A Randomized, Open Label, Parallel Efficacy, Active Control, Exploratory Clinical Trial to Evaluate Efficacy and Safety of an Ayurvedic Formulation (AYUSH 64) as Adjunct Treatment to Standard of Care for the management of Mild to Moderate COVID-19 Patients

Clinical Research Proposal

A Randomized, Open Label, Parallel Efficacy, Active Control, Exploratory Clinical Trial to Evaluate Efficacy and Safety of an Ayurvedic Formulation (AYUSH 64) as Adjunct Treatment to Standard of Care for the management of Mild to Moderate COVID-19 Patients

Background

COVID-19 has emerged as the latest pandemic, that erupted in the Wuhan City of People's Republic of China in December 2019, which is affecting human health and economy across the world. 1133758 cases have been reported globally as on April 5, according to the WHO Coronavirus disease 2019 (COVID-19) Situation Report – 76. The occurrence of the ongoing COVID-19 in developed countries also highlights the fact that developed countries and rich populations are not immune to the outbreaks of infectious diseases.

Coronaviruses (CoVs) belong to the family Coronaviridae and are enveloped, single-stranded, positive-sense RNA viruses. The SARS-CoV-2 belongs to the beta CoV genus which also includes the SARS-CoV-1 and the MERS-CoV. The lack of approved effective drug therapeutic protocols for CoVs would be a challenge for the treatment of the newly emerged COVID-19 infections worldwide.

Drug repurposing, which is defined as identifying alternative uses for approved or investigational drugs outside their defined indication, could be a possible way to overcome the time limitation of research and development needed to design a therapeutic drug to combat the pathogen. The drug repurposing or repositioning approach thus can facilitate prompt clinical decisions at lower costs than de novo drug development[1]. Though drug repurposing is sometimes based on chance observations, target-based repurposing of drugs depends on prior understanding of the precise molecular or cellular element that is recognized by the proposed drug[2,3].

Ayurveda and traditional systems of Medicine in India have been treating diseases of infectious and non-infectious origin equally with expansive success rates, treating the patients through an individualized person to person approach depending upon the presentation of clinical symptoms in each. Central Council for Research in Ayurvedic Sciences, apex body for research and development in Ayurveda in India under Ministry of AYUSH has developed a poly-herbal drug 'AYUSH 64' through extensive pharmacological, toxicological and clinical studies. The experimental studies of AYUSH 64 has shown that it was safe and non-toxic in the dose of 500 mg/kg of body weight for 12 weeks**.** It is found to be effective in fevers of unknown etiology, filarial lymphangitis and derangement of liver function besides its anti-malarial activity[4,5,6].

Taking leads from the clinical experiences of physicians who had successfully used AYUSH-64, for management of Influenza like Illness (ILI), a pilot study was conducted by this Council, which was concluded recently and is under the process of publication. This study was done in 30 cases of flu like illness, among whom, 28 participants recovered without any further medication. This lead to the idea of repurposing AYUSH 64 for use in the management of Covid-19 positive cases which also present with Influenza like symptoms owing to affliction of respiratory tract. The composition of AYUSH 64 includes, *Saptaparna* (*Alstonia scholaris* R. Br.) *Katuki* (*Picrorhiza kurroa* Royle ex. Benth), *Kiratatikta* (*Swertia Chirata* Pexbex. Karst) and *Kuberaksha*

(*Caesalpinia crista* Linn.). Studies on the ingredients of AYUSH-64 has shown anti-inflammatory and immunomodulatory activities. Animal study has demonstrated that total alkaloids from *Saptaparna* inhibited the production of inflammatory cytokines TNF-α and IL-8 in the BALF and lung[7]. *Swertia chirata* showed antiviral properties against Herpes simplex virus type-1 and crude extract of the whole Swertia chirata plant inhibited the expression of Vpr in Hela cells harboring the TREx plasmid encoding full-length Vpr (TREx-HeLa-Vpr cells)[89].

