the COVID-19 emergency should follow the ethical principles provided in the Section 2 of National Ethical Guidelines 2017 released by Indian Council of Medical Research (ICMR) in letters and spirit. The principles of Ethics are mentioned in Box -1

Box 1: Principles of Ethics (National Ethical Guidelines 2017)

1. Essentiality
2. Voluntariness
3. Non-exploitation
4. Social responsibility
5. Ensuring privacy and confidentiality
6. Risk minimization
7. Professional competence
8. Maximization of benefit
9. Institutional arrangements
10. Transparency and accountability
11. Totality of responsibility
12. Environmental protection

Of these, the very crucial and pertinent principles from the Investigator's perspective are

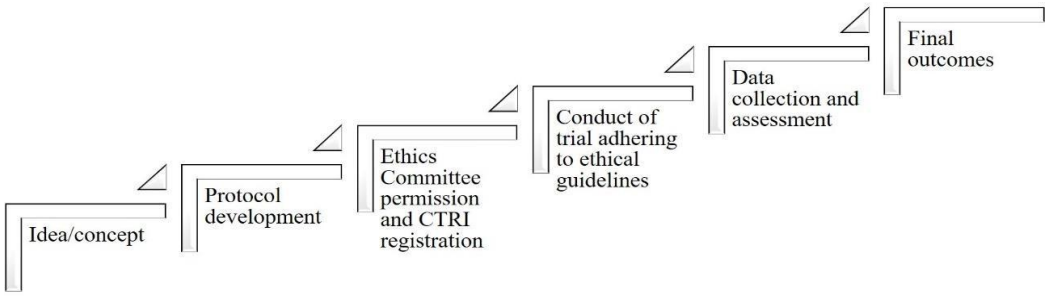
1. Principle of eligibility: Whether the proposed research is utmost necessary? Whether human trial is really required to answer the research question?
2. Principle of competence: Whether the investigators are competent enough to plan/conduct/monitor/evaluate the trial involving COVID-19 patients? Do the investigators have the appropriate and relevant qualification, experience and/or training?
3. Principle of Institutional arrangement: Whether the Institute where research is planned has the necessary infrastructure and expertise to support the COVID-19 research such as expertise in microbiology/virology or the required facility to dispose the infectious biomedical waste?

On this background, the investigators should refrain from 'Me too' research on COVID-19. The research should be based on sound knowledge of the entire process of clinical research from an abstract concept to a well-defined research question and from a research question to meaningful outcomes.

Clinical trial Registry

It is mandatory for any research involving human participants to undergo independent and unbiased review by the Institutional EC and then register with Clinical Trial Registry of India (www.ctri.nic.in) before enrolment of first study participant.

Fig 1: Clinical Trial Protocol – Development and Implementation



The investigator should abide by all local, national and international guidelines such as National Ethical Guidelines by ICMR and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) E6, WHO-GCP while implementing the trial protocol. In case of AYUSH interventions, the investigator should also follow AYUSH guidelines (where available) and General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine by WHO. In addition, the investigator should also refer Consolidated Standards of Reporting Trials (CONSORT) and its extension for reporting herbal medicines so as to collect, assess and present the data as per the requirement. Box 2 summarizes various guidelines and checklists to be followed for protocol development:

Box 2: Guidelines and Resources for Researchers

1. National ethical guidelines for biomedical & health research involving human participants, 2017 (www.icmr.gov.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017)
2. Clinical Trial Registry of India (www.ctri.nic.in)
3. Good Clinical Practice Guidelines for Clinical Trials of ASU Medicine (Link)
4. National AYUSH Morbidity and Standardized Terminologies Electronic Portal (www.namstp.ayush.gov.in)
5. Pharmacovigilance program for ASUH drugs (www.aiia.gov.in/pharmacovigilance0
6. Enhancing the QUAlity and Transparency Of health Research (www.equator-network.org)
7. CONSORT Statement (www.consort-statement.org)
8. Standard Protocol Items: Recommendations for Interventional Trials (www.spirit-statement.org)
9. STrengthening the Reporting of OBservational studies in Epidemiology (www.strobe-statement.org)
10. Presentation of Case Reports (www.care-statement.org)

Protocol for Trials on AYUSH Interventions

The components of clinical trial protocol are discussed as follows:

1. Title

In the title section, Investigator should provide a succinct description that conveys the topic (study population, interventions), acronym (if any), and basic study design – including the method of intervention allocation (e.g., parallel-group randomised trial; single-group trial) in the title.

For example, Evaluation of Comprehensive AYUSH Intervention (COVID-AYUSH-001) for treatment of COVID-19 patients with mild to moderate severity: An open label, randomized, controlled study.

2. Introduction

Typically, the introduction consists of free-flowing text, in which investigator explains the scientific background and rationale for the trial. Relevant background data, assumptions, clinical experiences, research papers etc should be discussed in introduction. The Introduction can have following components:

Background

The background section should summarise the importance of the research question. Broadly, it should cover disease statistics, existing treatment options with limitations and need for Integrative approach. Box 3 represents few important information resources for COVID-19.

Box 3: Online resources for COVID-19 statistics

- COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University: https://coronavirus.jhu.edu
- Rolling updates on coronavirus disease (COVID-19) by WHO: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
- COVID-19 India, Ministry of H & FW, Govt. of India: https://www.mohfw.gov.in/

Rationale

The rationale section should justify the need of the trial. This part should cover in brief the disease as per the relevant AYUSH system from Investigator's perspective. The length of this part should be restricted only for justifying choice of selected interventions.

The strength of AYUSH systems lies in the well validated theories and practices that can be used to understand diagnose and strategize treatments of newer diseases like COVID -19. These systems offer many effective strategies (medicines, procedures, diet, non-pharmacological regimens) for management of the clinical conditions (cough, fever, respiratory distress etc) associated with COVID-19. There are many time-tested medicines being used for this symptom complex in the practice of AYUSH systems. The investigator should justify selection of specific intervention from the variety of options available in AYUSH literature. Further, the Investigator should also report any evidence of the benefits and harms

of the interventions included in the trial and should suggest a plausible explanation for how the interventions might work.

3. Objectives

The study objectives reflect the scientific questions to be answered by the trial, and define its purpose and scope. It is a good idea to refine the research question using PICOT format (Box 4) before defining objectives. Once the research question is framed in this format, it becomes easier to frame objectives.

Box 4: PICOT format for ideal research question

(P): Population refers to the participants in whom the trial will be conducted
(I): Intervention refers to the treatment that will be provided to participants
(C): Comparison identifies what will be used as a reference group to compare with treatment intervention. This is often referred as control group
(O): Outcome represents the indicators to measure or examine the effect of intervention
(T): Time describes the duration for data collection or Type of design

Objectives should be specific, attainable in given time period and measurable. They can be written as primary and secondary. Primary will be the one which is directly linked to the research question and needs to be fulfilled at the end of the study so that research question can be answered. The examples of primary objective are:

Prophylactic trial: To compare number of individuals turning COVID-19 positive receiving AYUSH intervention with those receiving conventional management in a community where at least 1 confirmed case is identified

Treatment trial: To compare duration required for change in disease status (from symptomatic positive to asymptomatic negative) in patients receiving AYUSH interventions with those receiving conventional management in COVID-19 patients with mild to moderate severity

Recovery trial: To evaluate the duration required for mitigation of symptoms in individuals turned COVID-19 negative

The secondary objectives are either support the primary objective or supplement additional data. For any given trial, it is advisable to have only one primary objective as it dictates the study outcome, study design and even the sample size, while there can be many secondary objectives.

4. Trial design

The word ‘design’ is often used to refer to all aspects of how a trial is set up that includes details of articulation of various methods such as randomisation and blinding.

The preferred type of trials for COVID-19 is parallel group over other types such as crossover, factorial, single group (pre-post). Of the 2 groups running in parallel, the control arm will receive conventional management (as standard of care is not a right term for present condition)

while the other group will receive AYUSH intervention alone (stand-alone evaluation) or AYUSH intervention along with conventional management (add-on studies). However, in case of recovery trials where conventional management has no treatment open, single group (pre-post) trials can be undertaken.

Though the conceptual framework, such as superiority or non-inferiority is mostly missing in AYUSH trials, the studies can be designed to demonstrate equivalence or non-inferiority of AYUSH interventions compared to conventional management. The trials can be even of exploratory nature. If this framework is described in the design section, it needs to be considered even while calculating sample size.

Although most trials use equal randomisation (such as 1:1 for two groups), it is helpful to provide the allocation ratio explicitly. It should be noted here that the phase of the trial (I-IV) is not relevant terminology for the trials on AYUSH interventions in COVID-19.

5. Methods

Study setting

Investigator should mention in the proposal the description of study settings where data will be collected. It is mandatory to obtain approvals from the respective study sites before submitting a proposal. The study setting should have required facilities considering objectives and methods of trial. In case of multi-centric trial (same protocol being implemented at 2 or more places), the number of study sites should also be mentioned under this heading.

For example, the setting for prophylaxis trials can be community or quarantine centres but with the back-up of a clinical centre where samples (e.g. throat swabs for RT-PCR) collection is possible. The setting for treatment trials could be any of the following:

- A repurposed AYUSH facility for COVID management
- Home, if the patient is advised homecare and isolation
- A collocated AYUSH facility within an allopathic COVID management center
- An allopathic facility, which is a designated COVID 19 management center offering integrated AYUSH care

Eligibility criteria

A comprehensive description of the eligibility criteria that will be used to select the trial participants should be provided in the proposal. These criteria define to whom the results of a trial apply viz. the trial's generalisability (applicability) and relevance to clinical or public health practice.

As a principle, inclusion and exclusion criteria should ideally be mutually exclusive. For example, if inclusion criteria mention 'mild and moderate cases', it obviously implies that severe cases will be excluded.

The method of recruitment is not much applicable in COVID-19 treatment trials, as the patients will be recruited applying eligibility criteria to known active cases. However, the methods such as word by mouth or advertisement in newspaper can be used in prevention (prophylactic) trials, if the trials are to be carried out in community settings.

Typical and widely accepted selection criteria relate to the nature and stage of the disease being studied, the exclusion of persons thought to be particularly vulnerable to harm from the study intervention, and to issues required to ensure that the study satisfies legal and ethical norms. Informed consent by study participants is typically required in intervention studies. These criteria may have patient and disease characteristics as per principles and pharmacology of AYUSH systems.
For example, individuals of specific Prakriti/Mizaj/Constitution type can be included or excluded as per the nature of intervention or individuals having bleeding tendency, acid-peptic disorders can be excluded if the intervention comprises mainly of drugs that can generate heat in body like Maricha (*Piper nigrum*).

Some of the desired eligibility criteria for COVID-19 trials are listed below:

Inclusion criteria:

- Individuals of either sex above 18 (age below than this not eligible for consent) and below 60 years of age (in age above this complications and comorbidities increase)
- RT-PCR based diagnosis
    - Prophylactic trials: health workers, contacts, frontline workers, suspects (testing negative)
    - Treatment trials: cases of mild and moderate severity* (testing positive)
    - Recovery trials: recovered from COVID-19 as tested negative
- Voluntariness to participate in the trial

Exclusion criteria

- Individuals with uncontrolled, unstable comorbidities
- Individuals with pre-existing respiratory conditions
- Immunocompromised individuals or those on immunosuppressants
- Patients on or requiring parenteral nutrition (in case of treatment and recovery trials only)
- Pregnant and lactating females
- AYUSH system-based contraindications

*The Investigator should use only the standard and validated definitions/terminologies related to disease diagnosis and severity. Some of these definitions are provided in Table 1 and/or Box 5.

Table 1: US-CDC classification of COVID-19

Stage	Features
Asymptomatic	No specific clinical symptoms of COVID-19 disease
Mild to Moderate	Mild clinical symptoms up to mild pneumonia
Severe	Dyspnoea, hypoxia, or >50% lung involvement on imaging
Critical	Respiratory failure, shock, or multiorgan system dysfunction

(Ref: www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
last accessed on 28th April 2020)

Box 5: Clinical Classification of COVID-19 (BMJ Best Practices)

Mild illness

- 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.
- Older and/or immunosuppressed patients may present with atypical symptoms.
- Symptoms due to physiological adaptations of pregnancy or adverse pregnancy events (e.g.,dyspnoea, fever, gastrointestinal symptoms, fatigue) may overlap with COVID-19 symptoms.

Pneumonia

- Adults: pneumonia with no signs of severe pneumonia (see below) and no need for supplemental oxygen.
- Children: pneumonia with cough or difficulty breathing plus fast breathing (i.e., <2 months of age: ≥60 breaths/minute; 2-11 months of age: ≥50 breaths/minute; 1-5 years years of age: ≥40 breaths/minute) and no signs of severe pneumonia (see below).

Severe pneumonia in adults and adolescents

- Fever or suspected respiratory infection plus one of the following:
- Respiratory rate >30 breaths/minute
- Severe respiratory distress
- SpO_2 ≤93% on room air.

Interventions

Details of intervention:

The rationale behind selection of specific interventions for the trial, specially the AYUSH interventions viz. single drugs, formulations, procedures, diet, non-pharmacological regimens like Yoga etc. should be appropriately justified. Few tips for selection of AYUSH interventions are:

- It is advisable to have simple, easy to follow intervention module.
- Though almost all AYUSH systems recommend all the above-mentioned options for management of a patient, the number of different components of the intervention and their frequency of administration should be kept as minimum as possible. This will help to improve patient compliance.
- Before designing intervention plan, its feasibility in the setting where the trial will be implemented needs to be considered. For example, administering *vamana* (an Ayurvedic procedure, induced vomiting) may not be possible in every COVID hospital.
- The whole system research promotes use of 'personalized intervention' (designed by physician on case-to-case basis considering both host and disease state) or 'standard yet flexible' (similar changes in all patients according to progressive stages of the disease e.g. if patient improves from moderate to mild, the intervention will change, but not much scope for host factors) or 'standard and fixed' (standard intervention irrespective

of host and disease state). In any case, the Investigator should provide detailed plan of intervention. In case of first two strategies, a list of medicines from which the management of individual patient will be planned should be provided.

- Drug/formulations with controversial / rare / red listed / expensive / toxic ingredient should be avoided.
- For drug/formulation trials, information should include the dose, method of administration, timing and duration of administration, conditions under which interventions are withheld, etc.
- Wherever possible, evidence for selected interventions should be given. The evidence can be anecdotal or reported literature.
- There has to be description about standardization of drugs/formulation and SOPs for procedures, diet recipes and the non-pharmacological regimen.
- Above all, the investigator should take into consideration affordability, availability and sustainability of the selected interventions.

The investigator should describe the control intervention also thoroughly. In COVID trials, though the control group is to receive "conventional care" it is important to describe details of this care.

Concomitant Allopathic and AYUSH medicines which are continued / discontinued during the study duration should be specifically mentioned with details. If continued, daily recording of their dose administered should be recorded and also captured in the Case Record Form (CRF). If there is change in dosage / brand/ composition of these medications during the study period that should be mentioned with reason. If these medicines are stopped then it must be recorded with reason.

