

Proposal for COVID-19 project
(Study Protocol, Version no.6 dated 2020.09.25)

Topic: Based on the theory of “body constitution of Chinese Medicine” and “combination of prescription and syndrome” to improve COVID-19 susceptible body constitution of residents in Hong Kong

Researchers: Feng Yibin (PI), Wang Ning, Lai Yuen Kwan Agnes, Cheng Chien-shan, Zhang Cheng, Li Sha

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General information

- a. Title: Evaluating the effects of Chinese medicine in the prevention of COVID-19 in Hong Kong
- b. Sponsor: Chinese Medicine Development Fund, HK (accepted project)

c. Project PI: Feng Yibin

Title: Acting director, School of Chinese Medicine, the University of Hong Kong

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d. Researcher: Wang Ning

Project task: Data Processing

Title: Assistant Professor, School of Chinese Medicine, the University of Hong Kong

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Researcher: Lai Yuen Kwan Agnes

Project task: clinical data acquisition and expert advice

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Address: School of Nursing, the University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong

Researcher: Cheng Chien-shan

Project task: clinical data acquisition and analysis

Position: Research Assistant, School of Chinese Medicine, the University of Hong Kong

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Address: G/F, School of Chinese Medicine, 10 Sassoon Road, Pokfulam, Hong Kong

Researcher: Zhang Cheng

Project task: clinical data acquisition and analysis

Position: Ph.D. candidate, School of Chinese Medicine, the University of Hong Kong

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Researcher: Li Sha

Project task: clinical data acquisition and analysis

Post-doctoral researcher, School of Chinese Medicine, the University of Hong Kong

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Address: G/F, School of Chinese Medicine, 10 Sassoon Road, Pokfulam, Hong Kong

e: Relevant medical treatment at the clinical trial site:

Researcher: Lai Yuen Kwan Agnes, Zhang Cheng, Cheng Chien-shan. Li Sha

f: Names and addresses of clinical laboratories and other medical and / or technical laboratories:

Relevant research will be carried out in the Central or Sassoon clinic, School of Chinese Medicine, the University of Hong Kong

Central Clinic address: Room 703, 9 Queen's Road Central, Hong Kong

Sassoon clinic address: G/F, School of Chinese Medicine, 10 Sassoon Road, Pokfulam, Hong Kong

2. Research background:

In December 2019, COVID-19 has been outbreaks in a series regions of China and abroad. Its pathogen was initially identified as a new coronavirus with single strand positive RNA [1]. COVID-19 is considered to be a coronavirus associated with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which can affect the lower respiratory tract and manifest as pneumonia [2,3]. On January 31, 2020, the World Health Organization (WHO) officially announced that COVID-19 has become a "public health emergency of international concern" Although most provinces in China have inhibited the spread of COVID-19 after taking protective measures, the number of patients worldwide is still on the rise. According to WHO and recent reports, On 1st Sept, 2020, the total number of clinically confirmed cases in the world is 25327098, and the current total number in China is 90402 [4] China has incorporated COVID-19 into the class B infectious diseases in the law on the prevention and control of infectious diseases. Notably, it

adopted the prevention and control of class A infectious diseases. It is worth noting that residents of Hong Kong have also been seriously infected with COVID-19. According to the latest report released by the Department of Health in Hong Kong, the total number of patients with COVID-19 had risen to 4823 on Sept 1st, 2020. Therefore, it is very urgent to find effective control methods.

