Buddhist Tzu Chi Medical Foundation Hualien Tzu Chi Hospital

Consent Form for Clinical Trial Subjects

蓋本委員會戳章
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Revised version of Research Ethics Committee meeting 23 February 2021

Project name

Chinese：淨斯本草飲濃縮液對長新冠症狀-腸腦軸失調之身心症狀療效-隨機雙盲臨床試驗

English：Jing Si Herbal Tea Liquid Packet in the treatment of dyspeptic symptoms and psychophysical burden in patients with disorders of long-COVID gut-brain interaction --a double-blind, randomized, placebo-controlled study

Test agency: Buddhist Tzu Chi Medical Foundation Hualien Tzu Chi Hospital Gastroenterology	Entrusting unit/pharmaceutical factory: None Research funding source: Hualien Tzu Chi Hospital

Principal Investigator：Dr. Chen,Chien-Lin Department/Position：Gastroenterology/Director

Co-PIs：Dr. Wong,Ming-Wun Department/Position：Gastroenterology/ Attending Physician

Co-PIs：Dr. Yi,Chih-Hsun Department/Position：Gastroenterology/ Attending Physician

Co-PIs：Dr. Liu,Tso-Tsai Department/Position：Gastrointestinal examination room/Director

Co-PIs：Dr. Lei,Wei-Yi Department/Position：Gastroenterology/ Attending Physician

Co-PIs：Dr.Hung,Jui-Sheng Department/Position：Gastroenterology/ Attending Physician

Co-PIs：Dr.Liang,Shu-Wei Department/Position：Integrative Medicine/Residency

Co-PIs：Liu,Chin-Hung Department/Position：Tzu Chi University Master Program / Associate Professor

Co-PIs：Chen,Chun- Yao Department/Position：Tzu Chi University Life Science / Assistant professor

24-hour emergency contact：Dr. Chen,Chien-Lin Telephone：0988-282055

Subject name： Medical record number：

Participants are invited to participate in this clinical trial. This form provides participants with relevant information about this trial. The trial host or his authorized personnel will explain the content of the trial to participants and answer any questions participants may have. Before participants's questions are answered satisfactorily , please do not sign this consent form. Participants do not have to decide immediately whether to participate in this trial, please sign after careful consideration. Participants must sign a consent form to participate in this trial. If participants wish to participate in this trial, this document will be considered a record of participants's consent. Even with participants's consent, participants can withdraw from the trial at any time without giving any reason.

(1) Purpose of the test：

Buddhist Tzu Chi Medical Foundation Hualien Tzu Chi Hospital
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This trial is a clinical trial in a single center in Taiwan, and it is expected to enroll 150 people. This test is a double-blind randomized test, the purpose of which is to investigate the improvement degree of Jing Si Herbal Tea Liquid Packet on the physical and mental symptoms of gut-brain axis disorder (DGBI) and the change of intestinal flora. Gut-brain axis disorder (DGBI), including functional dyspepsia and irritable bowel syndrome, is a gastrointestinal problem after the infection of new coronary pneumonia, and it is also a disease that needs improvement in the efficacy of traditional western medicine. Jing Si Herbal Tea Liquid Packet develops Chinese herbal medicine food for the eastern region, looking forward to The discovery that Jing Si Herbal Tea Liquid Packet can improve gastrointestinal function and depression after infection with the new crown pneumonia virus can be used to improve the physical and mental symptoms of gut-brain axis disorder (DGBI).

Any treatment has risks, and clinical trials are no exception. Please consider carefully before deciding whether to participate in this trial.

(2) Research background or product status：

Jing Si Herbal Tea Liquid Packet

The ingredients of Jing Si Herbal Tea Liquid Packet are mugwort leaves, houttuynia cordata, Ophiopogon japonicus, Houttuynia cordata, Campanulaceae, licorice, perilla leaves, chrysanthemum and other eight native Taiwanese herbs that can clear away moisture, dispel cold, relieve lungs and resolve phlegm, and clear away dampness and heat. Chinese medicinal herb, current research has found that it can block the combination of the new coronavirus and cells, and can also reduce cell penetration and block the virus from penetrating cells, while targeting wild-type and mutant viruses D614G, B.1.1.7, 501Y.V2 Carrying out animal studies, it was found that Jing Si Herbal Tea Liquid Packet can reduce the ability of 60 to 70% of the virus to infect the upper respiratory tract, lung, heart, and intestine of mice and reduce the expression of FKBP51, a protein related to depression, by 40%. Use of Jing Si Herbal Tea Liquid Packet to help reduce viral load and systemic anti-inflammatory effects in COVID-19 patients. In our ongoing clinical study, for patients with functional dyspepsia (FD), Jing Si Herbal Tea Liquid Packet resulted in a 75% improvement in symptoms compared to a 33% improvement in placebo.