STUDY DESIGN:

Study Type	:	Interventional (Clinical Trial)
Estimated Enrollment	:	80 (40 Patients in each group)
Allocation	:	Randomized
Intervention Model	:	Parallel Assignment
Intervention Model Description	:	The main trial is an open label, randomised, controlled trial that will be conducted in the patients of COVID-19 in selected site. Randomization will be 1:1, stratified by severity of illness, to either with or without AYUSH-64 for 30 days. All patients will also receive a supportive care/treatment according to ICMR/WHO guidelines for COVID-19
Purpose	:	Treatment
Masking	:	None (Open label)
Control	:	Controlled
Timing	:	Prospective
No. of Groups	:	Two

TIMELINES:

- **Study duration** : 6 months
- **Pre-trial preparation & medicine procurement** : 15 days
- **Duration of intervention** : 30 days
- **Statistical analysis** : 30 days

Inclusion criteria:

1. Typical clinical presentation of acute onset febrile illness with cough and a RT_PCR based laboratory confirmation test for COVID-19
2. Typical clinical presentation of acute onset febrile illness with sore throat and dry cough with or without shortness of breath in a patient from a known 'hot spot' area or in close contact with a confirmed COVID-19 case with a negative laboratory test for COVID 19 and H1N1 influenza
3. Patients with either sex, 18 to 75 years age
4. Patients with mild-moderately severe disease
5. All patients must agree not to share medication
6. Patients willing to participate and sign an informed consent Understands and agrees to comply with planned study procedures.
7. Agrees to the give OP swabs and venous blood for testing as per protocol.

Exclusion criteria:

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

5. Patients on parenteral nutrition
6. Patients with known sensitivity or contraindication to any of the ingredients of study medication
7. History of bleeding haemorrhoids, haemoptysis, acid peptic diseases, ulcers and pulmonary diseases (tuberculosis, asthma, etc.)
8. Patients who are likely to worsen or planed ICU admission or ventilator support due to any reason
9. Pregnancy and lactation
10. Participation in a drug interventional clinical drug trial of any nature in the three month period preceding onset of COVID-19
11. Participation in any other clinical trial of an experimental agent treatment for COVID-19
12. Patients on any kind of Ayurveda treatment or any other alternative and complementary medicinal systems such as Homeopathy, Unani, Siddha and in particular requiring oral therapy of any kind.
13. Physician decision that involvement in the study is not in the patient´s best interest

Withdrawal Criteria**

The patient can withdraw from the study at any point of time without assigning any reason.
The study investigator can also withdraw the patient for reasons arising out of the study drug intervention such as- intervention treatment failure, progression to severe disease, requirement of critical support care (ICU), requirement of persistent oxygen support, need for ventilation, drug related toxicity, protocol violations etc. All patients withdrawing from the study will be requested to complete the formalities (including laboratory evaluation) of study completion case record form and outcome/ hospital discharge. However, they will be encouraged to continue the clinical and other assessments enumerated for post treatment study schedule.
There are several other reasons for patient to withdraw from the study such as:

a) Patients who worsen or need ICU admission or ventilator support due to any reason
b) Non-compliance of the treatment regimen
c) Participants not willing to continue the study
d) Drug related toxicity

e) Any serious adverse event that makes the participant unable to do the activities of daily living / any SAE

f) 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

g) Any other condition which the investigator feels might cause harm to the participant

All adverse events (AE), and in particular serious adverse

Interventions:

Group-I

Group I: (Ayurveda as add-on to standard care as per guidelines)

AYUSH 64

Dose	2 capsules (500 mg each) thrice daily
Dosage form	Capsules/Tablets
Route of Administration	Oral
Time of Administration	Thrice a day after food
Anupana	Water
Duration of therapy	1 month

Group-II

Conventional standard therapy as per ICMR/WHO parameters

OBJECTIVES

Primary Objectives:

To compare the efficacy and safety of a combination regimen of Standard of Care (SOC) plus a selected standardized Ayurvedic drug (AYUSH 64 as adjuvant) in the management of mild to moderate COVID-19 with that of standalone SOC (active control).