According to the theory of Chinese medicine, COVID-19 belongs to the category of "epidemic toxin". TCM has been used for thousands of years in the treatment of epidemic diseases. Through the long-term struggle with the epidemic, we have accumulated a lot of experience for the pathogenesis, transmission, prevention and control of the epidemic. In mainland China, TCM plays an important role in the treatment of COVID-19. The recent retrospective analysis of 52 cases by Zhang Boli's research group showed that 34 cases in the treatment group of integrated TCM and Western medicine were superior to 18 cases in the simple western medicine group in terms of various bio-indexes, including clinical symptoms disappearance, the time of body temperature recovery, the average length of stay in hospital, the score of TCM Syndrome Scale, the rate of CT image improvement, the rate of clinical cure, and the conversion from common type to severe type [5]. According to a case study of 799 people in Hunan Provincial Administration of traditional Chinese medicine, the average length of stay in hospital of integrated traditional Chinese and Western medicine treatment is 2 days shorter than that of Western medicine treatment alone, and the number of patients with obvious improvement of symptoms accounts for 64% of the total number of observation [6]. For the modern measures of epidemic prevention, it includes three approaches: **cutting off pathogens**, **controlling transmission routes**, and **reducing susceptible populations**. However, so far, the preventive measures of Chinese medicine for COVID-19 has not been included in the medical system of Hong Kong, although it is widely authorized and promoted in mainland China. Therefore, it is of great clinical significance to further develop the prevention of COVID-19 by Chinese medicine for **reducing susceptible populations**. The National Health Committee and the State Administration of TCM organized relevant experts to establish COVID-19 standardized diagnosis and treatment program. The updated diagnosis and treatment program describes the relationship between the dialectical classification of Chinese medicine and the stage of Western medicine. The pathogenesis of TCM can be summarized as "dampness, heat, toxin, blood stasis, deficiency" [7]. According to the statement of Tong Xiaolin, COVID-19 belongs to "cold dampness epidemic", which is caused by cold dampness epidemic virus. The disease is mainly caused by the deficiency of either yin or Yang [8]. According to a report on the clinical epidemiology of COVID-19 published by Lancet, the median susceptible population of COVID-19 is 49 years old (interquartile range is 41-58 years old), which means the majority of patients are middle-aged and elderly [9]. The body constitution of this kind of patients is mainly divided into "Deficiency of Qi and Yang" and "Deficiency of Qi and Yin". However, so far, the prevention of treatment of COVID-19 with TCM has not been included in the medical system of Hong Kong, although TCM therapy is widely authorized and promoted in mainland China. Therefore, It may be beneficial to provide TCM preventive measures to COVID-19 in Hong Kong. By using "Self-test for classification and judgment of body constitution by TCM theory" issued by Professor Wang Qi, a honorary Professor of School of Chinese medicine, the University of Hong Kong, we can identify the subjects with "Deficiency of Qi and Yang" or "Deficiency of Qi and Yin" [10]. According to the above-mentioned pathogenesis characteristics of COVID-19 in the prevention stage, "Invigorating Qi and Yang, invigorating Qi and Yin" may be conducted by TCM treatment. The changes of body constitution will be measured by questionnaires before and after TCM intervention, including scale

of self-test for classification and judgment of body constitution by Traditional Chinese Medicine (TCM) theory, Questionnaire of TCM symptom, and Fatigue scale.

In order to scientifically evaluate the preventive effect of TCM on COVID-19, it is very important to reveal the changes of COVID-19 related biochemical indexes before and after the intervention of TCM. According to the discussion on “Diagnosis and treatment of new coronavirus pneumonia (7th Edition)” issued by the National Health Commission of China, the following changes in biochemical indicators are closely related to the occurrence of COVID-19. Firstly, the decrease of leukocytes, lymphocytes, and bone marrow cells (including granulocytes, erythrocytes, and megakaryocytes) in blood routine examination; the increase of troponin and ESR. Secondly, the reduction of macrophages-related immune cells, such as monocyte. Thirdly, the increased index of liver function and cardiac function, including AST, ALT, and LDH. Fourthly, inflammation related factors, including IL-6 and C-reactive protein. Therefore, the analysis of the relationship model of TCM syndrome and molecular biological profiles can further provide a novel preventive mode for COVID-19.