If no conventional management is provided (stand-alone studies) then it has to be as per prevalent Government of India guidelines and recorded specifically that it has "not been provided" in the daily medication sheet and captured in the CRF. In case, allopathic medicines are given during the study duration then it must also be recorded specifically, with details of reason for administration, the name of the medicine with dose, along with any other relevant details, in the daily medication sheet as well as the CRF.

Duration of intervention:

Though the duration will be intervention specific, considering the spread and fatality of COVID-19 the duration that can be considered as:

- Prophylaxis trials: Maximum 12 weeks (3 months)
- Treatment trials: Maximum 4 weeks (28 days)
- Recovery trials: Minimum 12 weeks (3 months)

Criteria for discontinuing allocated interventions/withdrawal of a trial participant:

In case of COVID-19, one has to be vigilant about overall progress of the participant and ensure that no undue risks are taken to continue the participant in the trial. Following are few representative criteria for discontinuing interventions:

Prophylaxis trial:

- Participants who will develop symptoms along with positive RT-PCR report within first 7 days after starting the treatment
- In case of any serious adverse event

- Any other serious medical condition which the participant may acquire during the course of the trial which makes it difficult for the participant to continue in the trial
- Any other condition which the investigator feels might cause harm to the participant

Treatment trial:

- If the patient worsens or needs ICU admission/ventilator support
- If the patient adversely reacts to any component of intervention
- If the treating physician opines that the patient requires emergency rescue medication. The use of rescue medication will be documented in case report form and will be considered during analysis

Recovery trial:

- If the individual worsens
- If the individual turns COVID-19 positive as per RT-PCR test

In the event of the following clinical presentations, patients should be referred for modern medical care irrespective of the stage of the disease:

- SpO_2 less than 94% at room air
- Shortness of breath
- 50% lung involvement in imaging
- High grade fever (above 38.2 degree Celsius)
- Worsening of other symptoms
- Heart rate / Pulse rate: less than 50 or greater than 125 /min
- Respiratory rate > 24 breaths/min
- CRP > 100
- CPK > twice upper limit of normal
- Absolute lymphocyte count < 0.8
- Systolic Blood Pressure: less than 90 mm of Hg.
- PT results below 10 seconds or above 18 seconds and / or INR less than 0.7 and greater than 1.8. For those on blood thinners INR above 2.8.
- In addition, criticality of patient based on clinical judgment of treating physician.

If the participant is unwilling to continue or non-compliant, irrespective of prophylactic or treatment trial, will be withdrawn from the trial.

Outcomes

All RCTs assess response variables, or outcomes (end points), for which the groups are compared. Most trials have several outcomes, some of which are of more interest than the others.

The primary outcome measure is the pre-specified outcome considered to be of greatest importance to the stakeholders (such as patients, policy makers, clinicians, funders) and is usually the one used in the sample size calculation. It is reflection of the primary objective of the trial. Some trials may have more than one primary outcome. Having several primary outcomes, however, incurs the problems of interpretation associated with multiplicity of analyses and is not recommended.

Other outcomes of interest are secondary outcomes (additional outcomes). There may be several secondary outcomes, which include symptomatic relief, blood biochemistry, serology and unanticipated/unintended effects of the intervention.

Safety should always be viewed as important, whether it is labelled primary or secondary. All outcome measures, whether primary or secondary, should be identified and completely defined. The principle here is that the information provided should be sufficient to allow others to use the same outcomes.

When the outcomes are assessed at several time points after randomisation, the Investigator should also indicate the pre-specified time point of primary interest. In case of non-pharmacological interventions, it is desirable to specify who assessed outcomes (for example, if special skills are required to do so) and how many assessors there were. (Please refer CONSORT Extensions for non-pharmacological interventions.)

Where available and appropriate, the use of previously developed and validated scales or consensus guidelines should be reported both to enhance quality of measurement and to assist in comparison with similar studies. For example, assessment of quality of life is likely to be improved by using a validated instrument. The prospective investigators are advised to be well versed with expanding literature on COVID-19.

A systematic review of COVID trials on TCM registered on 19 different platforms included a total of 97 protocols. This review has reported 76 outcome measures from 16 outcome domains. The most frequently reported outcome was duration for negative conversion of SARS-CoV-2 RNA. The review has also reported large variation in instrument used for outcome measurement and measurement time frame. The authors have therefore highlighted need for developing a core outcome set (Box 6).

(Ref: RuijinQiu, Xuxu Wei, Mengzhu Zhao, et al. Outcome reporting from protocols of clinical trials of Coronavirus Disease 2019 (COVID-19): a review available at https://www.medrxiv.org/content/10.1101/2020.03.04.20031401v1 last accessed on 28th April 2020)

Box 6: Different outcomes domain reported in trials on TCM

- Mortality/survival
- Physiological/Clinical
  - Blood/lymphatic system e.g. C-reactive protein
  - Cardiac outcomes e.g. ECG
  - GI outcomes such as GI transit time
  - Hepatobilliary outcomes like LFT
  - Immune system outcomes such as HLA-DR, Immunoglobulins
  - Infection and infestation outcomes e.g. negative test for COVID-19
  - Renal outcomes viz. RFT
  - Psychiatric outcomes
  - Respiratory, thoracic and mediastinal outcomes such as Pulmonary Function Test, chest imaging, Ventilation requirement
  - Overall functioning such as recovery rate, time to recovery
  - Quality of Life using standardized and validated scales
- Resource use such as hospital, need for further intervention
- Adverse events/effects

One such outcome set, from which the Investigator can select the outcome measures for COVID-19 trials, is provided below:

Prophylaxis trials:

Primary outcome measure:

- Number of individuals turning COVID-19 RT-PCR test positive
- Average duration in which individuals turned positive

Secondary outcome measures:

- Number of individuals displaying symptoms such as fever, cough, dyspnoea
- Adverse events
- Improvement in immune status using immune status questionnaire (Ref: Int. J. Environ. Res. Public Health 2019; 16, 4743)

Treatment trials:

Primary outcome measure:

- Time taken to get COVID-19 RT-PCR test negative

Secondary outcome measures:

- Length of time to clinical improvement/disease progression*
- Duration of fever and respiratory symptoms
- Incidence of respiratory failure
- Number of days of treatment and hospitalization
- Requirement of Rescue medication
- Percent mortality
- Adverse events
- Quality of life (WHO QOL Brief)

***** Only the accepted, standard, validated definitions related to disease diagnosis and severity classification should be used (Section 5.2).

Recovery trials:

Primary outcome measure:

- Time taken to recover healthy status/normalization of daily life activities

Secondary outcome measures:

- Improvement in lung function test
- Decrease in perceived stress score
- Decrease in fatigue

It must be however noted that the above list is representative and does not cover all possible outcome measures. Since the outcomes are dependent on objectives, various other outcome measures can be considered. For example, if in a treatment trial, the objective is to assess impact of AYUSH intervention on patient's clinical condition (that means the patient will be followed even after disease progression) then outcome measures such as number of days on ventilation/in ICU, number of days required for normalization of oxygen saturation can be also deployed.

Laboratory investigations (for all types of trials)

- 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 (alpha and beta), Interleukin-6, Interleukin-4, Interleukin 17, Interleukin 13, MCP
- Nasal and throat swab for specific test for COVID 19 based on RT-PCR
- Immune Status (serology for specific anti SARS-CoV-2 IgM and IgG antibodies)

This is a comprehensive list of investigations. However, the Investigator should select (or even add) tests considering sample size, resources, logistics (available infrastructure, need to store or transport samples) and their relevance to research question. It is also worthwhile to understand the purpose behind each of the investigation. It could be any of the following:

- Screening
- Diagnosis
- Rule out comorbidities
- Monitor efficacy
- Assess safety
- Explore more about disease

Clarity on this aspect will help to select important laboratory investigations to support clinical findings.

Variables based on diagnostic and prognostic factors from AYUSH systems (for all types of trials)

As a part of outcome measures, use of such variables is certainly accepted and welcomed along with validated modern medical outcome measures. However, these variables should be employed thoughtfully. Following are few suggestions for their effective use:

- Do not select variables which overlap with standard and validated definitions of disease. For example, if Acute Respiratory Distress is defined and assessed using standard terminology, then self-developed score for dyspnoea/difficulty in breath may not have any further value addition.
- Do not use outcome measures those are not validated. The symptoms in general should not be graded (Grade 1, Grade 2 etc) and used as outcome variables.
- Do not use variables like Prakriti/Mizaj/Constitution which are non-modifiable as outcome measures. These should be treated as confounders and documented only at baseline. These variables are however important for sub-group analysis.
- Do consider the variables which have standardized instrument for assessment.
- Do consider only those variables which have clinical relevance in COVID-19. For example, including *bala* (improvement in strength) as a variable in patients receiving Ashwagandha, though relevant from pharmacology of Ashwagandha, may not be much relevant in COVID context.
- Do consider the duration required for assessment of these variables as it may not be possible to interview/inspect/examine COVID patients for long duration.

Time schedule of enrolment, interventions, and assessment

In historical context, it is important to know over what period participants will be recruited. The statistics of disease having infectious and contagious pathology like COVID-19 viz. number of active cases, magnitude of virulence, doubling rate is dynamic feature. In addition, medical management of the disease is also evolving very fast viz. development of vaccine, plasma therapy, stem cell therapy etc. These advancements may affect the conventional management given to participants during the trial. Hence, it is necessary to mention the schedule of enrolment and length of follow up.

There is no fixed rule about frequency of assessments during the follow up period. In case of infectious diseases like COVID-19, follow up period is not very long (Maximum 3 months for prophylaxis trials and 28 days for treatment trials), investigator should plan frequency of assessment at reasonable interval during this period (for example, monthly in case of prophylactic trials and weekly in case of treatment trials). Like laboratory investigations, investigator should consider factors viz. sample size, resources, logistics and relevance to research question while deciding frequency of assessments.

Sometimes, the follow up period can be extended even after stopping the treatment to assess sustainability of the intervention effect. It is good idea that in prophylactic trials, participants are followed for a period equivalent to the period for which intervention is administered.

A schematic diagram depicting these schedules is highly recommended. (Please refer CONSORT Statement)

Sample size

The sample size for a trial needs to be planned carefully considering scientific rationale and ethical reasons. It should balance clinical and statistical significance and logistics considerations. The balance in terms of feasibility (availability of patients & funds) and science

(minimum sample size required for meaning outcomes) should also be considered for calculating sample size. For example, a prophylactic study will need a large sample and 30 participants in each group will not be adequate to judge the potential of studied intervention.

The studies planned for evaluation/validation/comparison of interventions in COVID 19 are 'clinical trials' and not 'epidemiological studies' and hence prevalence of the disease is not required for calculating sample size for such studies. The elements of the sample size calculation for clinical trial are:

- the estimated effect size (which implies the clinically important target difference between the intervention groups in terms of primary outcome for example, 10% more patients turning negative in AYUSH intervention arm); decided by the Investigator based on clinical judgement
- the α (type I) error level; conventionally set at 5% (0.05)
- the statistical power [or the β (type II) error level]; conventionally set at 20% (0.20)
- the standard deviation of the measurements, for continuous outcomes; used from previously reported studies

(Ref: Prashant Kadam and Supriya Bhalerao. Sample size calculation. Int J Ayurveda Res. 2010; 1(1): 55–57)

If in the section of trial design, conceptual framework of the trial has been specified by the Investigator (superiority/equivalence/non-inferiority), then the effect size needs to be considered accordingly.

The investigator should indicate in the proposal how the sample size was determined. If a formal power calculation was used, (s)he should identify the primary outcome on which the calculation was based, all the quantities used in the calculation, and the resulting target sample size per study group. Details should be given of any allowance made for attrition or non-compliance during the study.

Investigator should seek help from statistician for calculating sample size.

Allocation of participants to study groups

The participants should be assigned to comparison groups in the trial on the basis of a chance (random) process characterised by unpredictability. The investigator should specify the method of sequence generation, such as a random-number table or a computerised random number generator.

In trials of several hundred participants, simple randomisation can usually be trusted to generate similar numbers in the two trial groups and to generate groups that are roughly comparable in terms of known and unknown prognostic variables. For smaller trials (which are generally carried out with AYUSH interventions), some restricted randomisation (procedures to help achieve balance between groups in size or characteristics) such as block randomization or stratified randomization may be useful.

Blinding

Blinding or masking is the process of keeping the study group assignment hidden after allocation. It is commonly used to reduce the risk of bias in clinical trials with two or more study groups. Any of the groups, viz. trial participants, investigators, care providers, data collectors, outcome assessors or data analysts can be blinded. The pre-requisite for 'blinded'

studies is that there should not be obvious differences between the interventions being compared.

Since it is not easy (though not impossible) to match AYUSH interventions (specially in case of whole system studies) with conventional management of COVID-19, blinding is mostly not possible and hence open label studies remains as a main option. However, the outcome assessors can still be blinded and an 'assessor blind' method can be used.

Data collection methods

Considering the critical importance of COVID-19, data from the trial participants should be collected extensively. All the below mentioned documents should be developed and retained.

- A CRF [WHO CRF for Novel coronavirus (COVID-19) - rapid version to be filled in COVID-19 trials with active cases as per guidelines]
- A database that stores the above information for each patient with the subsequent observations by the physician at every visit
- Reports of all laboratory investigations to help physicians understand efficacy of diagnostic tools and/or interventions

Data pertaining to AYUSH diagnosis, interventions and any patient specific observation should also be captured systematically to help

- guide physicians in future treatments
- document the decision tree from observations to diagnosis and from diagnosis to management plan (in case of personalized stand-alone interventions)
- gather evidence regarding the relative efficacy of various AYUSH interventions
- establish credibility, mainstream acceptance of AYUSH interventions globally

The investigators can use suitable platform for electronic health records (HER). The terminologies defined by 'National AYUSH Morbidity and Standardized Terminologies Electronic Portal (www.namstp.ayush.gov.in) should be used to maintain diagnostic data. The database of trials should follow principle of confidentiality. The EHR should allow a role-based access to investigators and the staff involved in trial activities.

Retention

Non-retention refers to instances where participants are prematurely 'off-study' (i.e., consent withdrawn or lost to follow-up) and thus outcome data cannot be obtained from them. The majority of trials will have some degree of non-retention, and the number of these 'off-study' participants usually increases with the length of follow-up. It is therefore desirable to plan ahead for how retention will be promoted in order to prevent missing data and avoid the associated complexities in both the study analysis and interpretation.

This is very relevant in case of prophylactic trials, where the participants may be asked to keep a compliance diary or a mechanism of regular telephonic follow-up may be instituted. It is also suggested that the participants are individually reminded on a daily basis with messages or another social media tool. All participants must be encouraged to register in the AYUSH SANJEEVANI Application

Statistical methods

Data analysis methods should be based on trial objectives and study outcomes. It is essential to specify which statistical procedure will be used for each analysis. Any additional analyses (e.g. subgroup analysis as per AYUSH system variables, age, sex, perceived risk categories in

case of prophylactic trials or disease severity in case of treatment trials), if planned/considered should be specified in the proposal. It is also important to describe details of the statistical analysis such as per protocol or intention-to-treat analysis and the statistical method that will be used to handle missing data (e.g. last observation carried forward, multiple imputation). In case of COVID-19 trials, intention-to-treat analysis is the best approach. For multi-arm trials, the comparisons will be based on the objectives.