Secondary Objectives:

a) To determine the therapeutic effect of a combination of SOC plus a standardized Ayurvedic drug (AYUSH 64) on surrogate markers of COVID-19 disease severity and complications, and recovery pertaining to broad based domain of acute phase reactants, pro-inflammatory cytokines, imaging assessment, anti-oxidant activity, organ dysfunction and damage

b) To determine the early and late post-recovery health benefits of a combination of selected standardized Ayurvedic drug (AYUSH 64) plus SOC using qualitative measure of health status (WHO Quality of life assessment questionnaire) and health related behaviour, habits and fitness questionnaire

c) To describe the clinical profile of COVID-19 with special reference to early symptoms, severity of disease, complications, course of disease, diagnostic investigations, biochemical and imaging abnormalities, patterns of recovery

d) To determine the predictors of early and late recovery from COVID-19 using a therapeutic combination of SOC plus a selected standardized Ayurvedic drug (AYUSH 64)

OUTCOMES

A) Primary Outcomes:

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

b) Proportion of patients showing 'clinical recovery'

Criteria of 'Clinical Recovery':

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

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

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

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

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

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

vii. Assessed by physician blinded to treatment allocation

viii. All of the above criteria ought to be fulfilled

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

Secondary Outcome Measures:

1. Percentage of patients with negative SARS-CoV-2 on nasal or throat swab in a 2 day continuous real time RT-PCR test beginning from 'first day of clinical recovery' or 'Day 10 after onset of symptoms depending on whichever of the two time points is first achieved
2. Timelines (days counted from onset of illness)- normal body temperature, absence or minimal cough (see 'clinical recovery' for the definition), absence of dyspnoea, onset of clinical pneumonia, pneumonia diagnosed on chest X-Ray or CT scan, time to supplemental oxygen, admit in intensive care unit, mechanical ventilation (non-invasive), mechanical ventilation (invasive), steroid use, respiratory failure, adult respiratory distress syndrome, cytokine storm syndrome, secondary infection, shock, septicaemia shock, hospital discharge, negative nose or throat swab confirmatory test, and all-cause mortality Duration of fever and respiratory symptoms [Time frame 1 month].
3. Proportion of patients developing an event that reflects clinical or otherwise improvement of worsening (the events are similar to those listed under Timelines, see above
4. Improvement on pulmonary function tests using simple 'home expiratory spirometer' device and peripheral pulse oximetry Change in Respiratory support level. [Time frame 1 month]

5. Improvement in selected laboratory parameters: blood haemoglobin, differential and total leukocyte counts, liver enzymes, renal functions, acute phase reactants, serum IL-6 and other selected cytokines, serum muscle enzymes (CK, CPK), serum ferritin, serum d-Dimer, anti-oxidant markers, serum BNP (cardiac function)
6. Serological Protective Antibody Assay (IgM and IgG)
7. Radiological Improvement on digital chest X - ray and or HRCT chest
8. Drug related: side effects and toxicity, and tolerability (Safety criteria: All adverse events occurring during the study will be recorded and monitored as per GCP-ICH guidelines. Safety would also be assessed in case of all withdrawals.)
9. Health status: WHO QOL brief, health related behaviour habit and fitness questionnaire based on visual analogue scale
10. Ayurveda evaluation/assessment parameters:

    a) Prakriti

    b) Symptoms: Nausea / Vomiting / Diarrhoea / Pain in abdomen / Hyperacidity / Skin rash / Burning micturition / Itching / Vertigo / Thirst / Fatigue / Sweating / Ulcers

    c) Ayurvedic disease subtypes

FOLLOW UP / MONITORING:

a) Disease symptoms*: Shwasa / Kasa / Jvara / Angamarda / Anannabhilasha /*

b) Ayurveda examination: Appetite (Agni), Tongue, Ama, Bowel, Urine, Skin, Sleep,

c) Adverse events: Nausea / Vomiting / Diarrhoea / Pain in abdomen / Hyperacidity / Skin rash / Burning micturition / Itching / Vertigo / Thirst / Fatigue / Sweating / Ulcers/Others

Method of Randomization: Subjects will be randomized into two groups. First group of patients will receive conventional treatment & AYUSH 64 and second group will receive only conventional treatment using a computer generated table.

