Clinical Treatment Protocol of Convalescent Plasma for Patients with COVID-19

(Trial Version 2)

To further strengthen the medical treatment for patients with the novel coronavirus disease (COVID-19), and promote the convalescent plasma treatment for such patients, we have developed this protocol according to the *Blood Donation Law* and other relevant laws and regulations. This document is also in line with the latest version of *Diagnosis and Treatment Protocol for Novel Coronavirus Disease* and related technical operating procedures and quality management requirements.

I. Organization and implementation

Under the leadership of the provincial health administrative departments and the health departments of major units of the military, the designated treatment hospitals shall organize and mobilize the eligible recovered COVID-19 patients to donate plasma voluntarily and free of charge. The blood product manufacturing units responsible for the prevention and control of the COVID-19 shall provide equipment and technical support. They will also carry out the collection and preparation of plasma, all in conjunction with provincial health administrative departments, provincial blood centers or central blood stations designated by the military (for centralized use of the treatment of critically ill patients by the designated hospitals).

II. Recruitment of plasma donors

i. Recruitment of plasma donors

1. The recovered COVID-19 plasma donor should meet all of the following requirements: The donation should made be no less than 3 weeks from initial symptom(s); the donor should meet the criteria for ending isolation and discharge in accordance with the latest edition of the *Diagnosis and Treatment Protocol for Novel Coronavirus Disease*; the donor should be between 18 and 55 years of age; male donors should weigh a minimum of 50 kg, and female donors a minimum of 45 kg; have no history of blood transmitted diseases; must be permitted by the clinicians after a comprehensive assessment on the patient's treatment and relevant conditions.

2. Identity verification of plasma donors: plasma donors should present valid identification documents before donating, and collection personnel should check and register. Using other's identity to donate plasma is prohibited.

3. Informed consent for plasma donors: all provincial health administrative departments shall formulate informed consent for plasma donors, including the contents of pre-donation notification and health consultation.

a. Duty of disclosure: before donating plasma, the collector shall perform the duty of disclosure to the donor in writing and obtaining the signed informed consent.

b. Contents of disclosure: refer to the contents of disclosure before blood donation in the *Technical Operation Regulations of Blood Station (2019)*, including the purpose of plasma donation, collection volume, possible adverse reactions and countermeasures, and contact information.

ii. **Health consultation, physical examination and blood test before plasma donation**

Plasma donors should truthfully describe their health status. For the physical examination of plasma donors in blood stations, refer to the *Technical Operation Regulations of Blood Station (2019 Edition)*. For the blood test before plasma donation, refer to the *Technical Operation Regulations of Plasmapheresis Center (2011 Edition)*.

A donation of 200 ml of plasma is regarded as a donation of whole blood. After plasma donation, a blood donation certificate will be issued and the plasma donors' information will be entered into the national blood management information system.

III. The collection and preparation of plasma

i. The collection of plasma

1. Collecting plasma: the plasma is collected by a blood component apheresis machine. A single collection is*200-400 ml* and the specific collection volume will be determined by the clinician after assessment. Samples shall also be retained for plasma quality testing. The interval between two samplings is no less than 14 days.

2. The specific operation of plasma collection must comply with the relevant requirements of the *Technical Operation Regulations of*

Plasmapheresis Center (2011 Edition) and the *Technical Operation Regulations of Blood Station (2019 Edition)*. The collection personnel shall closely observe the situation of plasma donors on site, and efficiently prevent and handle the adverse reactions.

3. Loading of plasma: each plasma sample should be divided into 100-200 ml/bag. The plasma loading should follow the principle of aseptic operation.

4. Freezing of plasma: if the collected or packaged plasma needs to be stored long term, it should be rapidly frozen to -20 ℃.

5. Storage of plasma: if the retention time does not exceed 48 hours, the plasma can be stored at 2-6 ℃. If the plasma needs to be stored for any longer is shall be frozen.

ii)The packaging of plasma

1. Labeling requirements: refer to the *Technical Operation Regulations of Blood Station (2019 Edition)*.

2. Chinese name on the label: 新冠康复者血浆.

3. English name on the label: COVID-19 CP (COVID-19 convalescent plasma)

4. Retention samples: are packed after passing the test, and retained in three sections. One section of which is a minimum of 8 cm (retained by plasma collection institution), and the other two sections a minimum of 3 cm (for the treatment hospital).

IV. Laboratory testing of plasma

Laboratory testing should be carried out by a plasma collection institution or a competent laboratory testing institution entrusted with:

i. General quality testing: The testing standard shall comply with the *Technical Operation Regulations of Blood Station (2019 Edition)*.

ii. Test items and testing methods: In accordance with the relevant requirements of the *Technical Operation Regulations of Blood Station (2019 Edition)*, the test includes the serological and nucleic acid test for markers of the hepatitis B virus, hepatitis C virus and HIV; two more basic serological tests and an ALT test for syphilis antibodies.

iii. Special testing:

1. The result of a single blood sample of COVID-19 nucleic acid is negative.

2. The qualitative testing of IgG antibodies in COVID-19 serum/plasma is reactive and the test is still positive after a 160-fold dilution according to the reagent specification; or the qualitative detection of total antibody in COVID-19 serum/plasma is reactive and the test is still positive after a 320-fold dilution according to the reagent specification. Enzyme linked immunosorbent assay (ELISA) or Chemiluminescence method can be used as the testing methods. Sufficient assessment or reference to assessment data should be carried out to ensure the quality of detection.

