Central Council for Research in Homoeopathy

New Delhi

STUDY PROTOCOL

HOMOEOPATHY AS ADJUVANT TO STANDARD TREATMENT PROTOCOL IN MANAGEMENT CORONA VIRUS INFECTION- A RANDOMISED, PLACEBO CONTROLLED, OPEN LEVEL STUDY

Version 2.0

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Study Summary

Title	Homoeopathy as adjuvant to standard treatment protocol in management coronavirus infection- a randomised, placebo controlled, open level study
Short Title/Public title	Homoeopathy as adjuvant in management coronavirus infection
Methodology	Randomised, Placebo Controlled, Open Level Study
Study Duration	1 year
Study Center (s)	
Objectives	**Primary Objectives:** • To assess and compare the effectiveness of homoeopathic treatment as an adjuvant to the standard treatment in coronavirus infection. **Secondary objectives:** • To assess and compare time to fever clearance • To assess and compare time to resolution of pneumonia • To assess and compare severity of symptoms. • To compare the period of hospital stay • To assess and compare time to recovery
Number of Subjects	
Main Inclusion Criteria	Patients with corona virus infection reporting at Hospital, with all the following shall be included: 1. Laboratory confirmed cases of Corona virus infection. 2. Age 18 years & above both sex 3. Willing to give signed written informed consent
Study Product	Indicated Homoeopathic medicines. Potency and dose will be given following hom. principles.
Protocol preparation - Dr. Debadatta Nayak, Scientist-II, CCRH	

HOMOEOPATHY AS ADJUVANT TO STANDARD TREATMENT PROTOCOL IN MANAGEMENT CORONA VIRUS INFECTION- A RANDOMISED, PLACEBO CONTROLLED, OPEN LEVEL STUDY

Introduction

Background

The recent outbreak of the novel coronavirus (COVID-19) and its declaration as pandemic by the World Health Organisation has led to a major concern around the globe. On 31 December 2019, WHO was alerted about outbreak of several cases of pneumonia in Wuhan City, Hubei Province of China which raised concern because the affected patients were geographically linked with a local wet market as a potential source. One week later, on 7 January 2020, Chinese authorities confirmed that they had identified a novel coronavirus, named "COVID-19" from coronavirus family that also included Severe Acute Respiratory Syndrome coronavirus SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV).[1] Coronaviruses are zoonotic and detailed investigations found that SARS-CoV was transmitted from civet cats to humans and MERS-CoV from dromedary camels to humans.[2] The genetic sequence of the 2019 novel coronavirus (2019-nCoV) enabled the rapid development of point-of-care real-time RT-PCR diagnostic tests specific for 2019-nCoV which is based on full genome sequence data on the Global Initiative on Sharing All Influenza Data [GISAID] platform.[3] Though scientist of China shared its genome sequence, the Australian scientists have for the first time recreated the virus.[4]

About the pandemic

So far, 1,83,047 globally confirmed cases are reported and 80,881 confirmed cases from China but 3,226 deaths making China "Very High" under WHO risk assessment.[5] Till March 22, globally, approximately 303,000 confirmed cases, including more than 12,900 deaths in approximately 150 countries[6]. Person-to-person transmission of this novel coronavirus in hospital and family settings may be suggested, as reports of infected travellers in other geographical regions surface.[7] As of 25th March in India, more than 600 cases reported from different states with 11 death[8].

Pathogenesis

The pathological features of COVID-19 have been shown to greatly resemble those seen in SARS and MERS coronavirus infection.[9, 10] Coronaviruses have a protein known as a replicase encoded in its genome which allows the RNA viral genome to be transcribed into new RNA copies using the host cell's machinery.[11] Coronaviruses have a non-structural protein – a protease – which can separate the proteins in the chain.[12, 13] The excess production of type 2 cytokines and an age dependant defect in T-cell and B-cell function could lead to a deficit in control of viral replication and more prolonged proinflammatory responses, potentially leading to a poor outcome in patients of COVID-19.[14]