SAFETY RECORDING

a. Adverse Events

All adverse events observed or reported by patients will be recorded in the CRF with information about severity (i.e., Asymptomatic whether mild or moderate) and possible relation to the study medication. Any serious adverse effects will be notified immediately to the study monitor.

b. Clinical Laboratory Parameters

The following laboratory tests will be performed as per the study schedule.

Laboratory investigations:

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

i. Haemogram, Platelet count, Total leukocyte differential count, Hemoglobin and ESR,

ii. Liver function test - Serum Bilirubin, ALT, AST, Alkaline phosphatase,

iii. Kidney Function Test (Serum creatinine, Blood Urea Nitrogen)

iv. Lipid profile (Total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides, VLDL)

v. Blood Sugar Level

vi. Urine Routine

vii. C-Reactive protein titer

viii. LDH, Ferritin

ix. Pro-Cal

x. CK, B-type natriuretic peptide (BNP), Troponin, D-Dimer

xi. Serum Electrolytes (Sodium, Potassium, Chloride, Iron Zinc, Manganese) Vitamin D, B12

xii. Oxidation Biomarkers-Superoxide Dismutase (SOD), Glutathoine (GSH)

xiii. Cytokine Panel (Interleukin-2, Interleukinl-4, Interleukin-6, Interleukin-10, TNF-α, Interleukin-1β, Interleukin-13), Monocyte Chemotactic Protein (MCP), Gamma Interferon. RATIONALE FOR CYTOKINE ASSAY: Cytokine assay can be used to study important anti-viral effects (gamma interferon), immune mediated inflammation (IL-6, anti-TNF, IL-17), TH 1 and TH 2 immune response and antibody producing B cell activity (IL4, IL13), activation of immune cells such as macrophage activation (MCP). (Intense up regulation and elevation of IL 6 and several other cytokines has been reported by several clinical case series and research in COVID-19 and can guide specific therapy (as in case of use of monoclonal antibody to IL-6 receptor being used to treat Cytokine storm in COVID 19))

xiv. Serum Immune Response tests (IgG and IgM) for COVID-19

xv. Urine Pregnancy Test for women of child bearing potential

Other Investigations:

i USG Abdomen and Pelvis

ii Color Doppler and 12 Lead ECG

iii Chest X-ray

iv HRCT Chest

STATISTICAL METHODS:

The design of the drug trial is exploratory in nature. Though a randomized selection of patients will be done to either of the two arms, the sample size is that of convenience (expert opinion) and the same is not statistically powered however, sample size (40 patients in each arm) is sufficient to draw meaningful conclusions. The statistical significance $p<0.05$(two sided) is predefined for analysis. Statistical analysis will be performed using standard tests to compare the two interventional arms for primary and secondary efficacy measures. Safety events will be also analyzed. Both intent-to-treat and per protocol completer analysis will be performed. Regression analysis will be done to identify predictors of response. Clinical symptoms, Subjective parameters and Laboratory parameters will be subjected to Univariate and multivariate analysis using Statistical Package for Social Sciences (SPSS) 15.0 version with appropriate statistical methods.

DEVIATION FROM THE PROTOCOL:

The trial should be conducted in compliance with the protocol. Deviations from the protocol should not be made except when necessary to alleviate an immediate hazard to trial patients. All the deviations from the protocol, including unplanned changes to interventions, examinations, data collection and method of analysis should always be reported to sponsors and IEC at the earliest along with the exact reason for that deviation.

In view of novel corona virus, Guidelines are frequently updated by the Government and ICMR. In view of it, the deviation from protocol (if any) will be informed to the IEC and Sponsor at the earliest.