Reference

- [1] Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares Global Emergency: A review of the 2019 Novel Coronavirus (COVID-19). *Int J Surg*. 2020.
- [2] Mahase E. Coronavirus covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. *BMJ*. 2020;368:m641.
- [3] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020.
- [4] <http://www.nhc.gov.cn>.
- [5] Xia Wenguang, An Changqing, Zheng Chanjuan, Zhang Jixian, Huang Min, Wang Yu, Yang Fengwen, Duan can, Li Zhengliang, Liu Qingquan, Zhang Boli. Clinical study on 34 cases of COVID19 patients by Integration of Chinese and Western Medicine. *Journal of traditional Chinese medicine*:1-7.
- [6] Huang Huiyong, Xiao Wenming, Wang Yingyi, Cai Hongkun, Chen Juan, Tan Hanyu. Analysis report of traditional Chinese medicine treatment for patients with new coronavirus pneumonia in Hunan Province [J/OL]. *Journal of Hunan University of traditional Chinese medicine*: 1-4
- [7] Huang xiongjie, Lai min, Jia Chunhua, Liu Wei. Traditional Chinese medicine in the world: 2020, 1-6
- [8] ong Xiaolin, Li Xiuyang, Zhao Linhua, Li Qingwei, Yang Yingying, Lin Yiqun, Ding Qiyong, Lei ye, Wang Qiang, song bin, Liu Wenke, Shen Shiwei, Zhu Xiangdong, Huang Feijian, Zhou Yide. Discussion on the prevention and treatment strategy of new coronavirus pneumonia (covid-19) from the perspective of "cold dampness epidemic" [J / OL]. *Journal of traditional Chinese medicine*: 1-6
- [9] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
- [10] Liu Yu, Wang Qi. Suggestions and analysis of standard revision of classification and judgment of constitution of traditional Chinese medicine [J]. *Journal of Beijing University of traditional Chinese medicine*, 2013,36 (05): 300-304.

2a. Table 1: The groups and expected COVID-19 preventive treatments:

All the constructive and intake dose of formula are conducted by the standard criteria of Nong's CM

Constitution of Chinese Medicine	Group	Formula
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Deficiency of Qi and Yang: shortness of breath; Laziness, chilly limbs, self-perspiration, sore waist and knees; light tongue, thin white moss, deep and fine pulse	CM-induced invigorating of Qi and Yang (QYang-group)	Yu-Ping-Feng and Xiang-Sha-Liu-Jun formula (Nong's CM) <u>5g twice daily for each formula</u> <u>(20g in total per day)</u>
	Placebo control of invigorating Qi and Yang (PQYang-group)	The placebo is made of 5% herbal medicine of nourishing qi and yang <u>10g twice daily per placebo</u> <u>(20g in total per day)</u>
Deficiency of Qi and Yin: tiredness and weakness, shortness of breath when moving; fear of heat, five heart hot, self-perspiration and night sweat; red tongue, thin white or light peeling, weak and fast pulse	CM-induced invigorating of Qi and Yin (QYin-group)	Yu-Ping-Feng and Liu-Wei-Di-Huang formula (Nong's CM) <u>5g twice daily for each formula</u> <u>(20g in total per day)</u>
	Placebo control of invigorating Qi and Yin (PQYin-group)	The placebo is made of 5% herbal medicine for nourishing qi and yin <u>10g twice daily per placebo</u> <u>(20g in total per day)</u>

2b. Summary of non-clinical research results that may have clinical significance.

This project is based on the reference of clinical observation and research on the prevention of COVID-19 by the theory of "Body constitution of TCM" and "Combination of formula and syndrome". In the early stage, we have reviewed a large number of papers and Diagnosis and treatment of new coronavirus pneumonia (7th Edition) published by national health commission regarding the TCM-related prevention of COVID-19. Finally, according to the theoretical knowledge of TCM, we may classify the susceptible body constitution of COVID-19 into "deficiency of Qi and Yang" and "deficiency of Qi and Yin", which might be of great significance for COVID-19 prevention.

2c. A summary of the known and potential risks and benefits, if any, of the subjects.

Subjects will be divided into four groups, including QYang-group, PQYang-group, QYin-group, and PQYin-group. According to different syndrome types, our clinic will provide timely medical help. Under normal condition, our TCM formula will not have obvious adverse reactions to the subjects with deficiency of Qi with either Yang or Yin. Moreover, Nong's Chinese Medicine is a renowned standardized production in Hong Kong. It has been in safety testing with specific intake dosage before it goes on the market. For the risk of specific TCM treatment, subjects with external self-perspiration, yin deficiency and night perspiration cannot use Yupingfeng formula, since it may aggravate the symptoms of sweating and yin deficiency. Subjects with dry mouth and tongue cannot use Xiangsha Liujun formula, because it may aggravate this symptom. Subjects without obvious deficiency of kidney yin should not take Liuwei Dihuang formula, because it will cause diarrhea and loss of appetite. We will exclude these kinds of subjects in this study. If subjects with fever, dry cough, fatigue, runny nose, sore throat, diarrhea and other side effects, we will terminate the clinical study of this subject and offer essential treatment for reducing the side effect. Meanwhile, we will report the situation to Hospital Authority during the current COVID-19 pandemic.