Clinical features

The 2019-nCoV infection has so far caused clusters of severe respiratory illness like severe acute respiratory syndrome coronavirus and was associated with ICU admission and high mortality in China. In a first-hand data reported from Hospital of China, it was found that, by Jan 2, 2020, 41 laboratory- confirmed 2019-CoV infection admitted hospital patients had a higher plasma level of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα. Fever, cough, myalgia or fatigue is most common symptoms reported whereas less common symptoms include sputum production, headache, haemoptysis and diarrhoea.[15, 16]

The Chinese CDC report[17] divided the clinical manifestations of the disease by following three severities:

S.No.	Disease severity	Symptoms	Occurred in % cases
1.	Mild Disease	Non-pneumonia and mild pneumonia	81%
2.	Severe disease	Dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO2) ≤ 93%, PaO2/FiO2 ratio < 300, and/or lung infiltrates > 50% within 24 to 48 hours	14%
3.	Critical Disease	Respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF)	5%

Homoeopathic in epidemics

Currently there is no specific antiviral treatment or any vaccine against COVID-19 infection. In such a condition, WHO recommended that "it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention" keeping in view no vaccine or anti-virals were available.[18] It is reported that India now has 126 confirmed cases of COVID-19 viral infection and India has reached the 2nd stage of pandemic which implies that the community transmission is expected within one month.[19] Homoeopathy being the second most popular system of medicine has been successfully reported to have a positive role in preventing epidemic diseases. The preventive role of Homeopathy in epidemic diseases is well known and reportedly been used for prevention during the epidemics of Cholera, Spanish Influenza, Yellow fever, Scarlet fever, Diphtheria, Typhoid etc. There is anecdotal evidence that homeopathy was successful during the Spanish flu epidemic of 1918 to 1919, in which at least 20 million people died worldwide, more than 500,000 in the United States alone. According to the historian Julian Winston, the death rates for patients treated with homeopathy (genus epidemicus) were 1 to 2% compared with a 30 to 60% mortality for those treated by conventional physicians.[20, 21]

In Indian scenario, CCRH had undertaken clinical trials in Dengue and Acute Encephalitis syndrome/JE with Homoeopathy as an add on to usual care in tertian care setups. In Dengue Hemorrhagic fever, add on Homoeopathy could bring early

improvement in platelet count and decrease in hospital stay by 2 days.[22] Similarly, in Acute Encephalitis Syndrome/Japanese Encephalitis homeopathy as an adjuvant to the institutional management protocol could decrease death rate by 15% in comparison to those who received only Institutional Management protocol.[23] In both the studies, adverse effect was not observed. Keeping in view the clinical success in above mentioned severe viral diseases and in absence of any anti-virals and vaccine against CVID-19, Homoeopathy as an adjuvant may be tested in COVID-19 patients as an adjuvant to the usual care.

2. STUDY OBJECTIVES

Primary Objectives:

- To assess and compare the effectiveness of homoeopathic treatment as an adjuvant to the standard treatment in coronavirus infection.

Secondary objectives:

i. To assess and compare time to fever clearance
ii. To assess and compare time to resolution of pneumonia
iii. To assess and compare severity of symptoms.
iv. To compare the period of hospital stay
v. To compare the use of conventional medication use.
vi. To assess and compare time to recovery

3. STUDY DESIGN

This shall be randomized, placebo controlled, open level study. Groups are as below:

- Group I: Standard conventional management + Homoeopathy
- Group II: Only Standard conventional management

3.1 Selection of patients

Inclusion criteria:

Patients with corona virus infection reporting at Hospital, with all the following shall be included:

1. Hospitalized patients with confirmed COVID-19
2. Age 18 years & above both sex
3. Willing to give signed written informed consent

Exclusion Criteria

1. Patients requiring ventilatory support
2. Immunocompromised patients

3. Severe heart, lung, kidney, brain, blood diseases or other important systemic diseases;
4. Subjects were considered to be unable to complete the study, or not suitable for the study by researchers.
5. Women during pregnancy;

3.2 Primary endpoint

Clinical recovery of patient or death

3.3 Outcome measures

i. To assess and compare time to fever clearance every 24 hours
ii. To assess and compare time to resolution of pneumonia (based on chest x ray)
iii. To assess and compare time to recovery in terms of 2 negative test for covid-18
iv. To assess and compare severity of symptoms as per Clinical syndromes associated with COVID - 19 infection
v. To compare requirement of conventional medication till resolution
vi. To compare period of hospital stay

4. Investigations:

Following investigations shall be conducted by person who reports symptoms corona infection. Plasma samples for cytokine measurement were obtained from patients around the transition period of fever.