ADVERSE EVENTS:

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

ADVERSE DRUG REACTION (ADR):

A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. (WHO, 1972). An adverse drug reaction, contrary to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.

Any adverse event, if observed during treatment period or during follow up visits should be clearly documented and its appropriate and timely management should be done. The Principal Investigator should report the same to the Ethics committee and the sponsor(s) at the earliest.

DRUG COMPLIANCE:

If there is more than or equal to 80% compliance, the participant would be continued in the trial. The compliance needs to be assessed at each follow-up by investigator on the admitted patients.

CONCOMITANT MEDICATION:

A concomitant medication (con-med) is a drug or biological product, other than a study drug, taken by a subject during a clinical trial. Participants registered under the trial will be issued treatment cards with the entire treatment regimen written on it. They will be instructed to avoid the use of any other drugs on their own for any ailment and will be clearly instructed to consult the treating Investigating physician for any symptom or complaint, or if they feel anything unusual. The Investigating physician will record any medication(s) he / she may prescribe to alleviate their ailments.

RESCUE MEDICATION:

RESCUE MEDICATION / Quick-acting medication / Fast-acting Medication - A medication intended to relieve symptoms immediately. This is in contrast to preventive medications, which are taken over a long period of time to prevent or manage symptoms.

To alleviate any emergency, the use of rescue medication is permitted as per the wisdom / discretion of the Principal Investigator. However, the same need to be documented in appropriate column in the Case Record Form.

Those patients under self isolation at home (as per latest guidelines of Govt. of NCT of Delhi dated 30/04/2020) will be advised to inform immediately use of any such medicine in condition of emergency.

DROP-OUTS:

An attempt shall be made to record the reason for drop outs, if any during the clinical trial.

ETHICS:

The trial will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki for biomedical research and ICMR ethical guidelines involving human participants (2006), and that are consistent with Indian / ICH Good Clinical Practice (GCP) guidelines.

INSTITUTIONAL ETHICS COMMITTEE:

Prior to commencement of the trial, the protocol, the participant information sheet and the consent form will be submitted to the Institutional Ethics Committee. Written approval of the same will be obtained from the IEC. Protocol amendments are also to be approved by the IEC according to the usual procedure.

PATIENT INFORMATION AND CONSENT FORM:

Prior to any trial related activity, the Principal Investigator will give the patient verbal and written information about the trial in a form the participant can read and understand. The Investigator would ensure that the participant is fully informed about the aims, procedures, discomforts and expected benefits of the trial. It must be emphasized that participation is voluntary and participants have the right to opt out of the trial at any time without any prejudice. A voluntary, signed witnessed Informed Consent should be obtained from the participant prior to any clinical trial related procedure.

CO-ORDINATION OF TRIAL

Co-ordination Centre:

Shri Dhanwantry Ayurvedic College and Hospital,
77, Chandi Path, Sector 46B, Sector 46
Chandigarh, 160047

DATA DOCUMENTATION AND ANALYSIS

Clinical symptoms, Subjective parameters and Laboratory parameters will be subjected to univariate and multivariate analysis using Statistical Package for Social Sciences (SPSS) 15.0 version with appropriate statistical methods. All information regarding clinical trial should be properly documented, carefully handled and meticulously stored in order to ensure its accurate interpretation and verification. Analysis will be done by **CCRAS's statistical Unit.** .

Study Schedule

STUDY PROCEDURES: TIMELINES AND EVENTS SCHEDULE

The overview is shown in Table .