2d. Route of administration, dosage, description and reason of the administration plan, and treatment cycle.

The administration route of Chinese medicine in this project is oral. The dosage and prescription scheme are established according to Table 1. The treatment duration was one month. The TCM formulas in the above table were designed by the clinical TCM practitioners of the School of Chinese Medicine, the University of Hong Kong, which was based on the clinical experience and Diagnosis and treatment of new coronavirus pneumonia (7th Edition). All the intake doses are shown in Table 1, which is taken from the standardized production in Nong's CM.

2e. This clinical trial will strictly implement according to the GCP outline (https://en.wikipedia.org/wiki/good_clinical_practice).

2f. Description of the population to be studied.

According to the contents described in the Diagnosis and treatment of new coronavirus pneumonia (7th Edition) and a Lancet study, the median age of the susceptible population is 49 years (interquartile range 41-58 years), and the majority of patients are middle-aged and elderly. The subjects characterized by "deficiency of Qi and Yang" and "deficiency of Qi and Yin" were regarded as the susceptible population.

2g. Research relevant literature and data, and provide research background basis:

The background of this study refers to Diagnosis and treatment of new coronavirus pneumonia (7th Edition) [1]. This project described the epidemiological characteristics of COVID-19 and the statements of "Combination of formula and Syndrome" with specific prescriptions. In this project, the design of formula and classification of susceptible individuals refer to "Diagnosis and treatment of new coronavirus pneumonia (7th Edition)", studies from Lancet and New England Journal of Medicine [2-4]. In addition, Professor Wang Qi from School of Chinese Medicine, HKU, established the criteria for classification and determination of body constitution of Chinese medicine [5]. Moreover, Questionnaire of TCM symptom, and the Chalder fatigue scale will be adopted for providing a theoretical basis for the design and implementation of the clinical research of this project [6]

References:

- [1] Diagnosis and treatment of new coronavirus pneumonia (7th Edition) <http://www.gov.cn>.
- [2] Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares Global Emergency: A review of the 2019 Novel Coronavirus (COVID-19). *Int J Surg*. 2020.
- [3] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020.
- [4] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
- [5] Liu Xuan, Wang Qi. Suggestion and analysis of classification and constitution of traditional Chinese medicine [J]. *Journal of Beijing University of traditional Chinese medicine*, 2013, 36(05):300-304.
- [6] Cella M, Chalder T. Measuring fatigue in clinical and community settings. *J Psychosom Res* 2010;69:17-22. 10.1016/j.jpsychores.2009.10.007

3. Research objectives:

3a. Evaluation of the improvement of COVID19-related susceptible body constitution by TCM preventive treatment.

3b. Clarify the distribution of COVID-19 susceptible residents in Hong Kong by questionnaires.

3c. Identify the changes of biomarker which may be fluctuated by COVID19 infection according to “Diagnosis and treatment of new coronavirus pneumonia (7th Edition)” held by National Health Commission and State Administration of TCM.