Investigator should seek help from statistician for statistical analysis.

Data monitoring

It is desirable that the study sites should set up a data monitoring committee (DMC) in view of the criticality of COVID-19 clinical trials. The primary mandate of the DMC is to protect patient safety. If adverse events of a particularly serious type are more common in the experimental arm compared to the control arm, then the DMC would consider termination of the study. This evaluation has to be made in consideration of risk/benefit. In many cases, the experimental arm could cause serious adverse events, but the resulting improvement outweighs these adverse events.

Harms

Evaluation of harms has a key role in monitoring the condition of participants during a trial. Here, the term "harms" is used intentionally instead of "safety" to better reflect the negative effects of interventions. Harms can be specified as primary or secondary outcomes.

An adverse event refers to an untoward occurrence during the trial, which may or may not be causally related to the intervention or other aspects of trial participation. This definition includes unfavourable changes in symptoms, signs, laboratory values, or health conditions. Hence, it is important to note baseline symptoms carefully and with all possible minute details, so those can be differentiated while assessing the causality of the adverse event with intervention. An adverse effect is a type of adverse event that can be attributed to the intervention.

The protocol should describe the procedures and frequency of harms data collection and should address the reporting of harms to Ethics Committee and data monitoring committee at the study site. In addition, the adverse events reported during clinical trials with Ayurvedic interventions have to be reported to National Pharmacovigilance Centre (NPC), All India Institute of Ayurveda, New Delhi (www.aiia.gov.in/pharmacovigilance). All adverse events reported with NPC are assessed for causality by the team of experts before labelling them adverse event or otherwise.

A list of probable adverse events that a study intervention is likely to produce (considering its AYUSH pharmacology) may be prepared in advance. The investigator should be vigilant about signs and symptoms mentioned in such list. For example, a patient receiving Ayurvedic drug, Pippali (*Piper longum*) is likely to develop acid-peptic disorder or the one receiving Bhallatak (*Semecarpus anacardium)* may suffer from blisters/ulcers. The investigator should ask the patient specifically about such events.

Auditing

Auditing involves periodic independent review of core trial processes and documents. It is intended to preserve the integrity of the trial and to prompt corrective action if necessary. The processes reviewed during auditing include participant enrolment, consent, eligibility, and

allocation to study groups, reporting of harms and completeness, accuracy, and timeliness of data collection while the documents include trial master file, informed consent documents, source documentation etc. Further, an audit can verify adherence to applicable guidelines; rules and regulations such as the ICH-GCP guidelines.

Audits can be done by exploring the trial dataset or performing site visits. The procedures and frequency of such visits is planned a priori and should be outlined in the protocol. Audit is generally done by a person or group of individuals independent of Investigator and funding agency.

6. Ethics and dissemination

Research ethics approval

No trial should be started without approval of the Institutional Ethics committee (EC). The role of Ethics committees (ECs) is very important while reviewing the protocols amidst the disrupted physical-socio-cultural environment like COVID-19 pandemic. The EC should ensure that need to undertake research quickly does not impact scientific validity and ethical standards. The EC should consider an expedited review/ scheduled or unscheduled full committee meetings, virtually or through tele-conferences as face-to-face meetings are not possible. This may be decided by Member Secretary on case-to-case basis depending on the urgency and need (Section 12, National Ethical guidelines). The EC may ask for involvement of a physician from modern medicine or an expert in microbiology/virology as a Co-Investigator in the trial being carried out in AYUSH facility.

Consent or assent

There is detail description about the consenting procedure for the research during emergencies and disasters in National guidelines which include few additional precautions (apart from those taken during routine research). The Investigator MUST refer the specific section in the guidelines and comply with the details.

In India, individuals above the age of 18 years are considered eligible for consent. For the trials planned in the individuals below this age, parent or guardian consent is taken. In addition, assent of children above the age of 7 years needs to be taken.

Confidentiality

COVID-19 has caused disruption of governance, infrastructure and communication networks which can lead to a breach of privacy and confidentiality. There can be stigmatization and discrimination which should be minimized at all stages of research, even after completion of study. The presentation of case report or case series should follow confidentiality and all related principles of national ethics guidelines 2017.

Access to data

Since the COVID-19 is sensitive issue from various aspects, the research team and funding agency will only have access to the data and final trial dataset.

Ancillary and Post-trial care

The ancillary care refers to the care provided beyond the scope of the proper and safe conduct of the trial and the treatment of immediate adverse events related to trial procedures. This provision of ancillary care reflects the fact that participants rely on research team for their overall health during trial period. The post-trial care refers to the arrangements for post-study

access by study participants to interventions identified as beneficial in the study or access to other appropriate care or benefits.

Both these aspects of care are more pertinent to clinical trials which are undertaken by Pharmaceutical Industry for regulatory purpose. However, even in case of COVID-19 AYUSH intervention trials (investigator initiated and financially supported by the Ministry of AYUSH), some appropriate follow up mechanisms can be suggested to the participants.

For example, continuation on AYUSH advisory for COVID-19 in prophylactic trials or prescription based on symptoms in the last assessment for therapeutic trials

Dissemination policy

The Investigator MUST communicate trial results to participants, healthcare professionals, the public, and other relevant groups (via publication, reporting in results databases, or other data sharing arrangements) after completion of the study. However, no information based on unjustified claims or the findings of interim analysis should be communicated in any form.

It is expected from the Investigator to undertake COVID-19 trials for altruistic purpose and not for any personal or professional interest.

6.6 CTRI registration:

Any clinical trial has to be registered with Clinical Study Registry of India (CTRI) after EC approval and before recruitment of the participant begins. If the trial is multicentric, after approval from at least one Ethics committee, CTRI registration can be done. In that case, the patient recruitment should be started only on that site, where EC approval is obtained. The status of the other sites EC approvals should be updated on CTRI accordingly as and when they are available. The trial status should be updated at every stage till the final publication of results.

7. Indemnity issues

The COVID-19 trials have put forth many indemnity issues for both, the trial participants and the Investigator.

Each participant recruited in the trial should be covered under clinical trial liability insurance policy. Such insurance policy taken will cover the compensations to the participants involved in the study and compensation or cost for medical treatment of any possible injuries to study participants, caused specifically due to any of the component of intervention.

At the same time, investigator safety should be also considered with importance. The investigator will be provided with PPEs. The ECs will consider the legal implications, if any, while permitting the trial.

8. Appendices

Informed consent material

The ideal consent document should include the purpose of the trial; potential benefits and risks; their right to refuse participation or to withdraw consent at any time; institutional affiliation and potential competing interests of the researcher; and sources of trial funding.

If the Investigator has any plan to subject the biological specimens (blood, saliva) collected from the trial participants later for any further research (which is not part of the present protocol, it must be specified in the consent document.

Biological specimens

Biological specimens (blood, saliva) obtained during the conduct of clinical trials can be stored in repositories (biobanks) for the current trial and future research. This process is usually governed by local regulation and has particular ethical considerations. The National Ethical Guidelines by ICMR (Section 11) should to be referred for further details.

Further reading:

1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement 2013 available at https://www.spirit-statement.org/about-spirit/ last accessed on 28th April 2020
2. CONSORT (CONsolidated Standards of Reporting Trials) 2010 statement available at http://www.consort-statement.org/consort-2010 last accessed on 28th April 2020
3. National Ethical Guidelines for Biomedical and Health Research Involving Human Participants released by ICMR, 2017 available at https://www.icmr.gov.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf last accessed on 29th April 2020
4. Natalie E. Dean, Pierre- Stéphane Gsell, Ron Brookmeyer, et al. Creating a Framework for Conducting Randomized Clinical Trials during Disease Outbreaks. N Engl J Med 382;14: 1366-69
5. WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis available at https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf last accessed on 28th April 2020

ANNEXURE ONE

Outline of a protocol to collect data of population based prospective studies on effectiveness and outcomes of AYUSH prophylactic interventions against COVID-19

Developed by Working Group constituted by Inter Disciplinary R&D Task Force, Ministry of AYUSH, Government of India.

Outline of a protocol to collect data of population based prospective studies on effectiveness and outcomes of AYUSH prophylactic interventions against COVID-19

1. Scope of Study

Safety and outcomes of AYUSH prophylactic interventions against COVID-19.

Safety and effectiveness of AYUSH interventions introduced for prophylaxis against COVID-19 in population groups classified as high, moderate, or low risk shall be studied. This study is specifically targeted for people who are not tested positive for COVID-19.

Studies considered here are prospective cohort / longitudinal cohort studies. They are interventional in nature.

2. How to use this document?

This document may be used as a baseline guidance while developing study protocols and data collection programs in the above situations.

3. The Study population:

All consenting adults, irrespective of gender and who has not been tested positive for SARS-CoV2 virus infection may be enrolled in the study, considering the specifications of the inclusion and exclusion criteria.

Those who are tested positive for SARS-CoV2 virus infections before enrollment shall not be subjects in this study. Any subject in the study, tested positive for SARS-CoV2 virus infection within 7 days of enrolment in the study, shall cease to be considered as a subject of the study.

In any category, a person developing flu and cold like symptoms will continue to participate in the study if not tested positive for COVID-19.

4. Classifying the study population:

There could be multiple cohorts in one study. The population in a study may be divided into subsets and further sub-stratified into smaller cohorts based on the similarity of characteristics of the subjects. The entire population receiving a specific type of AYUSH intervention for prophylaxis against COVID-19 may also be considered as one cohort.

Sub-groups of the cohort population, stratified based on the perceived risk for contracting COVID-19 for the purpose of classification and data anaylsis:

1. High risk exposure - Those in direct contact
    a. Health care workers dealing with COVID-19 patients
    b. Frontline workers dealing with COVID-19 patients
    c. Family members in direct contact with COVID-19 patients

2. Moderate risk exposure – Exposed but not in direct contact
    a. Health care workers
    b. Frontline workers
    c. People in quarantine (travel history, contact tracing etc.)

3. Low risk
    a. People in containment zones
    b. General population

Further sub-stratification that may be applied in the classification:

a. Age group
b. Region
c. Occupation
d. Comorbidities
e. Immune compromised

All the above may also be sub-stratified based on specific requirements of the protocol.

- If a person moves from one risk category to the other within the study cohort, within the study period, they will be considered within the higher risk category, which ever it is.

- These categorization of the enrolled population of study should be undertaken at the time of recruitment of the subjects.

5. Broad outline for inclusion and exclusion criteria

a. Inclusion criteria

a) Population as explained in under the heading “The Study Population” in this document
b) Not tested positive for SARS-CoV2 virus infection
c) Aged 18-60 years
d) Consenting to participate in the study and sign the informed consent

b. Exclusion criteria

a) Persons with severe primary respiratory disease or related complications that needs to be identified with COVID-19
b) Laboratory confirmed COVID-19 with or without symptoms
c) Pregnant and lactating mothers, and those who have a pregnancy plan.
d) Persons with serious, critical illness, or severe mental illnesses.
e) Those who are to be excluded in the study, as evaluated by the investigators

6. Demographic data to be collected:

a) Name:
b) Address:
c) Occupation:
d) Gender:

e) Marital Status:
f) Children:
g) Ethnic community:
h) Education:
i) Employment:
j) Income:

7. Co-morbidities: (to be noted on first visit):

- Diabetes, Heart diseases, Hypertension, Lung Disease, Renal Disease, Stroke, Cancer, Others

8. General Health Status Assessment: (on all visits)

- Vitals – Temperature, Pulse, Blood Pressure, Respiratory Rate, Height, Weight
- Nutritional Status

9. Lab data: (on first visit and every 15 days thereafter)

- CBC, Hb, ESR, CRP, Blood Sugar, CT, BT, CPK, Immune Markers. As done or specifically performed as part of the study.

- These lab data and may be documented as appropriate and possible based on the contextual setting of the study. The time series data and any additional lab investigations (if any) are to be collected as per the specific protocols.

- If the above tests are done as part of the study, these can be preferably examined at four time points at 15-day intervals.

10. Symptoms to be specifically noted, if present: (on all visits):

- Fever, Running Nose, Cough, Dry Cough, Breathing Difficulty, Body Ache, Diarrhea, Loss of smell, Loss of taste, Vomiting, Skin Rashes, Redness of eyes, Chills, Shivering, Headache, Sore Throat, Delirium

11. Immune Status Questionnaire : (on all visits)

- Immune Status Questionnaire to be administered as appropriate. At baseline, Immune Status of the last twelve months is assessed using ISQ. Subsequent assessment will cover the period from the point of the previous assessment of Immune Status. https://www.mdpi.com/1660-4601/16/23/4743

12. Other Parameters to be Assessed (on all visits)

- Appetite, bowels, sleep to be recorded

13. Concomitant Medications (Details recorded on all visits)

- Modern Medicine, AYUSH, Others

14. Any preventive measures followed before enrolment (on first visit)

- AYUSH Guideline/State Guideline/Others

16. Study interventions

- Study interventions can be any as defined by the investigation protocol. It could be a single internal medicine, a combination of several interventions (for example; internal medicine, food, water, steaming, and oil application); a combination of several select interventions from different systems of AYUSH (for example: Homeopathic medicine and Ayurveda nasal application, and Siddha medicine Kashaya), and may also include advisories for general disinfection like fumigation and life style changes. Name, Dosage, Duration of Use to be noted,

17. Duration of intervention

- 45 days / 90 days or until tested COVID-19 positive, whichever is earlier. It is preferred that the study should be for 45 days than 90 days, though depending on the resources available, a protocol may also be prepared for 90 days.

18. Frequency of Assessments

- Baseline on enrolment, 15 days, 30 days, 45 days or as specified or appropriate to the study

19. End Points

a. Primary Endpoint

- COVID-19 Test Positivity/Negativity

b. Secondary Endpoints

- General and specific health status as described above).
- Immune Status and Function as assessed by ISQ

20. Considerations for control group:

A Control Group may be assigned by identifying an Identical Population in appropriate strata and sub strata of the cohort not receiving any AYUSH prophylaxis intervention. This option may be considered with the approval of the ethics committee.

21. Ensuring follow-up:

People undergoing prophylaxis treatment may be asked to keep a compliance diary or a mechanism of regular telephonic follow-up may be instituted. It is also suggested that the subjects are individually reminded on a daily basis with sms messages, or another social media tool.

All subjects must be encouraged to register in the AYUSH SANJEEVANI Application

22. Conduct of the study:

The study intervention and documentation may be through household level practices documented through digital tools, telephonic interviews, direct documentation by Village health workers/ASHA workers, AYUSH practitioners or a multidisciplinary team of experts.

23. Title of the study:

Examples:

- A longitudinal cohort interventional study assessing the safety and outcome of "*XYZ AYUSH intervention*" as a prophylaxis against SAR-CoV2 virus infection among a population of health care workers at high risk of exposure to the virus at Pathanamthitta in Kerala.

- A prospective cohort interventional study assessing the safety and outcome of "*XYZ AYUSH intervention*" as a prophylaxis against SAR-CoV2 virus infection among police personnel delegated to COVID-19 management duty at New Delhi

- A prospective cohort interventional study assessing the safety and outcome of "*XYZ AYUSH intervention*" as a prophylaxis against SAR-CoV2 virus infection among family members of health worker taking care of COVID patients in Ahmedabad in Gujarat.