(3) Main inclusion and exclusion conditions of the trial：

Physicians or related researchers who carry out this research project will discuss with participants the necessary conditions for participating in this research. Please cooperate and honestly tell us participants's past health conditions. If participants are not eligible to participate in this study, participants will not be able to participate in this study.

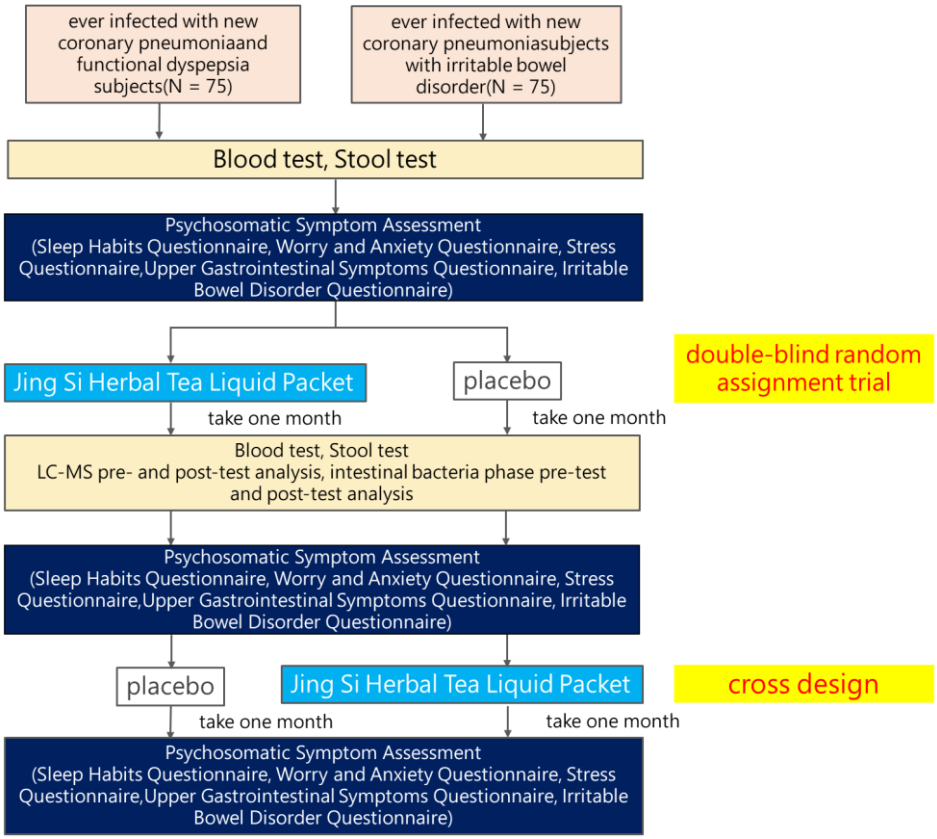
1. Inclusion conditions (conditions for participating in this study)：
   (1) Age between 20-70 years old.
   (2) Those who meet the definition of functional dyspepsia (FD).
   (Functional dyspepsia (FD) is chronic (once a week, lasting at least three months, at least six months before the first symptom) upper gastrointestinal symptoms (any of the following): postprandial abdominal distension, easy to feel full, Epigastric pain or burning sensation in the upper abdomen, and no symptoms of gastrointestinal bleeding or significant weight loss, no abnormality after upper gastrointestinal endoscopy).
   (3) Those who meet the definition of irritable bowel disorder (IBS).
   (Irritable bowel syndrome (IBS) is chronic (once a week, lasting for at least three months) lower gastrointestinal symptoms: abdominal pain combined with diarrhea or constipation, and no symptoms of gastrointestinal bleeding or significant weight loss, no abnormalities after colonoscopy) .
   (4) Be conscious and willing to sign the subject's consent form.
2. Exclusions (If participants have any of the following conditions, participants will not be able to participate in this study)：
   (1) Abnormal liver and kidney function;
   (2) Abnormal blood test and thyroid abnormality;
   (3) Have undergone surgery on the digestive tract;
   (4) Abnormal upper gastrointestinal endoscopy;
   (5) Abnormal colonoscopy examination;
   (6) Antibiotics are being used for infectious diseases;
   (7) Pregnant or breastfeeding women;
   (8) Suffering from heart, liver, or kidney failure;
   (9) Specific weakness, allergies, asthenia and cold constitution and chronic diseases.