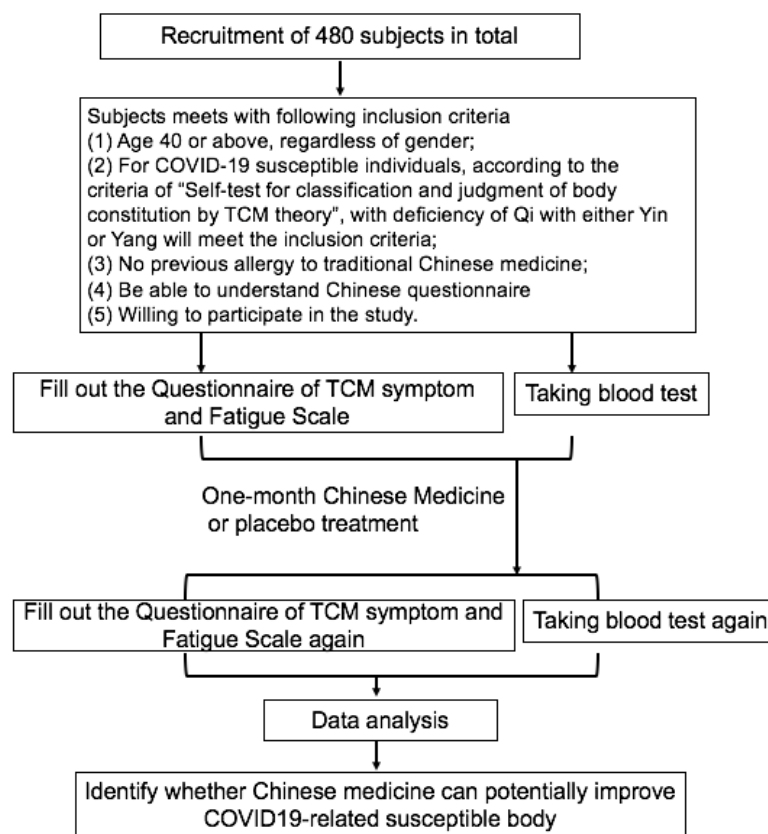
4. Experimental design:

4a. Specific description of the time points to be measured during the test.

There are two main time points in this clinical trial. The first is that one month after the TCM or placebo treatment as shown in Table 1, the subjects will receive both blood test and questionnaires, including “Self-test for classification and judgment of body constitution by TCM theory”, “Questionnaire of Chinese medicine symptom”, and Fatigue scale. According to the before-after changes of observation records in each questionnaire and blood test, the preventive effect of TCM was determined.

4b. Test type, design description and schematic diagram of test phase.

This study is a random, double-blind clinical research. All the subjects will be equally divided into TCM group (i.e. QYang-group, PQYang-group, QYin-group, and PQYin-group) and Placebo group for one-month specific treatment, which aims to investigate the preventive effect of TCM on the improvement of the body susceptibility to COVID-19. The study plan roadmap is shown below.



4c. Describe the actions taken to avoid deviations.

In order to reflect the objective reality of the experimental data as much as possible, we adopted a randomized double-blind clinical trial method. All subjects will be divided into four groups: QYang-group, PQYang-group, QYin-group, and PQYin-group. A total of 480 subjects were included.

4d. Expected duration of subject participation, including follow-up (if any)

The subjects of this project will last 1 month.

4e. Description of "stop rule" or "stop criteria" for individual subjects.

If the subjects have fever, dry cough, fatigue, runny nose, sore throat, diarrhea and other symptoms after taking the medicine, the subjects will immediately stop taking TCM or placebo. Meanwhile, subjects will give a certain degree of TCM clinical treatment. As these symptoms are similar to the epidemiological characteristics of the latent period of COVID-19, we will immediately report to HA in the current period of COVID-19 pandemic

4f. Description of placebo control (if any)

The placebo control group of this clinical trial is PQYang-group and PQYin-group. Their prescriptions are as follows: PQYang-group: the placebo is made of dextrin, bitterness agent, edible pigment, etc., and 5% herbal medicine of nourishing qi and yang; PQYin-group: the placebo is made of dextrin, bitterness agent, edible pigment, etc., and 5% herbal medicine for nourishing qi and yin.

4g. Record and collection of clinical data.

All clinical data will be recorded in the electronic versions.

5. Criteria for inclusion, exclusion and re-inclusion of subjects

Inclusion criteria:

- (1) Age 18 or above, regardless of gender;
- (2) For COVID-19 susceptible individuals, according to the criteria of "Self-test for classification and judgment of body constitution by TCM theory", subjects with deficiency of Qi with either Yin or Yang will meet the inclusion criteria;
- (3) No previous allergy to traditional Chinese medicine;
- (4) Be able to understand Chinese questionnaire;
- (5) Willing to participate in the study.