S. No.	Investigation	At baseline	
1.	Complete Blood Count	√	Every alternate day
2.	Serum albumin	√	
3.	ALT	√	
4.	AST	√	
5.	LDH	√	
6.	Creatinine	√	
7.	Serum Urea	√	
8.	CRP	√	
9.	Covid-19 viral load	√	
10.	Chest x-ray or Ct scan	√	Every 4th day

4.3 Sample Size

Convenient sampling.

4.5 Study Duration

01 years

4.6 Study centers

5. STUDY DRUG/INTERVENTION

Patients will be prescribed individualized drug as per the presentation of each case. Details as below:

5.1 Intervention group:

5.1.1. Group I: Homoeopathic treatment Group-

Patients shall be prescribed homoeopathic medicines, selected based on totality of symptoms by the homoeopathic investigator as an add on to standard management of Covid-19.

5.1.2. Group II: Placebo Group-

Patients shall be prescribed placebo as an add on to standard treatment for management of Covid-19.

5.1.3 Randomization

The randomization will be done through computer generated randomization chart.

5.1.4 Blinding of Study Drug

The study will be open level study.

5.2. HOMOEOPATHIC INTERVENTION (Group I)

5.2.1. Procurement & dispensing of medicine

- Homoeopathic medicines in dilutions of centesimal potency (30C, 200C, and 1M) for the trial shall be procured from any of the approved Good Manufacturing Practices (GMP) firms.
- Globules/pills of size 30 shall be used for medicating dilutions and dispensing alcohol shall be used for preparing placebo resembling the medicine. These globules shall be procured from same firms. One dose will constitute 4 globules moistened with the medicine or placebo.
- Investigator/ pharmacist will dispense the homoeopathic medicine/placebo to the patients as per the randomization chart provided to him/her.

5.2.2. Method of selection of individualized homoeopathy medicines

5.2.2.1. During acute crisis

After enrollment in the study, investigator will take the case on acute case recording format. Thereafter the investigator shall build totality of symptoms. Based on these symptoms, a group of medicines shall be evolved by the method reportorial/non-reportorial approach to the case. For this purpose, any repertory as per need of the case shall be used and all medicines mentioned against the selected rubric(s) in the repertory, irrespective of the grades thereof, will be considered. After repertorisation, however, only one medicine whose portrait confirms in the Materia Medica shall be selected as the first prescription with justification for the respective patient. The classical approach to prescribing need to be adopted and preferable prescription should be among drugs published in pharmacopoea.