(4) This test method and related procedures：

150 subjects with gut-brain axis disorder (DGBI) three months after being infected with new coronary pneumonia will be recruited in the outpatient department of gastroenterology, including 75 subjects with functional dyspepsia (FD) and 75 subjects with irritable bowel syndrome (IBS)) subjects; qualified subjects will receive blood and feces sampling and complete physical and mental symptom assessment (sleep habits questionnaire, anxiety questionnaire, stress questionnaire, gastrointestinal symptoms questionnaire, and

irritable bowel syndrome questionnaire) before treatment , and then according to the double-blind random assignment method, the Jing Si Herbal Tea Liquid Packet or the placebo will be assigned according to the coding order in the way of garbled characters generated by the computer, and the Jing Si Herbal Tea Liquid Packet or the placebo will be given by the research assistant. The host and None of the subjects knew what the assignment was. The experimenters took Jing Si Herbal Tea Liquid Packet or placebo in the first month, and after the end of the month, they received blood and stool tests and complete physical and mental symptom assessment (sleep habits questionnaire, anxiety questionnaire, stress questionnaire) , gastrointestinal symptom questionnaire, and irritable bowel syndrome questionnaire), the laboratory will conduct pre- and post-test biochemical analysis of blood (LC-MS pre-test analysis) and intestinal bacteria phase pre-test analysis, and then conduct a crossover test. I will take Jing Si Herbal Tea Liquid Packet for two months, and I will take placebo for the second month after taking Jing Si Herbal Tea Liquid Packet before. After the second month, I will do the third complete physical and mental symptom assessment (sleep habits questionnaire, anxiety, etc.). Anxiety Questionnaire, Stress Questionnaire, Gastrointestinal Symptom Questionnaire, Irritable Bowel Disorder Questionnaire), the test is completed.

Research Program Map：



Jing Si Herbal Tea Liquid Packet

In this experiment, Jing Si Herbal Tea Liquid Packet was used. Its ingredients are eight kinds of native Taiwan species, such as mugwort leaves, hinoki, Ophiopogon japonicus, Houttuynia cordata,

bellflower, licorice, perilla leaves, and chrysanthemum. , Dampness-clearing and heat-clearing Chinese herbal medicine, take Jing Si Herbal Tea Liquid Packet 15 ml once a day in the morning and evening.

(5) Possible risks and their occurrence rate and treatment methods：

※Jing Si Herbal Tea Liquid Packet and placebo are suitable for ordinary people; people with infirmity, allergies, coldness, chronic diseases, poor kidney function, infants under three years old, children, pregnancy, breastfeeding, and menstrual period, please use with caution; if any Discomfort please stop using. Do not drink before going to bed to avoid frequent urination at night and affect sleep.

If participants feel uncomfortable physically and mentally due to the long time of filling out the questionnaire, please inform the research host or other researchers at any time. If participants want to withdraw from this study, the investigators will respect participants's wishes.

Participants will be monitored regularly for side effects while participants are in the trial by the trial physician and other trial staff. Additional visits and tests will be scheduled as necessary. If participants have side effects, please inform the trial physician and other trial personnel, and the trial physician will decide to give appropriate treatment according to participants's situation.

If participants have any of these serious or dangerous side effects participants should as soon as possible：

1. Call the 24-hour emergency contact person.
2. Go to the nearest emergency room if necessary.

(6) Other alternative treatments and instructions：

Participants are not obliged to participate in the study. If participants do not participate in the study, the doctor will check participants's symptoms through routine examination and give appropriate drug treatment.