Exclusion criteria

- (1) Syndrome types are not related to "deficiency of Qi and Yang" and "deficiency of Qi and Yin";
- (2) Suspected or confirmed COVID-19 patients;
- (3) Fever, body temperature $> 37^{\circ}\text{C}$ with cough and other respiratory symptoms;
- (4) Those who have visited the epidemic area and have not completed isolation for 14 days after returning to Hong Kong

Criteria for inclusion in the test after exclusion

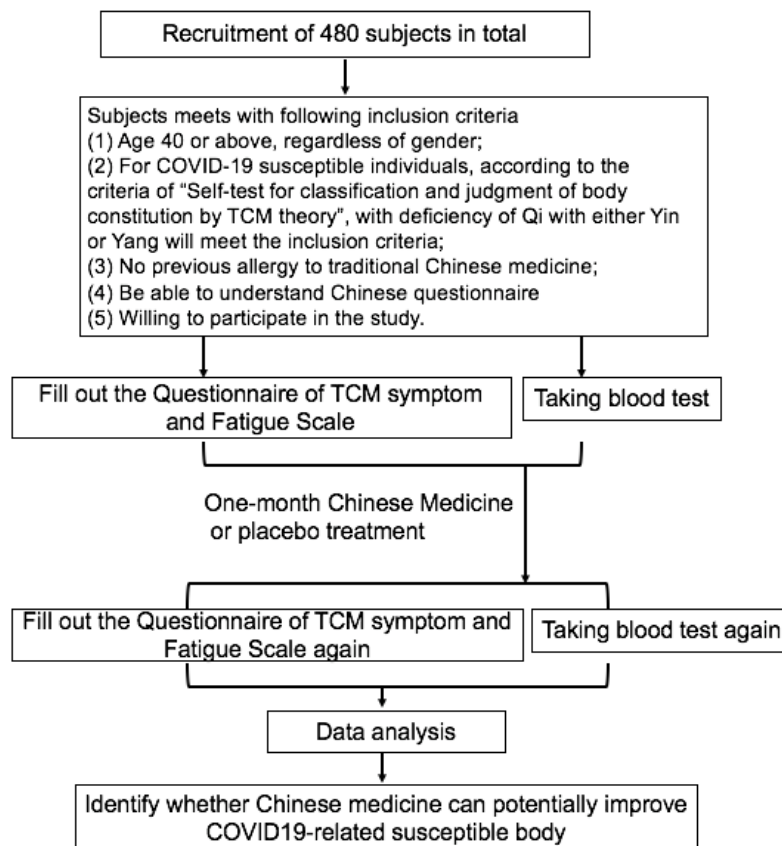
- (1) If subjects quit in the middle of the trial due to their own wishes, but they wish to return to the

clinical trial at certain time, we will investigate the subject again from the beginning of the trial.

(2) Respiratory symptoms such as transient fever, dry cough, fatigue, runny nose and sore throat were excluded. Patients with the disappearance of respiratory symptoms after 14 days (excluding those with latent infection of COVID-19) can be re-included in this trial.

6. Treatment of subjects

We will treat the included subjects with TCMs or placebos in our study according to the details as shown in Table 1. In addition, all the steps of treatment are shown as below.



7. Efficacy evaluation

● Primary outcomes:

Evaluation of the improvement of COVID19-related susceptible body constitution by TCM preventive treatment

After the preventive intervention of Chinese Medicine, the COVID19-related susceptible body constitution ("deficiency of Qi and yang" or "deficiency of Qi and Yin") may be improved, which will be measured by "Self-test for classification and judgment of body constitution by TCM theory", Questionnaire of TCM symptom, and Fatigue scale. For the treatment, the combination of "Yu-Ping-Feng formula" with either "Xiang-Sha-Liu-Jun formula" or "Liu-Wei-Di-Huang formula" will treat subjects with "deficiency of Qi and yang" or "deficiency of Qi and Yin" respectively.

● Secondary outcomes:

- (1) Clarify the distribution of COVID-19 susceptible residents in Hong Kong by questionnaires
- (2) Identify the changes of biomarker which may be fluctuated by COVID19 infection according to "Diagnosis and treatment of new coronavirus pneumonia (7th Edition)" held by National Health

Commission and State Administration of TCM.

The included biochemical indicators are as follows:

Blood routine: Complete Blood Count, Erythrocyte sedimentation rate

Liver function: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT)

Heart function: Lactate dehydrogenase (LDH), Troponin I

Kidney function: Creatinine, Blood urea

Inflammation and immune-related indicator: C-reactive protein, IL-6, CD4, and CD8

Confirmation of medication process:

We will make sure whether the subjects have taken the medicine or not through two methods, including patients' own record and return of the medicine package.