23. Protocol preparation

For IEC approval and submitting financial support applications detailed protocol has to be prepared in the following format or as per specified format, depending on the objectives of the study or application format of the organization:

- Title:
- Background:
- Objective

    - Primary
    - Secondary
- Proposed methods
- Study participants
- Inclusion criteria
- Exclusion criteria
- Study design
- Study Setting
- Intervention
- Outcome
    - Primary outcome
    - Secondary outcome
- AYUSH based assessments
- Sample size
- Data collection
- Data analysis
- Ethical considerations - Human participant protection
- Expected benefits
- Limitations of the study
- References

Further reading:

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines:

https://www.equator-network.org/?post_type=eq_guidelines&eq_guidelines_study_design=observational-studies&eq_guidelines_clinical_specialty=0&eq_guidelines_report_section=0&s=+&eq_guidelines_study_design_sub_cat=0
https://www.equator-network.org/wp-content/uploads/2015/10/STROBE_checklist_v4_combined.pdf

The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement

https://www.equator-network.org/reporting-guidelines/record/

ANNEXURE TWO

Outline for development of Case Record Forms for Population-Based Ayurveda Studies in COVID-19

Developed by Working Group constituted by Inter Disciplinary R&D Task Force, Ministry of AYUSH, Government of India.

OUTLINE FOR DEVELOPING CRFs

Population based Prospective Studies on effectiveness and outcomes of AYUSH prophylactic interventions on population at risk of COVID-19

Given below are pointers for developing Screening Visit, Baseline Visit, Midpoint Visit and Endpoint Visit CRFs.

SCREENING VISIT CRF

Demographic Details:

Name:
Address:
Occupation:
Gender:
Marital Status:
Children:
Ethnic community:
Education:
Employment:
Income:

Assign Subject ID which will be used in all CRFs. No identifying information to be included in CRFs after Subject ID has been assigned.

Identify which of the following groups the subject falls into

High risk exposure - Those in direct contact
- Health care workers dealing with COVID-19 patients
- Frontline workers dealing with COVID-19 patients
- Family members in direct contact with COVID-19 patients

Moderate risk exposure – Exposed but not in direct contact
- Health care workers
- Frontline workers
- People in quarantine (travel history, contact tracing etc.)

Low risk
- People in containment zones
- General population

Subjects presenting with flu and cold like symptoms must be referred for COVID-19 testing

Confirm Subject Eligibility

Inclusion criteria

1. Population as described in point 2
2. Aged 18-60 years
3. Consenting to participate in the study and sign the informed consent

Exclusion criteria

1. Persons with severe primary respiratory disease or related complications that needs to be identified with COVID-19
2. Laboratory confirmed COVID-19 with or without symptoms
3. Pregnant and lactating mothers, and those who have a pregnancy plan.
4. Persons with serious, critical illness, or severe mental illnesses.

Those who are to be excluded in the study, as evaluated by the investigators

Recruit subject into study if found eligible.

BASELINE VISIT CRF

Subject ID
Date of Enrolment

Check if tested positive for COVID-19 after the initial screening. Subject will not be enrolled if tested positive even though found eligible at time of screening.

Assessment of General Health Status

Does the subject suffer from any of the following symptoms?

Fever
Running Nose
Cough
Dry Cough
Breathing Difficulty
Body Ache
Diarrhea
Loss of smell
Loss of taste
Vomiting
Skin Rashes
Redness of eyes,
Chills,
Shivering,
Headache,
Sore Throat
Delirium

If the subject presents with any of these symptoms, put the enrolment on hold and refer for COVID-19 testing.

Check the vital functions

Temperature
Pulse
Blood Pressure
Respiratory Rate
Height
Weight
Appetite
Sleep
Bowel
Micturition

Check the Nutritional Status

Malnourished
Satisfactory
Obese

Assessment of Specific Health Status

Does the subject have any preexisting disease?

Diabetes
Heart diseases
Hypertension
Lung Disease
Renal Disease
Stroke
Cancer
Others

Perform the following blood tests before enrolment of subject

CBC
Hb
ESR
CRP
Blood Sugar
CT, BT
Immune Markers

Administer the Immune Status Questionnaire (ISQ)
https://www.mdpi.com/1660-4601/16/23/4743

Note the Concomitant Medications already being taken by the subject

Modern Medicines

AYUSH Systems

Others

Study Interventions
Specify the name, dosage and recommended duration of administration

MIDPOINT VISIT CRF

Subject ID
Date of Visit

Check if tested positive for COVID-19 after enrolment. Subject will be terminated from study if tested positive even after enrolment. Patient may be terminating from study immediately at any point in the study when tested positive for COVID-19.

Assessment of General Health Status

Does the subject suffer from any of the following symptoms?

Fever
Running Nose
Cough
Dry Cough
Breathing Difficulty
Body Ache
Diarrhea
Loss of smell
Loss of taste
Vomiting
Skin Rashes

If the subject presents with any of these symptoms refer for COVID-19 testing. Subject can continue in the study only if the test is negative.

Check the vital functions

Temperature
Pulse
Blood Pressure

Respiratory Rate
Height
Weight
Appetite
Sleep
Bowel
Micturition

Check the Nutritional Status

Malnourished
Satisfactory
Obese

Assessment of Specific Health Status

If patient has comorbidities check for any worsening

Diabetes
Heart diseases
Hypertension
Lung Disease
Renal Disease
Stroke
Cancer
Others

Perform the following blood tests before enrolment of subject

CBC
Hb
ESR
CRP
Blood Sugar
Immune Markers

Administer the Immune Status Questionnaire (ISQ)

Note the Concomitant Medications being continued by the subject

Modern Medicines

AYUSH Systems

Others

Study Interventions

Specify the name, dosage and recommended duration of administration

Check Compliance

Check for compliance with the protocol by examining dairy of medicine intake recorded by the patient.

ENDPOINT VISIT CRF

Subject ID
Date of Visit

Check if tested positive for COVID-19 after previous midpoint assessment. Subject will be terminated from study if tested positive even after enrolment and participation in study. Patient may be terminated from study immediately at any point in the study when tested positive for COVID-19.

Assessment of General Health Status

Does the subject suffer from any of the following symptoms?

Fever
Running Nose
Cough
Dry Cough
Breathing Difficulty
Body Ache
Diarrhea
Loss of smell
Loss of taste
Vomiting
Skin Rashes

If the subject presents with any of these symptoms refer for COVID-19 testing. Subject can continue in the study only if the test is negative.

Check the vital functions

Temperature
Pulse
Blood Pressure
Respiratory Rate
Height
Weight
Appetite
Sleep
Bowel
Micturition

Check the Nutritional Status

Malnourished
Satisfactory
Obese

Assessment of Specific Health Status

If patient has comorbidities check for any worsening

Diabetes
Heart diseases
Hypertension
Lung Disease
Renal Disease
Stroke
Cancer
Others

Perform the following blood tests before enrolment of subject

CBC
Hb
ESR
CRP
Blood Sugar
Immune Markers

Administer the Immune Status Questionnaire (ISQ)

Note the Concomitant Medications being continued by the subject

Modern Medicines

AYUSH Systems

Others

Check Compliance

Check for compliance with the protocol by examining dairy of medicine intake recorded by the patient.

ANNEXURE THREE

Outline to develop protocol to collect data on the safety and effectiveness/ outcomes of AYUSH interventions on asymptomatic and mild to moderate COVID-19 patients

Developed by Working Group constituted by Inter Disciplinary R&D Task Force, Ministry of AYUSH, Government of India.

Outline to develop protocol to collect data on the safety and effectiveness/outcomes of AYUSH interventions on asymptomatic and mild to moderate COVID-19 patients

Objective of this document?

To provide guidance for collecting data related to AYUSH interventions administered to COVID-19 patients who are asymptomatic or have mild to moderate clinical symptoms, in different health care settings.

How to use this document?

This document may be used as a base line guidance while developing study protocols and data collection programs in the above situations.

Scope of Study?

Safety and effectiveness / outcomes of AYUSH interventions for asymptomatic and mild to moderate cases of COVID-19.

Key points to note while designing the study:

Study type:

- If the study does not have a control arm, then it is an observational study.
- If it has a control arm then it can be a case control study, where similar population getting the standard of care at the same clinical establishment and willing to provide the informed consent for use of their clinical data for the study purpose shall be the control arm.
- With a control arm present, it could also be a randomized control study, depending on the randomization process involved in segregating the study subjects to study and control arm.
- Different levels of randomization may be selected depending on the blinding process (unblinded / single blind / double blind etc.).
- Depending on the setting and possibilities the best study methodology should be chosen.
- Since it is conducted on patients admitted as per Govt of India guideline / protocol, it is an add-on study.
- The study is to assess the safety and effectiveness of add-on “XYZ AYUSH intervention”.
- Effectiveness of the intervention may be further explained, and according to the objective of the study. For example:
    - Preventing the progression of the disease to mild to moderate from asymptomatic
    - Preventing the progression of the disease to severe / critical from mild to moderate
    - Time taken to be tested negative for SARS-CoV2 in RT-PCR
    - Severity and outcome of patients who are referred to higher centers owing to criteria for referral
    - Changes in investigational parameters
    - Changes in specific clinical symptoms; etc.

Study setting:

- The study should intend to collect data generated on COVID-19 positive cases who are asymptomatic or presenting with mild to moderate symptoms at:
    - A repurposed AYUSH facility for COVID management
    - Home, if the patient is advised homecare and isolation
    - a collocated AYUSH facility within an allopathic COVID management center
    - an allopathic facility, which is a designated COVID 19 management center offering integrated AYUSH care
- following prevalent govt. guidelines.

Interventions:

- The Intervention is any AYUSH intervention. It may be:
    - a single medicine, or therapy or change in activity etc.
    - a fixed regimen – a combination of medicines, or therapies or change in activities - introduced into the patient care continuum
    - a fluid regimen, with a specified spectrum of medicines, or therapies or change in activities - introduced into the patient care continuum and that shall be modified based on progressive stages of the disease and as per AYUSH specific rationale during the patient care.
- If no allopathic medicine is administered (if that is the case; which may vary from study to study and subject to subject in a study or day to day during the care) then it has to be as per prevalent GoI guidelines and recorded specifically that it has "not been provided" in the daily medication sheet and captured in the CRF. When allopathic medicines are given then it must also be recorded specifically, with details of reason for administration, the name of the medicine with dose, along with any other relevant details, in the daily medication sheet as well as the CRF.
- Concomitant Allopathic and AYUSH medicines which are continued / discontinued during the COVID -19 management period should be specifically mentioned with details. If continued, daily recording of their dose administered should be recorded and also captured in the CRF. If there is change in dosage / brand/ composition of these medications during the COVID -19 management period, that should be mentioned with reason. If these medicines are stopped then it must be recorded with reason.

Developing the Title and Objective of the study:

- While developing the Title or Objective of the study the following points may be noted as appropriate to the individual study:
- The study is a prospective in nature
- It is interventional if there is any additional element added to the GoI COVID -19 management advisory and if the study aims to look the safety and effect of the specific addition to the selected outcome.
- Study can be:
    - Single arm: no control arm (this can primarily establish the safety of the additional intervention)
        - **In case of absence of Case Control Group,** data from identical number of subjects in a population classified under the specified strata and sub strata of the cohort, not receiving any add-on AYUSH

interventions, from the same geographical location, being treated in an identical COVID-19 management facility, and managed during the same period of the study, may be used for comparative reporting and assessment, if approved by the IEC.

- Type of control (comparator arm): Standard of care or placebo or another intervention.
  - Case control: where the control arm is the standard of care
  - Placebo control: where the control arm is the placebo.
- Randomized control: depending on the allocation process involved in the segregation of the subject to the study or control arm
- Blinded: depending on the knowledge of allocation to the subject, investigator or site. (single blind / double blind / triple blind).

Few examples of a title:

- A prospective, interventional, single arm study to observe and assess the safety and effectiveness of "XYZ Ayurveda/Siddha medicine" in preventing the progression of severity of the disease in hospitalized SARS-CoV2 tested positive asymptomatic, mild or moderate COVID-19 cases, managed as per Govt of India COVID-19 management guidelines, at a repurposed Ayurveda/Siddha hospital.
- A prospective, interventional, case control non-randomized study to observe and assess the safety and effectiveness of "XYZ Unani regimen" in preventing the progression of severity of the disease in hospitalized SARS-CoV2 tested positive asymptomatic, mild or moderate COVID-19 cases, managed as per Govt of India COVID-19 management guidelines, at a COVID 19 management facility, administered by a collocated Unani clinical center.
- A prospective, interventional, randomized control study to observe and assess the safety and effectiveness of "XYZ Homeopathic medicine" in preventing the progression of severity of the disease in hospitalized SARS-CoV2 tested positive asymptomatic, mild or moderate COVID-19 cases, managed as per Govt of India COVID-19 management guidelines, at an COVID-19 management center offering integrated Homeopathic care.

Who shall be the study subjects?

Patients who are asymptomatic/pre-symptomatic or presenting with mild to moderate symptoms who have been approved by local authority and ethics committee for administration of AYUSH interventions

Sub-stratification for further analysis (to be collected with the first data set in the CRF).

Age group
Region
Occupation
Comorbidities
Diet and lifestyle

How to classify patients based on clinical presentation:

US CDC classifies mild to moderate, severe and critical stages of COVID-19 based on the following criteria. (as on 28th April 2020):

Stage	Features
Asymptomatic	No specific clinical symptoms of COVID-19 disease
Mild to Moderate	Mild clinical symptoms up to mild pneumonia
Severe	Dyspnea, hypoxia, or >50% lung involvement on imaging
Critical	Respiratory failure, shock, or multiorgan system dysfunction

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

Criteria for referral of patient to modern medical care facility

In the event of the following clinical presentations, patients should be referred for modern medical care irrespective of the stage of the disease

1. SpO2 less than 94% at room air
2. Shortness of breath
3. 50% lung involvement in imaging
4. High grade fever (above 38.2 degree Celsius)
5. Worsening of other symptoms
6. Heart rate / Pulse rate: less than 50 or greater than 125 /min
7. Respiratory rate > 24 breaths/min
8. CRP > 100
9. CPK > twice upper limit of normal
10. Absolute lymphocyte counts < 0.8
11. Systolic Blood Pressure: less than 90 mm of Hg.
12. PT results below 10 seconds or above 18 seconds and / or INR less than 0.7 and greater than 1.8. For those on blood thinners INR above 2.8.
13. In addition, criticality of patient based on clinical judgment of treating physician.
14. In patients with co-morbidities, blood pressure, blood sugar, heart function, lung function and renal function should be constantly monitored. In the event of worsening of co-morbid condition, patient should be referred to modern medical care, based on the treating physicians' observations and decisions.