(7) Expected benefits of the test：

At present, Jing Si Herbal Tea Liquid Packet can block the combination of the new coronavirus and cells according to animal experiments, and can also reduce the cell penetration and block the virus from penetrating cells, while targeting wild-type and mutant viruses D614G, B.1.1. 7. 501Y.V2 conducted animal research and found that Jing Si Herbal Tea Liquid Packet can reduce the ability of 60 to 70% of the virus to infect the upper respiratory tract, lungs, heart, and intestines of mice and reduce the expression of FKBP51, a protein related to depression, by 40%. Registered clinical trial (ClinicalTrials.gov Identifier: NCT04967755) on the effect of Jing Si Herbal Tea Liquid Packet on the reduction of helper virus load in COVID-19 patients. In this study, Jing Si Herbal Tea Liquid Packet was used to objectively examine patients with normal gut-brain axis disorders to evaluate their physical and mental symptoms and changes in intestinal flora before and after treatment.

Even with the above information, there is still no guarantee that participating in this trial will improve participants's condition or bring participants other direct benefits, but the results of the trial may

be helpful to the entrusting unit and/or the trial host, and will also be used in the future. May benefit other patients with the same disease.

(8) Contraindications, restrictions and matters that should be cooperated by the subjects during the trial：

When participants participate in this test, for participants's safety, please cooperate with the following
-Provide participants's past medical history, medical records and correct information about participants's current condition.
- Use Jingsi Herbal Drink Concentrate correctly according to the instructions.
- Do not give Jing Si Herbal Tea Liquid Packet to others. Please keep Jing Si Herbal Tea Liquid Packet (storage method: room temperature, refrigerated, etc.), and make sure that children cannot get it.
- For participants's safety, please inform the trial physician of any uncomfortable symptoms participants experience.
- If participants have any questions, please feel free to ask the test personnel (physician, nurse) directly.
- Inform the trial physician if participants have been hospitalized or participants's medical condition has changed between visits, or if participants wish to stop using Jing Si Herbal Tea Liquid Packet (or have already stopped using it).

(9) Confidentiality of subjects' personal data：

Hualien Tzu Chi Hospital will treat any identifiable records and personal privacy information as confidential according to law and will not make them public. The researchers will identify participants with a research code, which will not reveal participants's name, national ID number, address and other identifiable information. If the trial results are published, participants's identity will remain confidential. Participants also understand that if participants sign the consent form, participants agree that participants's original medical records can be directly reviewed by monitors, auditors, Hualien Tzu Chi Hospital Research Ethics Committee and competent authorities to ensure that the clinical trial process and data comply with relevant laws and regulations. personnel and undertake not to violate the confidentiality of participants's identity. In addition to the above-mentioned agencies having the right to review according to law, the investigators will carefully safeguard participants's privacy.

(10) Withdrawal and suspension of the test：

Participants are free to decide whether to participate in this trial; participants can withdraw or suspend participants's consent at any time during the trial, and participants can withdraw from the trial without any reason, and it will not cause any discomfort or affect the medical care of participants's doctor in the future.

When there is important new information during the execution of the trial (referring to participants's rights or affecting participants's willingness to continue participating), participants will be notified and further explained. Please reconsider whether to continue participating. Participants can decide freely and will not cause any discomfort. Or affect their future physicians to participants's medical care.

The program director may also suspend the entire experiment if necessary.

(11) Compensation for damages and insurance：

Trials must be risky. In order to ensure the possible protection for participants's damage due to adverse reactions during participation in the trial, please be sure to read this description carefully.：

1. Hualien Tzu Chi Hospital shall be responsible for compensation for damages caused by adverse reactions in accordance with the clinical trial plan formulated in this study. However, the expected adverse reactions recorded in the subject's consent form will not be compensated.
2. If adverse reactions or damages occur due to the clinical trial plan formulated in this study, the hospital is willing to provide professional medical care and medical consultation. Participants do not have to pay for medically necessary treatment of adverse reactions or damages.
3. Except for the compensation and medical care in the first two items, this research does not provide other forms of compensation. If participants are unwilling to accept the risk, do not take part in the trial.
4. Participants will not lose any legal rights by signing this agreement.
5. This study did not purchase human experiment liability insurance.
6. The test food has been insured for product insurance. (The insured is Dajiang Biomedical Co., Ltd.; policy number: 150110CG01568; product name: Jing Si Herbal Tea Liquid Packet, Jing Si Herbal Tea Dettol.)