8. Safety assessment

For this study, the adverse event may be any adverse sign (including abnormal laboratory test results), which is related or not related to the treatment, including abdominal distention and pain, nausea, diarrhea, gastrointestinal disease, headache, etc. If the above-mentioned occurred during the treatment, the subjects will immediately stop taking TCM or placebo. We will provide the essential TCM clinical treatment to the subjects.

9. Data collection and management

The quantitative variables between two groups will be analyzed by student's t test. In addition, if the comparative groups are more than two, Repeated measure ANOVA will be taken. The classified variables will be measured by chi square test. Through logistic regression and linear regression model, this paper will study the multi-factor analysis the data with $P < 0.05$ has statistical significance. The study leader will then decide whether to proceed with the trial based on the preliminary results and will report to the ethics committee.

We will give a unique serial number to the scale answer and blood sample according to each questionnaire collected. EpiData 3.1 will be used for data logging. It is a program designed for data logging to prevent invalid input. The raw data will be kept for 5 years after the completion of the study, and destroyed afterwards unless an application to IRB for further retention is approved. Personal identifying information will be removed before statistical analysis.

10. Quality control and quality assurance

(1) Research assistants will be trained in an appropriate research method, focusing on maintaining research integrity, data confidentiality and data protection.

(2) Data is randomly selected periodically for re-entry to determine accuracy.

(3) The researchers in this study can be gathered as an experienced team of TCM practitioners and biomedical experts in the School of Chinese Medicine, the University of Hong Kong

11. Medical ethics

Subjects in the study is entirely voluntary. The subjects will be required to sign a consent form before participating in the study component of the project and questionnaire and interviews. All subjects will be provided with a contact telephone number in case they have any quires about the project, and be reassured that they have the right to withdraw at any time point without any consequences.

12. Data processing and record keeping

All the data will be processed in R or SPSS for statistical analysis. The raw data in paper format will be kept in a locked cabinet for 5 years. Meanwhile, all the data will input into EpiData 3.1 for 5-year electronic storage after the completion of the study. All the information of subjects will be kept strictly confidential.

13. Publishing policy

The results of the study will publish at international conferences and peer-reviewed journals. All researchers involved in this study will have access to the final data. Subjects will be informed of the results of the study.

14. Supplementary materials

The scheme of risk control for COVID-19 infection is as follows

1. Before entering the clinic, the subjects and the medical staff should take the temperature and ensure that the temperature is normal before carrying out the clinical trial.
2. Since the subject may be a latent period patient of COVID-19. Therefore, the staff in the clinic must wear surgical masks and disinfect the clinic every 1-2 hours.
3. When the subjects are in close face-to-face contact with the examiner ($< 1\text{m}$), the examiner shall wear N95 or equivalent masks and goggles. If necessary, medical staff can wear isolation clothing in special circumstances.



香港大學及醫管局港島西醫院聯網研究倫理委員會

**Institutional Review Board of the University of Hong Kong/
Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB)**

Address: Rm 901, 9/F, Administration Block, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong Tel 2255 3923 2255 4086

Dr. Yibin Feng
School of Chinese Medicine
The University of Hong Kong
03-Nov-20

Dear Dr. Feng,

IRB Reference Number: UW 20-480

The HKU/HA HKW IRB is authorized by a joint agreement of the University of Hong Kong and Hospital Authority Hong Kong West Cluster to review and monitor clinical research. It serves to ensure that research complies with the Declaration of Helsinki and acts in accordance to ICH GCP guidelines, local regulations and Hospital Authority and the University policies.

In accordance with our standard operating procedures, we have duly performed ethics and scientific review of your application/submission. We hereby write to inform you that your application/submission has been approved by a full review with details shown below.