3. A qualified laboratory can carry out virus neutralization tests to determine antibody titer.

4. If the donor has a history of pregnancy or blood transfusion, it is recommended to screen for HNA and HLA antibodies.

5. According to the epidemiological characteristics of the area where the plasma donors are located, the test items may be increased when appropriate.

iv. Laboratory quality control: Laboratories carrying out relevant testing will strengthen laboratory quality control in accordance with relevant regulations.

V. Guidelines for the clinical application

i. Indications. Severe and critically ill patients with COVID-19, with rapid progression. The following principles can be followed:

1. The course of disease does not exceed 3 weeks; the nucleic acid test for COVID-19 is positive, or clinical experts determine that the patient is with viremia.

2. Severe patients with rapid disease progression, patients with early critical illness, or patients who require plasma therapy after comprehensive assessment by clinical experts.

ii. Contraindications and inappropriate use:

1. Contraindications: those with a history of allergy to plasma transfusion or human plasma protein products; a history of allergy to sodium citrate; a history of allergy to methylene blue (prohibited to

use the inactivated plasma by methylene blue virus); and other serious allergies or contraindications to plasma.

2. Inappropriate use: at the end of critical illness when multiple organ failure cannot be reversed; treatments other than the purpose of neutralizingCOVID-19; other inappropriate infusion situations according to the comprehensive assessment of clinicians.

iii. Infusion dose: determined according to clinical conditions and patient weight. Generally, the infusion dose is 200-500 ml (4-5 ml/kg).

iv. The principles of infusion.

1. Infusion shall be done according to the principle of cross-matching secondary compatibility. The plasma negative for irregular antibody screening of donors can be directly infused with ABO compatibility, and ABO homotype is preferred.

2. The first 15 minutes of infusion should be infused slowly, and closely monitored for adverse blood transfusion reactions. If there is no adverse reaction, the clinician will adjust the infusion rate according to the patient's condition.

v. Informed consent: clinicians will inform patients and their families in detail about the purpose and risks of the use of plasma collected from a patient recovered from COVID-19, and obtain their signed, written informed consent.

vi. Adverse reactions and their treatment: before, during, and after plasma transfusion, detailed records should be recorded, and close clinical observation should be made to see if there are any adverse reactions during plasma transfusion. The main types of adverse transfusion reactions include transfusion associated circulatory overload, acute lung injury, dyspnea, and hypotension; allergic reactions, non-hemolytic fever reaction, acute hemolytic transfusion reaction, delayed hemolytic transfusion reaction, infectious transfusion reaction, and other/unknown.

VI. Safety protection to laboratory personnel and requirements of laboratory

i. Protection of laboratory personnel:

1. The laboratory should strictly abide by the relevant regulations on laboratory bio-safety. In addition to collecting and submitting samples according to the original process, the following will be added: during the process of receiving and delivering samples, the laboratory staff shall spray disinfectant to the lid of the transfer box before opening and closing it. The staff must also pay strict attention to hand hygiene.

2. Attention shall be paid to keep the body fluid specimen upright to avoid spilling during transfer. In case of spilling, at least BSL 2 protection shall be adopted: medical protective mask or N95 respirator, latex gloves, isolation gown, medical protective cap, and proper hand hygiene. Goggles may be added if there is a risk of splashing (e.g. when opening the lid manually).

3. When wearing and removing the bio-safety protective articles, staff must follow the standard procedures. They must also properly perform hand hygiene (six-step hand-hygiene technique).

ii. Disinfection of workplace.

1. Indoor space of blood collection site, blood and specimen handover area: keep it well-ventilated, place articles in relevant areas, separate them into polluted and unpolluted, and replace them on time. UV disinfection shall meet the industry standard (UV germicidal lamp GB 19258-2012), with periodical performance testing and full record. Its cumulative use shall not exceed the prescribed time limit. The disinfection time should be a minimum of 30 minutes.

2. Working table and floor: before and after work, wipe with 75% ethanol or 0.05% (0.5g/L) chlorine disinfectant wipes (84 disinfectant, 100-folddilution). The disinfectant must be prepared and used within 24 hours.

3.After testing, the samples shall be stored with a lid. Positive or suspected positive samples shall be disinfected, placed in double-layer yellow garbage bags, sealed, sprayed with 75% ethanol to sterilize the surface of the garbage bags, and placed alone until the retention period is completed. When the retention period is finished, the samples shall be sterilized by autoclaving and treated as medical waste. The refrigerator that stores the samples must also be disinfected

4. In general, the available chlorine concentration is 0.1% (1g/L),and 0.5% (5g/L) in cases of severe contamination (when the

sample leaks or splashes). The laboratory can use dynamic air disinfection in the working state, and turn on the ultraviolet irradiation in the non-working state.

In addition, we shall avoid mass gatherings during plasma collection. We will protect the safety of blood donors and medical personnel in accordance with the relevant regulations of the state in response to COVID-19, and dispose of medical waste according to relevant regulations.