If participants do suffer damage caused by adverse reactions due to participants's participation in this trial, the aforementioned compensation includes reasonable medical expenses, but the following conditions should be met: participants use the trial drug according to the instructions of the trial doctor; participants's damage is not caused intentionally; participants obey the trial doctor medical advice.

(12) Preservation, use and reuse of subjects' samples (including their derivatives), personal data

1. Preservation and use of samples (including their derivatives)

The specimens and related materials participants provide will be used in this test plan and stored in the laboratory of Professor Liu, Chin Hung, Department of Pharmacology, Faculty of Medicine, Hualien Tzu Chi University until December 31, 2024. When the storage period expires, it will be Destroy according to law. In order to protect participants's personal privacy, the investigators will replace participants's name and related personal information with a test number to confirm that participants's specimen and related information are kept completely confidential.

If participants have doubts about the use of specimens and related materials, or have any need to destroy specimens or data, please contact us immediately (Contact Person: Dr. Chen, Chien Lin; Tel: 0988-282055; Contact Unit : Gastrointestinal Examination Room; Tel: 03-8561825 ext. 13224; Address: No. 707, Section 3, Zhongyang Road, Hualien City), and the investigators will destroy participants's specimen and related materials. Participants can also contact the Research Ethics Committee of Hualien Tzu Chi Hospital (Tel: 03-8561825 ext. 12124) to assist participants in resolving any disputes over the use of specimens and related materials in research.

2. Storage and reuse of remaining samples

This test does not save the remaining specimens for reuse, and participants's specimens will be destroyed after the storage period expires。

3. Storage and use of personal data

The personal information and related information participants provide will be used in this trial project and stored in the gastrointestinal examination room of Hualien Tzu Chi Hospital until December 31, 2027. When the storage period expires, it will be destroyed according to law. In order to protect participants's personal privacy, the investigators will replace participants's name and related personal information with a test number to confirm that participants's relevant information is kept completely confidential.

If participants have doubts about the use of relevant data, or have any need to destroy the data, please contact us immediately (contact person: Dr.Chen, Chien Lin: 03-8561825 to 13224; address: No. 707, Section 3, Zhongyang Road, Hualien City), the investigators will destroy participants's relevant information. Participants can also contact the Research Ethics Committee of Hualien Tzu Chi Hospital (Tel: 03-8561825 ext. 12124) to assist participants in resolving any disputes over the use of personal data in research.

(十三) Subject rights：

1. If participants have doubts about the nature of the trial work during the trial, have opinions on the rights and interests of patients, or suspect that participants have been victimized by participating in the research, participants can contact the Research Ethics Committee of Hualien Tzu Chi Hospital for consultation, Tel: 03-8561825 Ext. 12124.
2. 2. During the trial, any major findings related to participants's health or disease that may affect participants's willingness to continue the clinical trial will be provided to participants immediately. If participants decide to withdraw, participants's physician will arrange for participants to continue receiving medical care. If participants decide to continue in the trial, participants may be required to sign an updated consent form.
3. In order to carry out the experimental work, participants must accept the care of Dr. Chen, Chien Lin. If participants have any questions or conditions now or during the trial period, please feel free to contact Dr. Chen, Chien Lin, Department of Gastroenterology, Hualien Tzu Chi Hospital (24-hour contact number: 0988-282055).
4. This consent form is in duplicate. The trial host or his authorized personnel has given participants a copy of the consent form, and has fully explained the nature and purpose of this research. Physicians have answered participants's questions about drugs and research.
5. Subsidy for participating in the experimental research plan. In order to compensate participants for the transportation and time spent on participating in the experiment, participants will receive a subsidy of NT$600 after signing the agreement, and a subsidy of NT$600 after the experiment is over. NT$1200.

6. If after the test is over, participants are found to have unexpected safety concerns that directly affect participants, participants will also be notified.

(十四) Expected commercial interests that may be derived from this research：

Information obtained from this trial may lead to the discovery, invention, or development of commercial products, and all such rights belong to the commissioner. Participants and participants's family will not receive any financial benefit or monetary compensation for the research and development results, inventions or other discoveries in this information, or have the ownership of the results of the above inventions.