Broad outline for inclusion and exclusion criteria

Inclusion criteria

1. People who have been tested positive to be infected with SARS-CoV2 virus and presenting with no symptoms or mild to moderate symptoms

Exclusion criteria

1. COVID patients with symptoms classified as severe or critical.
2. Persons with severe primary respiratory disease or other pneumonia

3. Pregnant women
4. Persons with serious complications of diseases such as cancer, heart disease, stroke, disabilities, mental illnesses, etc., and who are considered to be excluded from the study as evaluated by the investigators
5. COVID-19 positive cases participating as subjects in the interventional arm of other COVID-19 clinical trials

CRF:

- WHO CRF FOR NOVEL CORONAVIRUS (COVID-19) - RAPID VERSION TO BE FILLED AS PER GUIDELINES. https://www.who.int/docs/default-source/coronaviruse/who-ncov-crf.pdf?sfvrsn=84766e69_2
- If there are AYUSH specific criteria added as per Study requirement, add them as additional data collected in additional sheets.
- -< C> =LGHGLI [KG <B J>G GKGF<LBDCF HBLYI< BH <;G %&'

Demographic Data to be collected

Name:
Address:
Occupation:
Gender:
Marital Status:
Children:
Ethnic community:
Education:
Employment:
Income:

Co-morbidities:

Diabetes, Heart Disease, Hypertension, Lung Disease, Renal Disease, Stroke, Cancer, Others

General Health Status Assessment

Vitals – Temperature, Pulse, Blood Pressure, Respiratory Rate, Height, Weight, and SPO2 Height need to be checked only the time of first data collection in the CRF. Weight may be checked every week or daily as the need be, the other parameters need to be checked and noted at different times periodically in the day or as required in clinical management. It is recommended that separate charts are used for recording these parameters.

Nutritional Status: Hypo, Hyper, Normal

BMI: (to be calculated from Height and Weight).

Specific Health Status Assessment

CBC, Hb, ESR, CRP, Blood Sugar, CPK, PT INR, SPO2 (pulse oximetry), COVID test as per ICMR guidelines. Immune Markers as per requirement of the study. Test for COVID-19 positivity may be conducted as per prevalent GoI guideline, or as required in the study.

Other medical reports available may be reviewed

Symptoms to be looked for and recorded:

- Fever, Running Nose, Cough, Dry Cough, Breathing Difficulty, Body Ache, Diarrhea, Loss of smell, Loss of taste, Vomiting, Skin Rashes, Redness of eyes, Chills, Shivering, Headache, Sore Throat, Delirium
- Any other symptoms

Concomitant Medications

Modern Medicine, AYUSH, Others

- **AYUSH Interventions**

  In the WHO CRF, include the entire AYUSH regimen (medicines, lifestyle, food, therapies, yoga, counselling and so on with dosage when relevant)> Ref to Question: "Experimental agent?" in the CRF: Tick Yes, and then explain in the space if Yes, Specify.

  - Medicated water/Medicinal formulations/steaming/gargling/nasal application/fumigation/food/lifestyle/yoga/Meditation/physical activities
  - Name, Dosage, Duration of Use to be noted, People undergoing treatment at home may be asked to keep a compliance diary.

- **Duration of AYUSH intervention**

  - Until tested negative or if patient progresses to more severe stage of the disease or as per protocol

Assessments

Arrest or delay in progression:

- progress in asymptomatic to mild to moderate stage
- progress in from mild to moderate to severe or critical stage
- time to test negative
- ease and time of convalescence and residual symptoms / health problems, post infection

Primary Endpoint

- Time to test COVID-19 Negative (days from admission; days from first testing positive; days from first noticed symptoms)
- Time to point of referral (days from admission; days from first testing positive; days from first noticed symptoms)
- Progress from asymptomatic to mild to moderate (days from admission; days from first testing positive; days from first noticed symptoms)
- Progress from mild to moderate to severe or critical stages (days from admission; days from first testing positive; days from first noticed symptoms, days from change in status from asymptomatic to symptomatic).

Secondary Endpoints

- General and specific health status measured by modern and AYUSH parameters (as relevant to the objective of the study)
- If part of the study, specify details of the following:
    - Requirement of rehabilitation for the discharged patient
    - Progress of the disease, its severity and outcome of the disease if the patient is referred
    - Cost of management at the AYUSH facility and at the referral facility
- Additional AYUSH system / study specific outcomes (OPTIONAL) - If such specific parameters are part of the study objectives, develop additional questions and include then into the CRF using additional pages as per the study requirements (in the initial data collection form, daily follow up form and discharge form of the CRF).

Statistics:

- The protocol should be prepared after detailed discussion with biostatisticians.

Consent:

- The study should be conducted only with the informed of consent of the subjects involved, even if they are only providing data or serving in the control arm. Any deviation from this process has to be specifically approved by the Ethics committee clear with reason provided.

Ethics approval:

- Before initiating any study, appropriate ethics committee approval should be obtained. Needless to say, approval of scientific committee must be obtained before submission of proposal to ethical committee.

CTRI registration:

- All study involving human participants should be registered with the Clinical Trial Registry of India

Approval for interventional drug

- It is preferable to obtain the no objection from Ministry of AYUSH, if a new drug / formulation is used in the study.

References used in the document:

https://www.who.int/docs/default-source/coronaviruse/who-ncov-crf.pdf?sfvrsn=84766e69_2

For IEC approval and submitting financial support applications detailed protocol has to be prepared in the following format or as per specified format, depending on the objectives of the study or application format of the organization:

Title: *as per the examples given*

Background: *write why and what you want to do. Give a brief of the expected outcome and benefit. A bit also about the reason for selecting the intervention including its safety.*
Objective: *Safety / effectiveness / Outcome*
Primary: *Look in document*
Secondary: *Look in document*

Proposed methods: *discuss with biostatistician and other clinicians and Look in document*

Study participants: *select from document or as per study*

Inclusion criteria: *select from document or as per study*

Exclusion criteria: *select from document or as per study*

Study design: *discuss with biostatistician and other clinicians and Look in document*

Study Setting: look in document and explain

Intervention

Outcome

- Primary outcome: *select from document or as per study*
- Secondary outcome: *select from document or as per study*

AYUSH based assessments: *as per study*

Sample size: *discuss with biostatistician*

Randomization, sequence allocation & allocation concealment (if any): *discuss with colleagues and biostatistician and as per the study design*

Blinding (if any): *as per protocol*

Case Control (if planned): *as per protocol*

Data collection: *in WHO CRF. Mention if there are additional information being collected. Periodicity of the data collection. Mention if the data is collected in electronic format or paper. Also mention if it is collected from reports, or case sheets or direct examination of the patient or as informed by the clinical care staff or collected using other communication equipment considering the accessibility restrictions to the patients.*

Data analysis: *Mention by whom, when and how. Discuss with biostatistician*

Ethical considerations - Human participant protection, use of resources: *Mention of Ethic committee approval. Insurance (if any) and safety assurance mechanisms in place for subjects, clinical staff and investigators.*

Expected benefits: *Take from introduction, Connect to objectives and outcomes*

Limitations of the study: *Mention all conceivable*

References: *Provide*

Link to Electronic CRFs to be used in Interventional AYUSH studies for COVID-19

1. https://worldhealthorg-my.sharepoint.com/personal/gopalakrishnag_who_int/_layouts/15/Doc.aspx?sourcedoc=%7B7b14c43e-d06f-4212-a10b-22cb990464fe%7D&action=default&slrid=6744529f-a0e7-9000-5a62-ed43c673bc15&originalPath=aHR0cHM6Ly93b3JsZGhlYWx0aG9yZy1teS5zaGFyZXBvaW50LmNvbS86eDovZy9wZXJzb25hbC9nb3BhbGFrcmlzaG5hZ193aG9faW50L0VUN0VGSHR2MEJKQ29Rc2l5NWtFWlA0Qm5QaWtOOFVkMkRlZW9LXzB3WTQyRkE_cnRpbWU9aGliVkFkbjMxMGc&cid=db79bab2-c9bb-45d3-90cf-68dca5ff734f

2. https://worldhealthorg-my.sharepoint.com/:x:/g/personal/gopalakrishnag_who_int/EVXHJSTY8sZEqIsrwesg6zEB-fdP1g9RosQ2djD2RQvRRA?e=4%3ag5qjBh&at=9

ANNEXURE FOUR

Illustrative Stand Alone Treatment Protocol for Ayurveda Interventions in the management of COVID-19

Developed by Working Group constituted by Inter Disciplinary R&D Task Force, Ministry of AYUSH, Government of India.

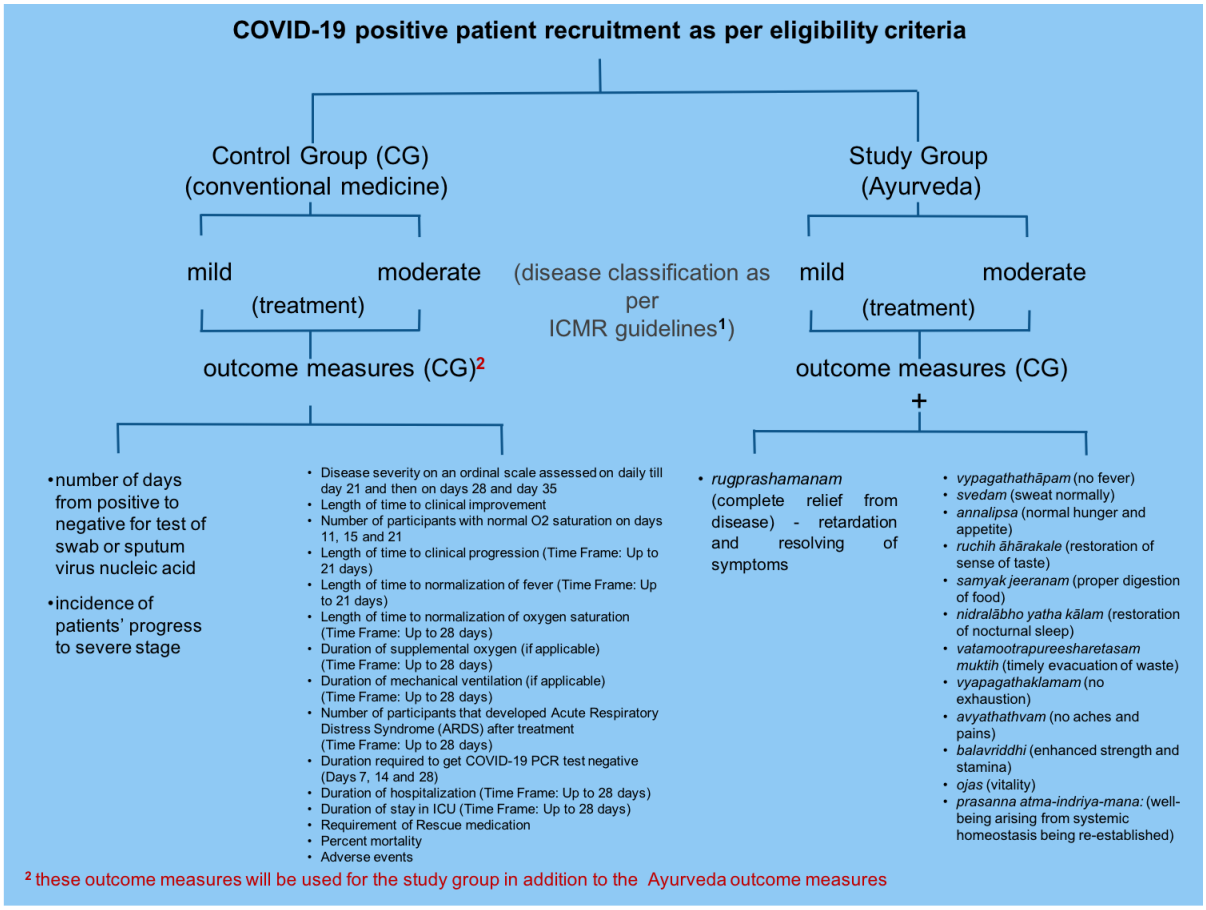
Contents

Summary

Title : Treating COVID-19 positive patients with mild and moderate symptoms via administration of comprehensive Ayurveda intervention: a Multi-centric Randomized Controlled Trial

Null hypothesis (H_0) : Ayurveda intervention will not arrest the progression of the disease and restore health in COVID-19 patients with mild to moderate symptoms.

Based on scientific publications and information in public domain on COVID-19, and personal communication with doctors treating COVID-19 patients, a structured understanding of the disease from the standpoint of Ayurveda has been developed, using its theoretical framework. This has been used to arrive at the therapeutic management. The flowchart given below gives a snapshot of the study details.



[1] https://www.mohfw.gov.in/pdf/RevisedNationalClinicalManagement GuidelineforCOVID1931032020.pdf

Preamble

This Working Group, constituted by Prof. Bhushan Patwardhan, Chairman, 'Interdisciplinary AYUSH Research and Development Task Force' formed by Ministry of AYUSH (No. A. 17020/1/2020-E.I dated 02nd April 2020), Government of India, has been given the task of preparing a document for execution of clinical trial for 'Standalone treatment' by AYUSH systems of COVID-19.

AYUSH is the acronym of the various medical systems (**A**yurveda, **Y**oga & Naturopathy, **U**nani, **S**iddha and **H**omeopathy) practiced in India. Recently, Sowa-Rigpa, the medical tradition practiced in the Trans-Himalayan region has also been included in the AYUSH systems. The document prepared by this WG has focused on Ayurveda. However, the basic structure and layout can be easily adapted and adopted by the other AYUSH systems.

Ayurveda - Existing knowledge

"*Skin diseases, fever, consumption, conjunctivitis and all contagious diseases spread from person to person, by indulgence in bodily contact, by (coming into contact with another's) breath, eating with others in the same plate, sharing of bed and seat, through (contact with) clothes, ornaments, and cosmetics*"

Susruta Samhita (SS), Nidānasthān, Chapter 5, Verses 33-34

"It is not difficult to treat epidemic diseases, provided the herbs are collected, preserved and administered properly (verse 4); Vitiation of factors (air, water, location and seasons) leads to the simultaneous manifestations of diseases (epidemic) having the same set of symptoms leading to the destruction of a country (verse 6); One does not suffer from these (epidemic) diseases even while all these four vitiated factors (air, water, place and season) are at work if he/she is administered with medicines and treatment as given below .... (verses 12-18)"

Caraka Samhita (CS), Vimānasthān, Chapter 3 on *Janapadoddhvamsa* / Epidemics*

**Janapadoddhvamsa - Janapada/community + Udhwamsa/destruction*

Ayurveda is an officially approved system of medicine in India. There is a huge infrastructure accessible in terms of registered practitioners, dispensaries, colleges, hospitals, pharmacies, research centres, etc. It is only logical to expect that in a crisis like COVID -19, the system is of use to the public. Its knowledge base and support system should be used in trying times as the current one.

Ayurveda as a science of life encompasses both health and disease. It has a wide array of principles and practices to deal with health and disease. The uniqueness of Ayurveda is its theoretical framework. The clinical practices and the theories form the backbone of Ayurveda and have a living continuity of practice, documentation and validation for over a millennium. The strength of Ayurveda lies in these well validated theories and practices that can be used to understand, diagnose and strategise treatments of newer diseases like COVID -19. Ayurveda shall be of immense use in the management of COVID -19 crisis.