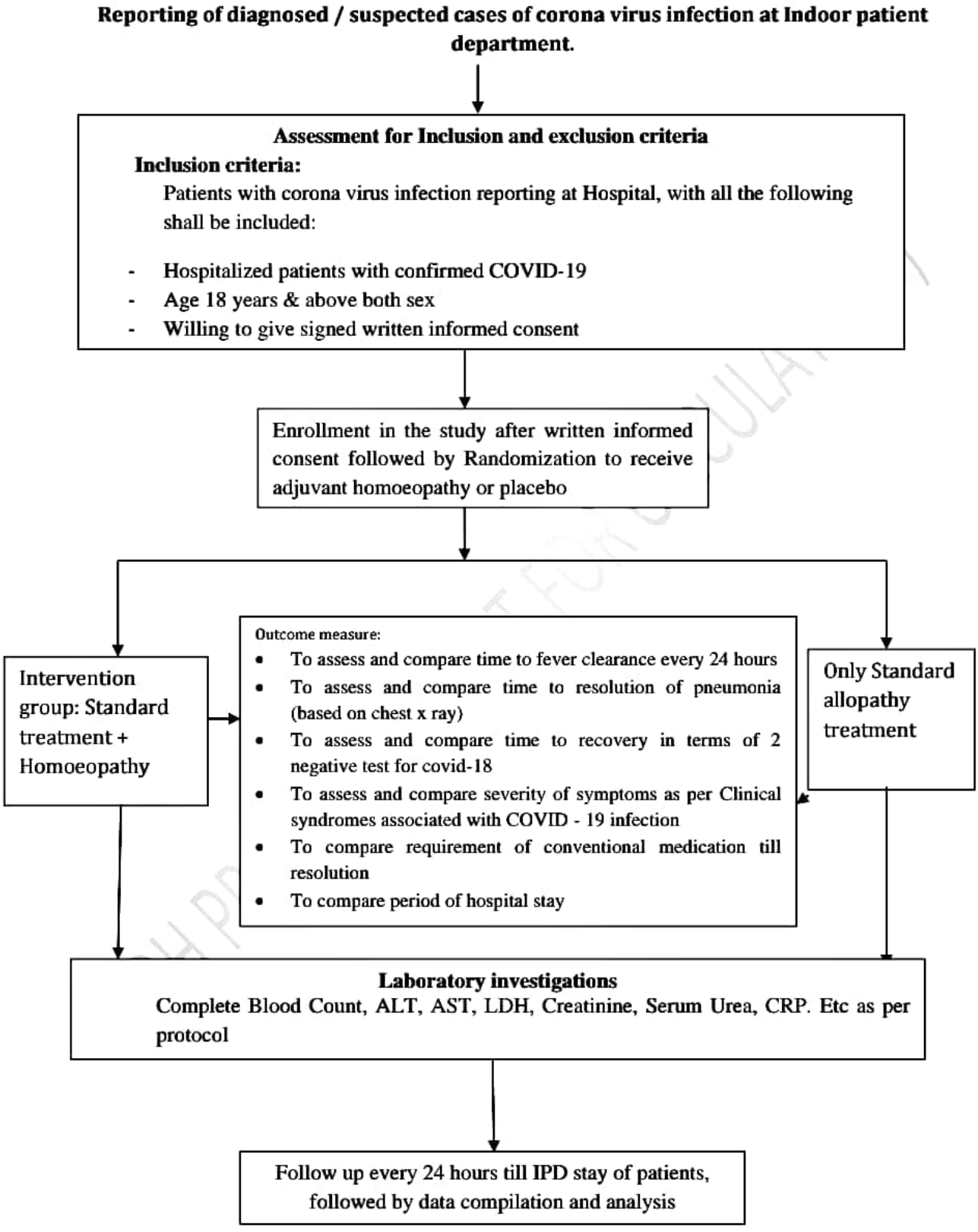
5.2.2.2 Prescription details

I.	**Prescription**	Prescription will be the indicated medicine in centesimal potency (30C/ 200C/1M).
II.	**Dosage**	Four pills of size 30 globules in the required potency.
III.	**Repetition**	Indicated medicine will be repeated as per the need of each case. Repetition can be done 2 to 6 hourly or even oftener, depending upon the intensity of symptoms.

5.2.4 Follow up & second prescription (for symptomatic cases)

The period of treatment and follow up will be till the time the patient is admitted to the hospital or reaches the primary end point as specified, whichever is before, with the first prescription being given on the first day of enrolment. Homoeopathic doctor will record all his observations pertaining to presenting complaints and to the selected drug in every visit.[24]

Figure 1. Flow chart of study



5.4 Change of Prescription/Therapy:

In case there is no perceptible change (neither worse nor better) after considerable time after administration of medicine the same medicine may be repeated in higher potency.

In case there is no perceptible improvement after adequate repetition of medicine in different potencies, the investigator must look for any obstacle (s) to cure and steps may be taken to remove them. A record of such advice followed by the patient is to be kept in the case follow up. In case no such obstacle(s) found, change of medicine is to be considered for 2 times.

If there is no change in sign and symptoms of the patient after adequate repetition of selected medicine(s), in various potencies judiciously, those patients will be treated as per standard care of the respective institution and their records to be kept separately.

6. General supportive care

Advice the patient as follows:

- As per standard institutional protocol
- Plenty of fluid intake
- A nutritious, well-balanced, healthy diet and hygiene must be maintained.

7. STATISTICAL PLAN & SUBJECT COMPLIANCE MONITORING

The overall significance level of the primary outcome will be explorative. All the data shall be assessed for normal distribution. Comparison of the baseline characteristics will use standard parametric/nonparametric statistical techniques, such as Fisher's exact test for categorical data, and the Kruskal-Wallis test for ordinal data and parametric tests for continuous data.