Protocol title	: Based on the theory of "body constitution of Chinese Medicine" and "combination of prescription and syndrome" to improve COVID-19 susceptible body constitution of residents in Hong Kong
Study site(s)	: As stated in application form
Date of full review	: 21-10-2020 (Date/Month/Year)(Membership of the review panel is listed at the end of this letter in note 1)
Documents approved	: 01. Clinical Research Ethics Review Application Form : 02. Study Protocol; Version No. 6 dated 2020.09.25 : 03. Information Sheet and Consent Form; Version No. 07 dated 2020.10.29 (English and Chinese) : 04. Self-test for Classification and Judgement of Body Constitution by TCM Theory (Chinese Version) : 05. Questionnaire of Symptom Diagnosed by Traditional Chinese Medicine Theory (Chinese Version) : 06. Chalder Fatigue Scale (Chinese Version)
Documents reviewed	: 07. Short CV of Principal Investigator
Regular Progress Report(s) Required	: Every 12 months from the date of initial approval and during the period of the study

You, being the principal investigator of the study at your study site, are reminded to comply with our requirements and to maintain communication with us during the period of the study by undertaking the principal investigator's responsibilities including (but not limited to):

- if the study is an industry-sponsored clinical study, submitting to us a copy of the fully executed indemnity agreement satisfying the Hospital Authority's requirement prior to commencement of the study (if it has not been submitted yet);
- observing and complying with all applicable requirements under our standard operating procedure ("HKU/HA HKW IRB SOP"), the Declaration of Helsinki and the ICH GCP (if applicable);
- submitting regular progress report(s) at the required intervals (as specified above) in accordance with the requirements in the IRB SOP;
- not implementing any amendment/change to any approved study document/material without our written approval, except where necessary to eliminate any immediate hazard to the subjects or if an amendment/change is only of an administrative or logistical nature;
- notifying us of any new information that may adversely affect the rights, safety or well-being of the subjects or the proper conduct of the study;
- reporting any deviation from the study protocol or compliance incident that has occurred during the study and may adversely affect the rights, safety or well-being of any subject in accordance with the requirements in the IRB SOP;

- submitting safety reports on all SAEs observed at your study site or SUSARs reported from outside your study site in accordance with the requirements in the IRB SOP; and
- submitting a final report in accordance with the requirements in the IRB SOP upon completion or termination of the study at your study site.

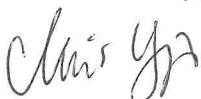
In addition to the above, you are also reminded to observe and comply with other applicable regulatory and management requirements including (but not limited to):

- if required by Hong Kong laws or regulations, obtaining a certificate for clinical trial through the Hong Kong Department of Health and complying with the associated requirements; and
- obtaining the necessary consent from the management of your institution/department in accordance with the requirements of your institution/department.
- obtaining prior approval before commencing the study from the appropriate head(s) of the study site (e.g. Head / COS / Nurse Manager / Department Manager, etc) with regards to the use of facilities and subject recruitment logistics/arrangement. It is advisable to print IRB's Reference Number on all recruitment materials for potential and actual study participants.

• comply with the with new reporting requirement of study results with effect from June 2015

as stated in the World Health Organization (WHO) Statement on Public Disclosure of Clinical Trial Results for any phases of clinical trials on: (1) the main findings within 12 months, or at most within 24 month, of study completion, and (2) the key outcomes within 12 months of study completion. These results must be posted in a free-to-access, public available, searchable clinical trial registry. The full text of the WHO Statement is available in <http://www.who.int/ictpr/results/reporting/en/>.

Yours sincerely,



Mr. Chris Yip

HKU/HA HKW IRB Secretary

(Note 1: IRB Review Panel of the meeting held on : 21-Oct-20)

<u>Membership</u>	<u>Name</u>	<u>Position/Affiliation</u>	<u>Gender</u>
Chairman	Dr. Lui, Sing Leung	Chief of Service, Medicine, TWH	M
Member	Prof. Cheung, Yiu Fai	Professor, Paediatrics & Adolescent Medicine, HKU	M
	Dr. Ip, Wing Yuk	Clinical Associate Professor, O&T, HKU	F
	Ms. Lam, Priscillia	Department Manager, Physiotherapy, QMH	F
	Dr. Luk, James	Chief of Service, Medicine & Geriatrics, FYKH	M
Non-scientific Member	Prof. Chiu, Andy	Chair Professor of Law - No Affiliation with HKU and HKW Cluster Hospitals	M
	Mr. Lai, Chi Tong	Advisor - No affiliation with HKU and HKW Cluster Hospitals	M