'Diseases are innumerable and newer ones would keep appearing' says Caraka (1) and provides methods to diagnose and treat new diseases. Ayurveda, with its strong theoretical base and extensive pharmacopoeia with innumerable drugs, is capable of dealing with a wide range of diseases, old or new, known or unknown. Interestingly, Ayurveda also talks of epidemics and the management during this phase in detail. Ayurveda has extensive experience in treating various kinds of fever (virus and bacteria are not new to mankind and have been there since time immemorial), cough and respiratory conditions (2-4). Ayurveda has many effective strategies (medicines, procedures, diet, regimens) for management of the clinical conditions (cough, fever,

respiratory distress) associated with COVID-19. There are more than 400 (this is a conservative number) time-tested and still in-use medicines for these conditions in Ayurveda (5). There is no dearth of medicines in Ayurveda and its use *will hence not be a blind experiment*.

Ayurveda can put together an excellent treatment protocol with a wide variety of medicines for the Coronavirus epidemic, which from the typical symptoms of fever and respiratory conditions, appears to be induced by predominant involvement of *kapha* and *vata doshas*. At the same time, it is important to carry out scientific studies / clinical trials and assess the therapeutic efficacy of Ayurveda / AYUSH interventions. This is the aim of this proposal.

A brief outline of the scientific rationale

Ayurveda sees health as a reflection of the ability of the system to adapt to stress (endogenous and exogenous as in COVID-19). It exists as a continuum with the environment, from soil to plants and animals to our gut and other organs. Diseases, except traumatic injuries, are considered as disruptions within system. Ayurvedic management involves bringing the system back to balance. The science of Ayurveda is so structured that the very same principles that are applied in the treatment of known diseases can be readily used to treat new, unknown conditions. The Ayurvedic approach identifies and treats the disease causing factors (*doshas*) that reside in the body itself but have gone off equilibrium condition, to bring about cure.

Infectious diseases *(aupasargika vyadh*i) were known in the days of yore (6). The mechanism behind such diseases was also understood in terms of *doshas* (the underlying principles in Ayurveda), pathogenesis (*samprāpti)*, signs & symptoms (*lakshanās*), the location (*sthāna*) and treatment (*chikitsā*). For example, in COVID-19, the signs and symptoms (cough, fever and Acute Respiratory symptoms) are induced predominantly by *kapha* and *vata* along with other *doshas* in *uras* (chest region) (location) according to Ayurveda.

In the COVID-19 (as in any other viral disease), two factors, which can be managed by two different strategies, play a major role - (i) the virus itself (the pathogen) - Allopathy has an anti-pathogen approach (ii) the infected person (host) – Ayurveda, predominantly has a pro-host strategy. While the strategy of allopathy is to contain the virus using pharmaceutical agents, *Ayurveda has a pro-patient strategy*.

Ayurveda will adopt a multi-pronged approach addressing the fever, cough and respiratory distress, improving the patient's immunity, and giving the right diet and regimen (customised to age, season, occupation and other factors). Also it may be pertinent to point out that many of the plant ingredients (eg. pepper, ginger, cumin and coriander seeds) used in ayurvedic medicines have been shown to exhibit anti-viral, anti-bacterial and anti-microbial properties (7, 8)

In this proposal, Ayurveda principles (1) will be applied to understand, interpret, diagnose and treat COVID-19. The comprehensive treatment strategy (diet, regimen, medicines) are entirely based on classical, time-tested and documented information in Ayurveda including the management principles specifically advised for during epidemics (9). All strategies adopted are backed by authentic textual references. *The study will adopt the 'Whole Systems Research' (WSR) approach.* WSR is customized trial for evaluating the efficacy of holistic, multi-modal interventions, including polyherbal drug combinations, diet and lifestyle prescriptions as used in traditional medical systems like Ayurveda (10).

References

1. Caraka Samhita, Sutrasthān, Chapter 18, Verses 42-47.
2. Treatment of *Jvara*/fever, Chapter 3, Caraka Samhita, Chikitsasthān.
3. Treatment of Respiratory disorders, Chapter 17, Caraka Samhita, Chikitsasthān.

4. Treatment of cough and related disorders, Caraka Samhita, Chapter 18, Chikitsasthān.
5. Some of the Ayurveda texts which lists a number of time-tested medicines for treating various types of fever, cough and respiratory conditions are given here - (i) Caraka Samhita, (ii) Susruta Samhita, (iii) Sahasrayoga, (iv) Bhaishajya Ratnāvali, (v) Shārangdhāra Samhita, (vi) Ashtānga Sangraha (vii) Ashtānga Hrday, (viii) Kashyapa Samhita, (ix) Cakradatta, (x) Yoga Ratnākara, (xi) Bhāvaprakāsh, (xii) Arkaprakāsha, (xiii) Vangasena Samhita, (xiv) Rasendrasāra Sangraha, (xv) Rāja Nighantu,(xvi) Vaidya Chintāmani, (xvii) Basasvarājeeyam, to name a few.
6. Susruta Samhita, Nidānasthān, Chapter 5, verses 33-34)
7. Pushpa R et al. Antivira potential of medicinal plants : an overview. Intl Res J Pharmacy, 4, 8-16, 2013.
8. Akram M et al. Antiviral of medicinalmplants against HIV, HSV, influenza, hepatitis and coxsackievirus : A systematic review. Phytotherapy Research, 2018. https://doi.org/10.1002/ptr.6024
9. Caraka Samhita, Vimānasthān, Chapter 3
10. Ram Manohar R. Whole System research and Ayurveda. Anc Sci Lif, 31: 37, 2011

Protocol

Item	Description
Administrative information	
1. Title	Treating COVID-19 positive patients with mild and moderate symptoms via administration of comprehensive Ayurveda intervention: a Multi-centric Randomized Controlled Trial
Introduction	
2. Hypothesis	Null hypothesis (H_0): Ayurveda intervention will not arrest the progression of the disease and restore health in COVID-19 patients with mild to moderate symptoms

3. Ayurvedic perspective of COVID-19

Based on scientific publications (> 30 articles) and information in public domain on COVID-19, and personal communication with doctors treating COVID-19 patients, a structured understanding of the disease from the standpoint of Ayurveda has been developed, using its theoretical framework. This is important since Ayurveda's viewpoint and understanding of health and disease is very different to those of Modern Medicine (MM). For brevity, a few references (1-4) are provided here. Figure 1 gives a snapshot of the pro-host understanding of Ayurveda. The aetio-pathogenesis of the disease is established through a structured process and compilation of causative factors, components involved in the evolution of disease, signs and symptoms, medical history, and clinical examination.

1. *Nidāna* (causative factors)
   Agantuja / external factor (in this case virus) causes an imbalance in the system and the disease takes root in the body initiating an intrinsic disease process through *sannipatha dosha* (predominantly *kapha vata*) vitiation
2. *Samprāpti nirupana* (assessment of factors involved in the evolution of the disease)*
   - *Dosha- Kapha Vata Pradhana*
   - *Agni* (digestive power) - *Jatharagni Mandya* (reduced power of digestion)
   - *Sthāna - Prānavahā srotas* (physiological/functional channels of the pulmonary/cardiopulmonary system)
   - *Adhishtāna* (seat of affliction) - *uras* (chest)
3. *Lakshana* (Symptomatology)
   - *Jwarā* (fever)
   - *Angamardhā* (body pain)
   - *Kāsa* (cough)
   - *Shwasa* (respiratory distress)
   - *Anannābhilasha* (loss of appetite)

* These are also the factors to be corrected for breaking the pathological pathway. For brevity, only some of the factors are mentioned here.

References

1. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet, 395, 1054-1062, 2020.
2. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirius-infected pneumonia in Wuhan, China. JAMA, 323, 1061-1069, 2020.
3. Corona cough - what does it sound like? https://www.hulldailymail.co.uk/news/uk-world-news/what-coronavirus-cough-sound-like-3963800 (accessed on 07.4.2020)
4. Coronavirus incubation period: how long before symptoms appear. https://www.healthline.com/health/coronavirus-incubation-period (accessed on 07.4.2020)

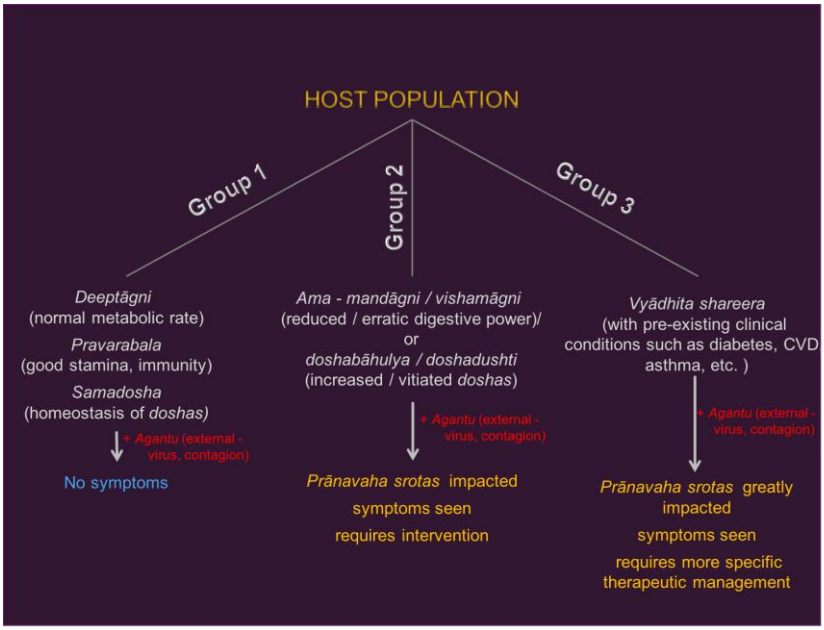


Figure 1: Snapshot of the pro-host understanding of Ayurveda in COVID-19

Ayurvedic treatment strategy

Figure 2 shows the flowchart of disease progression according to Ayurveda and the specific time points, where Ayurveda can intervene, arrest and reverse the progress of the disease. Homeostasis or good health

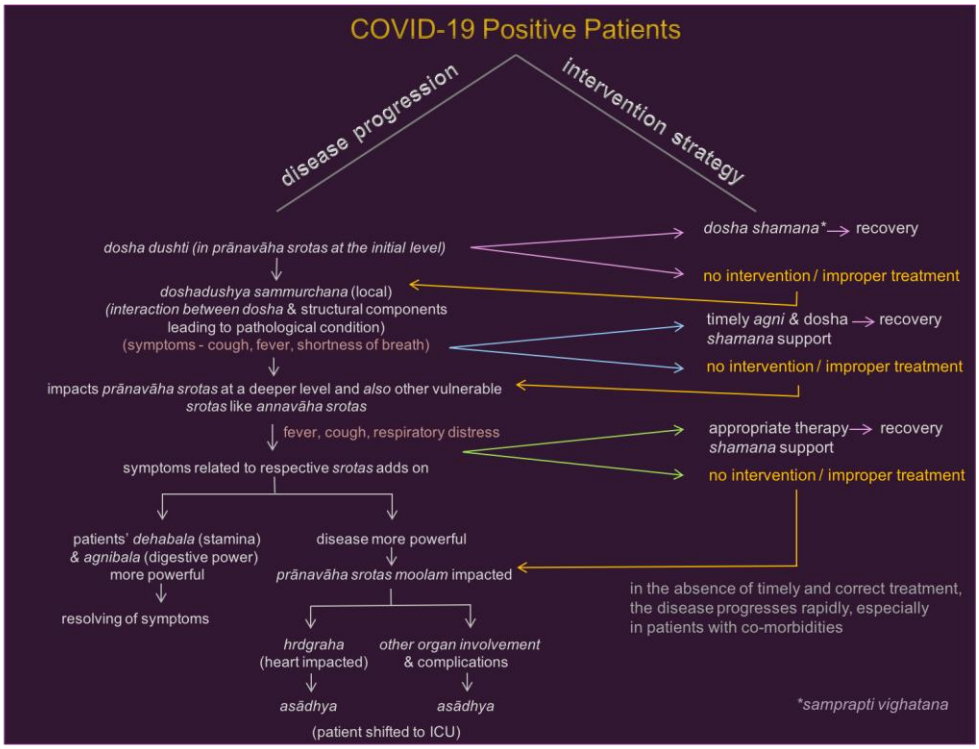


Figure 2: Flowchart of COVID-19 disease progression from standpoint of Ayurveda. The various stages of intervenion are indicated. It is to be noted there could be involvement of other srotas as well at the initial level.

is achieved by reversing the aetio-pathogenesis for not only disease cure but also for sustained wellbeing in all dimensions (body, mind and soul) (SS Shāreerasthān, Chapter 15, verse 41). Ayurveda's c comprehensive therapeutic approach (*chikitsa*) includes diet-lifestyle-medicine therapies and also uniquely personalised (even in an epidemic).

1. *Nidāna Parivarjana (removing the causative factors)*[1]

   - All diet and activities which aggravate the vitiated *kapha* and *vata doshas* are to be avoided to prevent any further aggravation of the disease.
   - To counter the aggravated *dosha* with the help of diet (can be called therapeutic nutrition) and regimen

2. *Treatment strategy and arresting the progression of disease*
   - Administering medicines (*Aushadha chikitsa*) acting on *dosha*, *dushya* (vitiated tissue elements), *agni*, and immunity (*vyādhi kshamatva*)

     The medicines will also do *āmapāchana*[2] (Targeting Gut health) - the treatment begins with this strategy, namely addressing the Gut Health.

   - *Ahāra* (diet as per the factors involved) should be easy to digest and which improves the digestive power. These generally include food processed with digestives like pepper, dry ginger and coriander seeds[3].

     By medicines and diet, the first stage of disease management, namely *āmapāchana* takes place.

   - Administering anti-*doshic* medicines[4], with properties to tackle fever (*jwara)*, cough (*kāsa)* and respiratory distress (*shwāsa)*. This will arrest the progress of the disease and resolve the the existing symptoms.
   - Personal hygiene and social distancing as mentioned elaborately in Ayurveda

[1]*Jwara* (fever) being an *aupasargika vyādhi* (infectious disease) is contagious. Therefore, personal hygiene and social distancing as mentioned in Ayurveda has to be followed (SS, Nidānasthān, Chapter 5, Verses 33-34). Although the virus is considered the causative factor in allopathy, Ayurveda will consider the virus as a triggering (*agantu*) factor only since not everyone exposed to the virus is affected (many remain asymptomatic and recover). So, the therapeutic strategy will not involve attacking the virus but treating the patient.

[2]*Ama* is a concept in Ayurveda, which can be best understood as accumulation of toxic metabolic by-products at various levels of physiology. *Ama* can also be correlated to the concept of free radicals. More simply, *āma* is the by-product of poor digestion and according to Ayurveda, *āma* is one of the major factors in all diseases. State of *ām*a indicates to Gut health, which in recent times has been taken cognisance of in health and disease. *Amapāchana* refers to removal of the toxins and restoring the gut health.

[3]Pepper, dry ginger and coriander seeds have antipyretic properties as per Ayurveda and have antiviral / antibacterial activities as per modern science (J Ethnopharmacol,145, 146-151, 2013).

[4]From an Ayurveda standpoint, all fevers / diseases (and in this case Covid-19) will be considered to have different stages (*avastha*) like *ama, nirama* (without *ama*), fever associated with constipation, fever associated with loose motion, etc. The administration of appropriate medicines at the appropriate stage of the disease is left to the discretion of the treating physician.