(十五) Instructions for signing the consent form：

1. **The consent form should be signed and dated after the research director or his authorized personnel explain the research content to the research subjects and answer all the questions of the research subjects; then ask the research subjects or their related persons to consider and sign.**
2. **Timing of signing by legal representative/person with consent/guardian/assistant：**

＊ Article 79 of the Medical Law / Article 12 of the Law on Human Research / Article 5 of Good Clinical Practice Guidelines for Drugs / Article 6 of Precautions for Collection of Human Specimens for Research / Articles 13 and 15 of Civil Law：

(1) If the subject is incapacitated (a minor under the age of seven or a person declared under guardianship), the legal representative shall do it; for a person declared under guardianship, the guardian shall act as his legal representative.

(2) The subject is a person with limited behavioral capacity (a minor over the age of seven, or a mental disorder or other mental defect, which causes him to express or accept the expression of intention, or the ability to recognize the effect of the expression of intention, and has obvious Insufficient and subject to the auxiliary declaration of the court), the consent of the person himself and his legal representative or assistant shall be obtained.

(3) Although the subject is not incapacitated or limited in capacity, but is unable to communicate and judge effectively due to confusion or mental and intellectual impairment, a person with the right to consent shall do so. The person with the right to consent is the spouse and relatives living together.

(4) When the research object is a fetus, the mother should agree.

(5) The provision of autopsy should be subject to the written consent of the person's closest relative or the person himself before his death.

3. **Witness signing timing：**

＊ Article 21 of Good Clinical Practice Guidelines for Drugs / Article 3 of the Civil Code：

(1) When the subject, legal representative or consenting person cannot read it, witnesses should be present to participate in all discussions about the subject's consent form. Witnesses should read the consent form of the subject and provide any other written information of the subject to witness that the research director or the person designated by him or her has accurately delivered the content to the subject, legal representative or person with consent explain, and make sure they fully understand

the content of all materials.

(2) The subject, legal representative or person with the right to consent shall still sign and date the subject's consent form. However, fingerprints can be used instead of signatures.

(3) After the witness completes the oral statement and confirms that the consent of the subject, legal representative or person with the right to consent is completely voluntary, he shall sign and date the subject's consent form.

(4) Personnel involved in the research shall not be witnesses.

(5) If a fingerprint, cross, or other symbol is used to sign the document, the two signatures on the document will also have the same effect as the signature.

4. **Instructions on the sequence of signatures of persons with the right to consent：**

＊ Article 12 of the Human Body Research Act: Except for fetuses or corpses, research objects are limited to adults with meaningful abilities. However, this does not apply to those who are obviously beneficial to a specific population group or cannot be replaced by other research objects. When the research object is an adult with the proviso of the preceding paragraph, the consent of the related party should be obtained in the following order：

(1) Spouse.
(2) Adult children.
(3) Parents.
(4) Brothers and sisters.
(5) Grandparents.。

According to the written consent of the related party in the preceding paragraph, the written consent can be carried out by one person; if the related parties express disagreement, the order of each item in the preceding paragraph shall be determined. For persons in the same order as mentioned in the preceding paragraph, the closest relatives shall be prioritized; for those of the same degree of kinship, the cohabiting relatives shall be prioritized; for those without cohabiting relatives, the elders shall be prioritized。

(十六) Signature

1. The trial host, or co-host or its authorized personnel have explained in detail the nature and purpose of the above-mentioned research methods in this research plan, as well as the possible dangers and benefits.

Trial host/co-host signature：_____

Date：_____ Year ____Month____Day

Signatures of other researchers involved in presentations and discussions during the consent process：_____

Date：_____ Year ____Month____Day

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2. 2. After the explanation, I have a detailed understanding of the above-mentioned research methods and possible risks and benefits. Questions about this experimental plan have also been explained in detail. I agree to accept and voluntarily participate in this study and will have a copy of the consent form.

Subject signature：_____ Date：_____ Year ____Month____Day

Telephone：

＊ **When the subject of the case meets the item (2) of [Instructions for Signing the Consent Letter], the signature in this field must be completed。**

3. Signature of the legal representative/person with the right to consent：_____

Date：_____ Year ____Month____Day

Relationship with subject (please circle): self, spouse, father, mother, son, daughter,

others：_____

Telephone：

＊ **When the subject of the case meets the item (3) of the [Consent Letter Signing Instructions], the signature in this field must be completed。**

Witness 1 signature：_____

Date：_____ Year ____Month____Day

Telephone：

Witness 2 signature：_____

Date：_____ Year ____Month____Day

Telephone：