7.1 Steps to Maximize Adherence and Retention

- All the participants shall be motivated to adhere to study treatment and for measurement of various investigations from time to time by the investigator.
- Patients will be asked to contact the investigator for any problems faced by them during the study period.

7.2 Prior and Concomitant Therapy

As study intervention is adjuvant to conventional medicine, patients will continue taking conventional treatment as per standard treatment protocol. Other than intervention patients shall not take any other intervention or herbal treatment for disease.

8. SAFETY AND ADVERSE EVENTS

a. Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

b. Stopping Rules

Should the trial be terminated prematurely, as far as possible each individual patient should undergo a complete final examination or at least a final telephone interview, regarding the state of the patient's health, and if necessary, from the point of view of drug safety and validity of the trial results.

c. Medical Monitoring

It is the responsibility of the study team to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9. DATA HANDLING AND RECORD KEEPING

a. Confidentiality

The patients will be informed by the investigator that all trial results recorded will be treated in strict confidence. During documentation and analysis of the trial, the individual patients will only be identified by their patient number, whereas the name of the patient and any personal data are subject to the data protection regulations.

b. Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

c. Screening Forms

The study Screening form (SF) is the primary data collection instrument for the study. All data requested on the SF must be recorded. All missing data must be explained. If a space on the SF is left blank because the procedure not done or the question not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes

must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

d. Record Handling

1. Record keeping

The original records of patients will be maintained at the centers.

10. STUDY MONITORING, AUDITING, AND INSPECTING

a. Study Monitoring Plan

. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

b. Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, government regulatory bodies of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

11. ETHICAL CONSIDERATIONS

This study is to be conducted according to standards of Good Clinical Practice. This trial will be conducted in accordance with the requirements of the Declaration of Helsinki 1964, the Revisions of Tokyo 1975, Venice 1983 Hong Kong 1989, Somerset West 1996, Edinburgh 2000, First clarification- Washington 2002, Second clarification- Tokyo 2004 & Seoul 2008.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC), in agreement with local legal prescriptions, for formal approval of the study conduct. As this will be placebo control randomized study consent of patient shall be taken after providing sufficient information for subjects to make an informed decision about their participation in this study.

This consent form will be submitted with the protocol for review and approval by the EC for the study. The formal consent of a subject, using the EC approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable guardian/ head of family and the investigator-designated research professional obtaining the consent.

12. PREMATURE WITHDRAWAL OF THE PATIENT

Every patient is free to withdraw from the trial at any time for any reason and without prejudice. Any participants who withdraws from the trial shall undergo a complete final examination if possible, or at least a final telephonic interview at the time of withdrawal from the study, regarding the state of the health by the investigator, and if necessary, also from the point of view of drug safety and the validity of study results. The reasons for the withdrawal are to be recorded in the in the patient's case record.

13. PREMATURE STUDY TERMINATION

The Council after consensus with AIIMS study team is entitled to terminate the trial prematurely at any time for medical and/or organizational reasons. This decision will normally be made on the recommendation of the Councils Scientific Advisory Committee.

14. STUDY FINANCE

The study will be conducted from funding by PRANA.

15. PROTOCOL AMENDMENT

The investigator must meet the study requirements as specified in the protocol.

Protocol amendments are possible only in exceptional cases (e.g. where the health or well-being of the patient is affected) and only after authorization by the Council. Every amendment must be justified in writing and signed by all those concerned. Circulating protocols will be numbered and a list of their distribution will be remained. The investigator will update all circulating protocols by adding the amendment.

In the case of administrative or technical amendments which do not affect the health of patients, an administrative change is possible after agreement of all those concerned. These are also to be justified in writing and all those concerned are to be informed.

Should a protocol amendment change the design of the trial fundamentally, or increase the potential risk to patients, a renewed approval by the Ethics Committee and Protocol Review Board as well as a renewed patient's informed consent is required, also from those patients already enrolled into the trial, as far as they are affected by this change.

16. EXPECTED OUTCOMES

The results of the study will be able to predict the role of add on homoeopathic treatment for management of Coronavirus infected. If found effective, this could prove to be a vital contribution in public health care for a disease with high mortality. Further the cost-effectiveness of homoeopathy will enable developing countries in controlling such deadly disease effectively.

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