4. Interventions ***(all medicines are from classical texts with highest level of authenticity)***	**Mild stage of COVID-19** ***Medicines*** *Vyāgryādi kwātha (kashāya*) [Ashtānga Hrdyam (AH), Chikitsasthān, Chapter 1, Verse 61] Dose: 30-50 ml, twice a day on empty stomach *Tāleesadi churna* (CS, Chikitsasthān, Chapter 8, Verses 145-147) Dose: ½ tsp with honey thrice a day *Sitopalādi churna* (CS, Chikitsasthān, Chapter 8, Verses 103,104) Dose: ½ tsp with honey thrice a day *Ashwagandādi churna* (Sahasrayoga, Churna yoga 8) Dose : ½ tsp with honey thrice a day *Sudarshana churna* tablet (Shārangdāra Samhita, Madhyamakhanda, Chapter 6, Verses 26-36) Dose : 2 tablets to be taken with water at room temperature thrice a day on empty stomach *Vilwadi gutika* (AH, Uttarasthān, Chapter 26, Verses 84-85) Dose : 1 tablet twice a day on empty stomach *Agastya rasāyan* (CS, Chikitsasthān, Chapter 17, Verses 57-62) Dose: 1 tsp, twice a day on empty stomach *Indukāntha ghrta* (Sahasrayoga, Ghrta Prakarana 16) Dose: 5-15 ml in melted form, twice a day on empty stomach *Amrtārishta* (Sahasrayoga, Arishtayoga, Verse 3) Dose : 15-30 ml, twice a day after food *Triphala pippali churna* (Shārangdāra Samhita, Madhyamakhanda, Chapter 6, Verse 37) Dose: ½ tsp with honey twice / thrice a day ***Kriya (procedures)*** • *Dhoopana* (inhalation) – *Aparajita dhoopa* (AH, Chikitsa sthān, Chapter 1, Verse 163) or *Pathyadi dhoopa* (AH, Chikitsasthān, Chapter 3, Verse 53) • *Nasya* (nasal drops) - *Anu taila* (AH, Sutrasthān, Chapter 20, Verses 37-38) • *Gandoosha* (holding liquid in mouth) / *kavala* (gargle) – *sasaindhavaghrta* (AH Chikitsasthān, Chapter 1, Verse 127) ***Diet*** • *Peya* (watery par-boiled rice gruel) / *yusha* (soup of pulses), which are easy to digest (Shārangdāra Samhita, Madhyakhanda, Chapter 2, Verses 167-168) • *ushnodaka* (hot water) (CS, Chikitsasthān, Chapter 4) • *Dhānyanāgara pāna* (CS, Chikitsasthān, Chapter 8, Verse 70) • Hospital menu should avoid food and drinks that aggravate *kapha vata doshas*. For example, heavy food, yoghurt, buttermilk, excessive sweet and sour, day sleep, cold food and drink, etc. will aggravate *kapha*. Similarly, cold food and drink, excessively dry and pungent food, Heavy and hard to digest food aggravate all *doshas.*

	Regimen • rest, avoid head bath • to avoid keeping late hours at night, irregular food habits and suppression of natural urges, all of which aggravate *vata* • personal hygiene and social distancing *administration of appropriate medicines at the appropriate stage of the disease is left to the discretion of the treating vaidyas. All medicines will be obtained from a GMP licensed medicine manufacturer ***Control Group***- Standard of care therapies as per the latest guidelines released by ICMR.
4. Interventions *(all medicines are from classical texts with highest level of authenticity)* (*contd..*)	**Moderate stage of COVID-19** ***Medicines*** *Vyāgryādi* or *Drākshadi kwātha (kashāya*) Dose: 30-50 ml, twice a day on empty stomach *Pathyādi kwātha (kashāya*) (AH, Chikitsasthān, Chapter 3, Verse 53] Dose: 30-50 ml, twice a day on empty stomach *Tāleesadi churna* Dose: ½ tsp with honey thrice a day *Ashwagandādi churna* Dose : ½ tsp with honey thrice a day *Sudarshana churna* tablet Dose : 2 tablets to be taken with water at room temperature thrice a day on empty stomach *Amrtottara kwātha (kashāya*) (Sahasrayoga, Kashāya Prakarana 12) Dose : 30-50 ml twice a day on empty stomach *Sanjeevani vati* (Shārandgdāra Samhita, Madhyamakhand, Chapter 7, Verses 18-21) Dose: 2-4 tablets twice a day on empty stomach *Vidāryādi ghrta* (AH, Chikitsasthān, Chapter 3, Verse 10) Dose: 5-15 ml in melted form, twice a day on empty stomach *Guduchi kantakāri ghrta* (AH, Chikitsasthān, Chapter 3, Verse 3) Dose: 5-15 ml in melted form in melted form twice a day on empty stomach *Vāsārishta* (Sahasrayoga, Arishta yoga, Verse 23) Dose : 15-30 ml, twice a day after food *Triphala Pippali Churna* (Shārangadāra Samhita) Dose : ½ teaspoon with honey thrice a day ***Kriya (procedures)*** • *Dhoopana* (inhalation) – *Aparajita dhoopa* or *Pathyadi dhoopa* • *Nasya* (nasal drops) - *Anu taila* • *Gandoosha* (holding liquid in mouth) / *kavala* (gargle) – *sasaindhavaghrta*

4. Interventions ***(all medicines are from classical texts with highest level of authenticity)*** **(*contd..*)**	***Diet*** • *Peya* (watery par-boiled rice gruel) / *yusha* (soup of pulses), which are easy to digest • *ushnodaka* (hot water) • *Dhānyanāgara pāna* Hospital menu should avoid food and drinks that aggravate *kapha vata doshas*. For example, heavy food, yoghurt, buttermilk, excessive sweet and sour, day sleep, cold food and drink, etc. will aggravate *kapha*. Similarly, cold food and drink, excessively dry and pungent food, Heavy and hard to digest food aggravate all *doshas.* ***Regimen*** • rest, avoid head bath • to avoid keeping late hours at night, irregular food habits and suppression of natural urges, all of which aggravate *vata* • personal hygiene and social distancing *administration of appropriate medicines at the appropriate stage of the disease is left to the discretion of the treating vaidyas. All medicines will be obtained from a GMP licensed medicine manufacturer ***Control Group***- Standard of care therapies as per the latest guidelines released by ICMR.

4.1. Rationale for the choice of medicines

<u>*Select indications are mentioned below:*</u>

Vyāgryadhi kwātha (kashāya)
fever of *vata* and *kapha* origin, difficulty in breathing (*shwāsa*), cold/cough (*kāsa*), rhinitis (*peenasa*), abdominal colic (*shoola*)

Taleesādi churna
cough, common cold, difficulty in breathing

Sitopalādi churna
cough, common cold, difficulty in breathing

Ashwagandādi churna
Jwara, reduces *vata* and pacifies *kapha*, *kāsa*, *shwāsa*, strengthens the body

Sudarshana churna tablet
Tridosha hara, for all types of fever. *Kirata Tikta* (Swertia chirata), a potent antiviral herb is its main ingredient. Interestingly, this medicine contains other antiviral and antibacterial herbs like *guduchi* (Tinospora cordifolia), turmeric, neem, etc.

Vilwādi gutika
Jwara, *visha* (poison), *vishoochika* (gastroenteritis)

Agastya rasāyan
all types of cough (*kāsa*), respiratory problems (*shwāsa*), irregular fever (*vishama jwara*), loss of taste (*aruchi*), chronic rhinitis (*pinasa*). It improves the respiratory strength and builds immunity.

Indukāntha ghrta
vata imbalance, fever (*jwara*), strengthens body (*bala vardhaka*)

Amrtārishta
fever, *kapha* predominant conditions

Drākshadi kwātha (kashāya) *Vata-pitta jwara,* nausea, vomiting, headache *Triphala pippali churna* *Tridoshahara*, specially indicated in fever associated with cough and breathing discomfort *Pathyādhi kwātha (kashāya*) *Kapha vata jwara, kāsa, shwāsa* *Amrtottara kwātha (kashāya*) fever, elimination of toxins (*āmapāchana*) *Sanjeevani vati* fever, *āmapāchana* (eliminates toxins) *Vidāryādi ghrta* respiratory disorders, consumption, reduced immunity *Guduchi kantakāri ghrta* *Vātaja kāsa*, *agni deepana* (improves digestion) *Vāsarishta* cough (*kāsa),* respiratory distress (*shwāsa),* throat related disorders (*khanta roga)*	
5. Objectives	***Primary:*** To prevent progression of COVID-19 positive patients suffering from mild or moderate symptoms to severe stage. ***Secondary:*** To restore health and to reduce • Severity of disease symptoms • Length of hospitalization • Percent of patients requiring ICU • The length of stay in ICU • Mortality
6. Trial Design	Multi-centric, Randomized Controlled Trial
Methods: Participants, interventions and outcomes	
7. Eligibility criteria	***Inclusion Criteria*** *General* • 18 years or older • COVID-19 positive as determined by RT-PCR or other approved commercial or public health assay • Informed consent for the study *Allopathy* • mild stage (cough, fever) • moderate stage (cough, fever, breathlessness) but with respiratory rate < 24 per minute and oxygen saturation > 94% *Ayurveda* • *jwara, kāsa* (mild) • *jwara, kāsa, shwāsa* (moderate) ***Exclusion Criteria*** *General(https://www.mohfw.gov.in/pdf/RevisedNationalClinicalManagementGuidelineforCOVID1931032020.pdf)* • Participation in any other clinical trial of an experimental treatment for COVID-19 • Patients with severe COVID-19 disease defined as follows

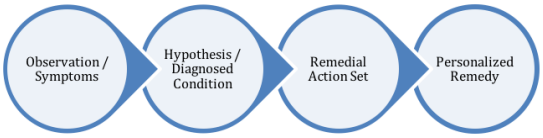
7. Eligibility criteria	▪ respiratory distress (≥30 breaths per min) ▪ oxygen saturation at rest ≤85% ▪ severe disease complications (eg, respiratory failure, requirement of mechanical ventilation, septic shock or non-respiratory organ failure) *Allopathy* • Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30) • Pregnant women or women who are breastfeeding • Immunocompromised patients taking (presently or anytime during last 90 days) immunosuppressant medication • Diabetics with >9% HbA 1c • Patients on antimicrobials, antibiotics, antifungals during last 30 days • Patients on NSAID during last 30 days • Patients with active malignancy *Ayurveda* • patients with bleeding disorders* • patients on immunosuppressants • *pandu* (Hb<7 - anemia comes under *pandu*) • *dhātu kshaya* (reflected by BMI < 18) * patients with bleeding disorders require a different choice of medicines, not included in the list provided here
8. Outcome measures	**Expected end points from the intervention** ***Primary :*** *Allopathy* • Number of days from positive to negative for test of swab or sputum virus nucleic acid • Incidence of patients progress to severe stage Severe stage defined as ▪ respiratory distress (≥24 breaths per min) ▪ oxygen saturation at rest ≤94% *Ayurveda* • retardation and resolving of symptoms (*rugprashamana* - complete relief from disease) ***Secondary :*** *Ayurveda* • *vypagatatāpam* (no fever) • *svedam* (sweat normally) • *annalipsa* (normal hunger and appetite) • *ruchirāhārakale* (restoration of sense of taste) • *samyak jeeranam* (proper digestion of food) • *nidralābho yatha kālam* (restoration of nocturnal sleep) • *vatamootrapureesharetasam muktih* (timely evacuation of waste) • *vyapagataklamam* (no exhaustion) • *avyathathvam* (no aches and pains) • *balavriddhi* (enhanced strength and stamina) • *ojas* (vitality)

Outcome measures (*contd..*)	• *prasanna atma-indriya-mana:* (well-being arising from systemic homeostasis being re-established) *Ref - AH, Nidanasthān, Chapter 2, Verse 79; SS Shāreerasthān, Chapter 15, Verse 41 *Allopathy* • Disease severity on an ordinal scale assessed on daily till day 21 and then on days 28 and day 35 1. Not hospitalized, no limitations on activities 2. Not hospitalized, limitation on activities 3. Hospitalized, not requiring supplemental oxygen 4. Hospitalized, requiring supplemental oxygen 5. Hospitalized, on non-invasive ventilation or high flow oxygen devices 6. Hospitalized, on invasive mechanical ventilation 7. Death • Length of time to clinical improvement Time to clinical improvement is defined as the time to normalization of respiratory rate, fever, and oxygen saturation for 24 hours; alleviation of cough for 72 hours. • Number of participants with normal O2 saturation on days 11, 15 and 21 • Length of time to clinical progression (Time Frame: Up to 21 days) Time to clinical progression, defined as the time to death, mechanical ventilation, or ICU admission • Length of time to normalization of fever (Time Frame: Up to 21 days) Fever normalization as defined by: Temperature < 97.8^0F sustained for minimum 24 hours • Length of time to normalization of oxygen saturation (Time Frame: Up to 28 days) Oxygen normalization as defined by: peripheral capillary oxygen saturation (Sp02) > 94% sustained minimum 24 hours. • Duration of supplemental oxygen (if applicable) (Time Frame: Up to 28 days) • Duration of mechanical ventilation (if applicable) (Time Frame: Up to 28 days) • Number of participants that developed Acute Respiratory Distress Syndrome (ARDS) after treatment (Time Frame: Up to 28 days) • Duration required to get COVID-19 PCR test negative (Days 7, 14 and 28) • Duration of hospitalization (Time Frame: Up to 28 days) • Duration of stay in ICU (Time Frame: Up to 28 days) • Requirement of Rescue medication • Percent mortality • Adverse events
9.Participant timeline	Participants will be provided with study medication orally for 21 days, with close follow-up on weekly basis or as and when required within a week. Participants will be assessed as per the schedule mentioned in outcome measures.

10. Sample size	Total 124 subjects will be randomized in the control and study groups for RCT. The sample size is calculated using the predicted recovery rate by physicians and the formula given below: n = [(Zα/2 + Zβ)^2 × {(p1 (1-p1) + (p2 (1-p2))}]/(p1 - p2)^2 where n = sample size required in each group, p1 = proportion of subject cured by Drug AYUSH = 0.9 p2 = proportion of subject cured by Placebo ALLOPATHY = 0.6 p1-p2 = clinically significant difference = 0.3 Zα/2: This depends on level of significance, for 5% this is 1.96 Zβ: This depends on power, for 80% this is 0.84 n = 31 for each arm *Reference:* Sakpal T. Sample size estimation in clinical trial. *Perspectives in Clinical Research*. 2010;1(2):67.
11. Withdrawal criteria	Patient will be withdrawn from the study • If patient progresses to severe stage requiring ventilator support • If the patient adversely reacts to any intervention • If the treating physician opines that the patient requires emergency rescue medication. The use of rescue medication will be documented in case report form and will be considered during analysis • If the patient is unwilling to continue
Methods of Intervention assignment	
12. Data assessment and collection	All analyses will be performed from the intention-to treat principle. Missing data will be dealt with statistical imputation methods. In addition, structuring the data capture of Ayurveda treatment workflow of COVID-19: A Diagnostic Process Architecture will be followed

Data of Ayurveda diagnosis, treatment protocol and patient observations will be systematically captured to help

- guide physicians in future treatments
- document the decision tree to build a case for standardization of treatment and third-party scrutiny
- gather evidence regarding the relative efficacy of various Ayurveda interventions to establish credibility , mainstream acceptance of Ayurveda interventions by the global medical system



Given the critical importance of treating COVID-19, a brief outline of the larger process for data capture is given below:

- A case history template spreadsheet or form for capturing physician's observations at every visit
- A case history database that stores the above information for each patient with the following operations
- Pre-canned Analytics reports to help physicians understand effectiveness of diagnosis and/or interventions
- Enable correlation based learning using Machine Learning techniques for additional insight (global)

13. Adverse events	Health status of the participants will be monitored and Adverse events will be reported in case report form. The ADR form (Appendix 1) will be used as the template. All the Serious Adverse Event (SAE) will be reported as per applicable ethical and regulatory guidelines.
14. Ethics Committee approval	IEC approval will be obtained from the selected clinical study site (s) before initiation of the study (ICMR guidelines will be used) and registered on CTRI website
15. Clinical trial sites	Chennai, Bangalore, Pune (tentative)
16. Research Team	Working Group members
17. Others	The following studies will also be carried out: • Analytical spectroscopic techniques for phytochemical analysis of the formulations used in the treatment of patients • Assessment of clinical biomarkers • Pre-clinical studies including specific bioassays

ANNEXURE FIVE

Outline Protocol for integrative medicine trial for COVID 19

Developed by Working Group constituted by Inter Disciplinary R&D Task Force, Ministry of AYUSH, Government of India.