Baseline Visit: (Visit 1)

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

Visit 1 (Baseline)	Providing with Patient Information Fact Sheet for thorough study.
	Signing of Informed Consent.
	Complete medical examination form: medical history, comprehensive physical examination, co-morbidity, medication history.
	Symptom Assessment, Vital Parameters
	Record Baseline Symptoms
	Comprehensive Ayurvedic evaluation.
	Laboratory work up- general health and advanced test and cytokines as in Appendix O
	Ultrasound abdomen and Pelvis, Chest X-ray, HRCT chest,
	Colour Doppler and 12 Lead ECG
	Pulse Oximetry
	Health Related-Behaviour Fitness (HR-BHF) VAS questionnaire, Self-Reported Questionnaire (Mobile app)
	Dispense study medication and begin medication log entry

Daily evaluation till discharge

Day 2 up to-Discharge) (Daily Assessment):	Symptom Assessment, Vital Parameters
	Brief Ayurvedic Evaluation
	Laboratory work up
	Pulse Oximetry
	Monitor Adverse Events

Visit on 7th, 15th, 23rd	Symptom Assessment, Vital Parameters
	Brief Ayurvedic Evaluation
	Laboratory work up (RT-PCR) as and when required for two consecutive days Full laboratory workup on 7th, and 15th day.
	Pulse Oximetry
	Monitor Adverse Events
	Health Related-Behaviour Fitness (HR-BHF) VAS questionnaire, Self-Reported Questionnaire (Mobile app)
	Chest X-ray (15th day)
	Drug Compliance, Dispense study medication

Visit on 30th	Symptom Assessment, Vital Parameters
	Brief Ayurvedic Evaluation
	Laboratory work up (RT-PCR), clinical workup, serological work up
	Pulse Oximetry
	Monitor Adverse Events
	Health Related-Behaviour Fitness (HR-BHF) VAS questionnaire, Self-Reported Questionnaire (Mobile app)
	Chest X-ray /HRCT
	Drug Compliance
	Completion and Outcome Report

	Screening (Before Intervention)	**Baseline**	**7th day**	**15th day**	**23rd day**	**30th day**
Informed consent & PIS	**Y**					
Medical history		**Y**				
Laboratory Investigations	Only COVID-19 test	Y (all lab investigations except COVID RT-PCR	Y (all lab investigations except	Y (all lab investigations except		*(all lab investigations including COVID RT-PCR test

			COVID RT-PCR	COVID RT-PCR		
Chest X-ray		**Y**		**Y**		**Y**
Clinical Examination		**Y**	**Y**	**Y**	**Y**	**Y**
Concomitant Medication			**Y**	**Y**	**Y**	
Assessment of ADRs			**Y**	**Y**	**Y**	
Assessment of Medication compliance			**Y**	**Y**	**Y**	
Temperature Chart/Pulse Oximetery		**Thrice daily**				

*** In patients who are not discharged or not attained sero negativity by 15th day, the investigations shall be done on 30th day.**

LABORATORY & OTHER INVESTIGATIONS

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

i Blood/Serum (routine): Haemogram, Platelet count, Total leukocyte differential count, Hemoglobin and ESR, Blood sugar level (Fasting), Liver function test and Liver Enzymes (SGOT,SGPT, Alkaline Phosphatase), Renal functions (Serum creatinine, Blood Urea Nitrogen), Lipid profile (Total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides, VLDL)

ii Serum (inflammatory markers, organ damage):C-Reactive protein titer, lactate dehydrogenase, ferritin, Pro-Calcitonin, Troponin, D-Dimer,

iii Special tests: Blood for Vitamin D, Vitamin B12, Oxidation Biomarkers (Superoxide Dismutase(SOD), Glutathoine (GSH)

iv Cytokine Panel:Interleukin (IL) IL-2, IL-1 beta,IL-4, IL-6,IL-10, IL-13, IL-17, TNF-α, Monocyte Chemotactic Protein-1 (MCP), Interferon gamma, TGF-bet

v Serum Protective Antibody Response: IgM and IgG against SARS-CoV-2

vi Routine Urinalysis, Urine Pregnancy Test for women of child bearing potential

vii Confirmatory Diagnostic Test: Nasal and/or Throat swab for real time RT-PCR for SARS-CoV-2 (See AppendixO)

viii Other Investigations: USG Abdomen and Pelvis, ECHO-Color Doppler and 12 Lead ECG , Chest X-ray, HRCT scan Chest

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