A framework for integrative medicine trial for COVID 19

Background:

A novel beta-corona virus named 2019 novel coronavirus (2019-nCoV) causes Coronavirus disease. Coronavirus is the common cause for the common cold, next to Rhinovirus. Additionally, Corona causes gastroenteritis in children and adults. SARS-CoV-2 is a stable variant of Coronavirus detected in 2002 caused atypical pneumonia leading to the serious acute respiratory syndrome. Although SARS-CoV-2 is a stable virus mutation are common in Coronavirus (occurs in RNA sequence during replication)[1]. Laboratory diagnosis made by isolating virus from the respiratory secretions and serum testing for antibodies.

Prof C Huang et al., Jin Yin-tan Hospital, Wuhan, China published the clinical features of COVID 19 in The Lancet in January 2020. His team reported that on the 9th day, 51% of patients developed dyspnoea and 27% ARDS on the 11th day[2]. As pandemic evolved the presentation of the disease changed. A 23 years old medical student from Wuhan was admitted in Kasaragod quarantine ward (India's 3rd case) on the 31st January 2020 with symptoms of mild sore throat; discharged on the 16th February 2020. As numbers increased, treating allopathic physicians of "COVID hospital Kasaragod" recently shared their Indian experiences with Indian Medical Association members. Clinical features of COVID included sore throat, rhinorrhea, fever, cough, diarrhoea, breathlessness (7%), anosmia and 27% of patients had no symptoms. Although the Coronavirus strictly confined to the mucosal cells of respiratory tract SARS-CoV causes oedema in alveolar space resulting in hypoxia. Whatever the cause of hypoxia resultant systemic changes adds to the complexity, especially in patients with other co-morbidities. As a result, unfortunate fatalities are increasing world-wide. Infections caused by Corona causes brief short-term immunity and reinfection is a possibility. Physicians used antivirals, hydroquinone and bronchodilators[3].

This document gives the integrative medicine framework for any clinical trial using AYSUH medicines for a possible supportive measure for COVID pandemic in the absence of proven effective allopathic medication.

Clinical reasoning for the selection of AYUSH Drug for Integrative Medicine protocol:

The role of AYUSH in acute & emergency care is lower than allopathy. It is not sure in what duration AYUSH medicines could reduce the inflammation especially to control the fluid imbalance probably caused by the binding of the virus on the angiotensin-converting enzyme receptor-2 on the respiratory surface epithelium (based on SARS; not known if the same is the mechanism in COVID 19). However, the holistic nature of ayurveda allows selecting the drug for trial based on cumulative clinical presentation, although micro-level correlation may

not be possible. Following are the clinical leads on which 'intense'[4] Ayurveda 'clinicians'[4] could brainstorm on the drug selection for the clinical trial on COVID 19.

1. Use drugs that can effectively reduce the duration of respiratory symptoms of sore throat, cough and low-grade fever. If drugs can reduce symptoms in one week, it would decrease the chance of inflammation-causing high protein oedema of alveolar space and hypoxia.
2. To building immunity and reduce reinfection meaning the treatment initiated should be continued for a specified duration even after patients tested COVID negative
3. The same strategy may be useful to administer to volunteers from health care providers in COVID hospitals
4. Critical things for success would be easy to administer drugs, quick-acting drugs, that help to reduce symptoms and recurrence of respiratory infection and reduce oxidative stress. There are reports of single ayurveda drugs increasing the oxidative stress[5].
5. Homoeopathy drugs are known to produce an immediate effect. Consider the possibility of using homoeopathy drugs under AYSUH

Study design:

Double-blind, randomised control study adhering to CONSORT guideline should be the choice of study design. However, if by the nature drug can not be masked, lower levels of evidence could be taken up, such as open-label randomised control study.

Sample Size: Consult the statistician

Site of study: Multicentric study in COVID hospitals would give a required number of patients. More than one integrative medicine protocol would be ideal as ayurveda experts opinion divided on the drug selection. Integrative Medicine protocol requires a collaborative team of ayurveda and allopathy.

Inclusion Criteria*:

1. Freshly detected and confirmed positive (through RT-PCR) COVID-19 patients with or without requiring admission in a COVID hospital.
2. Patients who have consented (written informed consent) to get treated with the ayurvedic….., or homoeopathic….., or integrative medicine…… (experimental drug) as the primary treatment.
3. Patients on specifically targeted to treat COVID-19 treatment
4. The patient is in the age group between 18-65 years or as directed by the ethics committee.

5. The patient has a persistent fever as per WHO guideline (in degrees) and may or may not be receiving antipyretics. The patient has a history of cough for ≥ 3 days and a headache on the first day or persisting. The patient has a history of body aches or tiredness or unusual fatigue lately (≥ 7 days). Other features of COVID if present shall not exclude patients
6. Disease severity classification: Use ICMR classification of severity if available. If not, available severity tests, e.g., the six-minute walk distance test[6], or on the ability to take a deep breath and, or not able to hold for ≥ 20 seconds.
7. Patient's ability in the investigator's opinion to comply with ayurvedic, or homoeopathic drugs administered. In this context, *prakriti* and *vikriti* analysis become essential, along with agni and other ayurvedic clinical features. Lower rates of mortality in India could also be due to the genetic background or theory of herd/cross-immunity. Since AYUSH doctors would be part of the team of allopathy doctors in COVID hospitals, a detailed examination and recording case sheet should be done[7]. Correlation to ayurvedic and homoeopathic miasms are possible if in future genetic correlation is obtained for Indian COVID manifestation.

Exclusion criteria:

1. Suspected patients with COVID19, but not confirmed by RT-PCR test
2. Haemoptysis (although it is a symptom of COVID in India there are many other causes)
3. Patients in dyspnoea, or on the ventilator
4. Associated with co-morbidities; diabetes mellitus, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, or Known TB, HIV, HBV, HCV infection, and other co-morbidities that would come in the way of selection of ayurvedic and homoeopathic drug. AYUSH drugs selected should be compatible with co-morbidities
5. Any other contraindications specific to AYSUH protocol

Study arms:

1. Only ayurveda, or only homoeopathy, or ayurveda and homoeopathy
2. Standard COVID allopathic treatment of the hospital
3. Integrative medicine arm is an add on the combination of 1 and 2 above

It is ideal for keeping the maximum of three arms in a site.

Study duration:

- If the objective is to cover the duration of COVID one month is recommended
- If prevention of recurrence or immunity enhancement is the objective; three months

Drug administration:

Write complete details of drug administration with Anupama if necessary, time of administration and dietary regulations, the dose, frequency and monitoring methods.

Baseline data:

1. Gender & Age
2. Demographic data (height, weight, Body Mass Index [BMI], Body Surface Area [BSA])
3. Presenting history, medical history, menstrual history, treatment history. The totality of symptoms in homoeopathy
4. Systemic examination information from allopathy and ayurveda
5. Clinical laboratory tests (haematology, biochemistry, urine analysis and serology)
6. Pregnancy test (for female)
7. Electrocardiogram (ECG) and chest X-ray PA view or CT scan of the chest within 24 hours from the day of check-in or admission
8. Intensive care unit monitoring studies used in the site
9. Cytokine and chemokine studies for select sites

Clinical endpoints:

1. Defervescence of Fever: Body temperature be measured using infrared thermal scanner every hour up to 24.00 hours post-dose (within ± 30 mins from the scheduled time) every day till the last dosing. Finally, it gets measured in days from onset
2. Pulse Oximetry: Oxygen saturation is measured at every two hours up to 24.00 post-dose by using pulse oximeter for at least 30 seconds for each measurement or continuous oxygen saturation monitoring up to 24.00 hours. A window period of ± 45 minutes is allowed for oxygen saturation measurement
3. Chest X-Ray/Radiological clearance: A chest radiograph at admission (Day 1) and on days 4, 7 and 14. However, treating allopathic doctors would require a more frequent X-rays if pneumonia is suspected.
4. Incidence of respiratory failure: Requiring ventilator support. Those patients who required ventilator support should be excluded from the subgroup analysis.
5. The rapidity of virologic clearance: Perform ICMR approved COVID-19 tests on days 4, 7 and 14. If the test result on any day reported negative (absence of COVID-19 infection), then the test shall be repeated ≥ 24 hours from the last test to confirm the result
6. Incidence of other complications and mortality: To be recorded during the trial
7. Ayurvedic *phalashruti* based on the drug used in the trial

Ethical approval: Ethical approval for any trial is mandatory and mere administrative sanction from the head of the institution not be sufficient. Before enrolment into the study, a patient must be familiarised with the study goals and objectives, the study design and procedures, and must be made aware of possible adverse effects, and benefits associated with participation in the study. The patient must sign two copies of Informed Consent Form (one copy to be kept by the patient, the other one retained at the site).

Last note: In 2012, the Middle East respiratory syndrome (MERS) identified as a viral respiratory illness caused by a coronavirus (Middle East respiratory syndrome coronavirus, or MERS-CoV). COVID 19 sequences may need a re-evaluation is select sites based on a random selection of patients to compare it with MERS-CoV if most patients of COVID in the site are people who travelled from the Middle East

Members of the Task Force

(Order No. **A.17020/1/2020-E.1** of Secretary, Ministry of AYUSH. Dt. 02.04.2020)

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12	Prof M S Baghel	Former Director IPGTRA	Member
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14	Dr. K. Kanakavalli	DG CCRS	Member
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➢ Dr. **Rama Jayasundar**, AIIMS, New Delhi - (Chair)

- Sri. P.R. Krishnakumar, Arya Vaidya Pharmacy, Coimabattore
- Vd Ramesh Varier (Kottakkal Arya Vaidya Sala, Kottakkal
- Vd M. Prasad, Ashtangam Ayurveda Chikitsalayam & Vidyapeedam, Kootanad)
- Vd Dr. SG Savitri, Ayurveda Academy, Bangalore
- Vd Yogesh Bendale, Rasayu Clinic, Pune
- Dr. C V Krishnaswamy, Diabetologist, Chennai
- Mr. Rajiv Vasudevan, AyurVAID Hospitals

3. Test Materials and their TQM (Total Quality Management):

➢ Dr **D C Katoch**, Advisor Ayush - (Chair)

➢ Dr **K S Dhiman** - (Convener)

o Dr. Pulok Mukherjee, Jadavpur University Kolkata
o Dr Amit Agarwal, Natural Remedies, Bangalore
o Dr Lal Hingorani, Pharmanza Herbals
o Dr Kartikeya, Kartikeya Herbals, Hyderabad
o Dr Sunder, Himalaya Drug Co., Bangalore

4. Experimental Studies (Preclinical research)

➢ Dr. Madhu Dixit, THSTI National Chair, THISTI (DBT), Faridabad - (Chair)

➢ Dr. N Srikant, DDG, CCRAS, New Delhi - (Convener)

o Dr. Y K Gupta, Representative of ICMR, New Delhi
o Dr Nirmala Rege, Prof Pharmacology KEMH, Mumbai

- o Dr K. Satyamoorthy, Dir Life Sciences, Manipal University
- o Dr Kalpana Joshi, Dir Biotech, SI, SPPU, Pune
- o Dr Padma Venkat, Director, Public Health, SRM Univ., Chennai
- o Dr Devi Prasad Chattopadhyay, Director, ICMR / NITM, Belgavi
- o Dr A Rey, Pharmacologist, Hamdard Univ., Delhi
- o Dr Ravi Shankar, Pharmacologist (Retd.), IPGTR&A, Jamnagar

5. Screening committee for short listing ideas/ proposals & Call for Proposals

- ➢ Dr Manoj Nesari, Advisor Ayu., Ministry of AYUSH - (Chairman)
- ➢ Dr Sanjeev Sharma Director, NIA, Jaipur - (Convener)

- o Dr M.S. Baghel, Ex. Director, IPGTR&A GAU, Jamnagar
- o Dr. Mohd Aslam, Advisor, DBT
- o Dr Vishvajanani, representative CSIR
- o Dr Hoti, Scientist, NITM, Beglgavi
- o Dr B.S. Prasad, Principal, KLE Ayurveda college, KLE Univ., Belgaum
- o Dr Arun Gupta, Head – Clinical Research, DRDC
- o Dr Ahalya Sharma, Principal, Govt Ayu College, Bangalore

- ➢ DGs of all Councils of Unani-Homoeo-Siddha viz.,
  - The Director of National Institute of Unani to be member
  - One member from the same field may be co-opted
  - ▪ Dr. Anil Khurana , DG, CCRHM to chair the Homoeo sub-group
    - The Director of National Inst. of Homoeo to be member
    - Dr Issac Mathai, Soukhya, Bangalore
  - ▪ Dr. Kanakavalli, DG, CCRS to chair the Siddha sub-group
    - The Director of National Inst. of Siddha to be member
    - One member from the same field may be co-opted

6. Nutrition and Nutraceutical (Global markets)

- ➢ Dr V. Prakash ex Director CSIR CFTRI, Mysuru - (Chair)
- ➢ Dr Anupam Strivastava, Director, RAV, New Delhi - (Convener)

- o Dr Dinesh Kumar Bharadwaj, NIN Hyderabad
- o Dr Sanjay Sharma, Nutra-Regulatory, GSK
- o Dr Meeta Kotecha, Professor, NIA, Jaipur
- o Dr Asmita Wele, Bharatiya Vidyapeeth Deemed Univ., Pune
- o Dr Satya Laxmi, Scientist, NIN, Pune

7. Epidemiology, Survey and Documentation

- ➢ Dr **Mohan Gupte**, Ex Director, NIE, Chennai [Now in Pune] - (Chair)
- ➢ Dr P **Unni Krishnan**, U N Univ., Chennai - (Convener)

- o Dr Nandini Kumar, Ex DDG, ICMR (Convener)
- o Dr Sandra Albert, Director, IIPH, Shillong
- o Dr. Pawan Kumar Godatwar, NIA, Jaipur
