[CCHRPP Consensus] Version 2.0: Consensus on Clinical Trial Management under Level 1 Significant Public Health Emergency Response (Infectious Disease)

Original The CCHRPP Working Committee CCHRPP *Yesterday*

Since the new year of 2020, the novel coronavirus pneumonia epidemic situation has remained in the focus of every Chinese, and 30 provinces, municipalities and autonomous regions nationwide have successively declared to initiate the level 1 significant public health emergency response program. The Party Central Committee and the State Council have called the public not to go to public places and places where people get together for the purpose of actively preventing and controlling the novel coronavirus pneumonia epidemic situation and reducing the spread risk. This will be most likely to affect the smooth implementation of clinical trials, which makes it particularly necessary to discuss how to respond to the situation. To this end, the Organizing Committee of China Forums of Clinical Research Capacity Building and Human Research Participants Protection (CCHRPP) has invited multiple veteran experts in the clinical trial sector to set up a working committee. On January 30, 2020, the committee discussed and achieved the Consensus on Clinical Trial Management under Level 1 Significant Public Health Emergency Response (Version 1.0) based on the current novel coronavirus infection as the example. After publishing, we have received a positive response from different sectors of the industry and solicited more valuable suggestions. Therefore, on February 1, we supplemented and refined the preliminary version and reached the **Consensus on Clinical Trial Management under Level 1 Significant Public Health Emergency Response (Infectious Disease) (Version 2.0)** to serve as a reference for people engaged in the sector.

I. General Principle

The general principle is to respond to the call of the Party Central Committee and the State Council and follow the prevention and control requirements set forth by the National Health Commission for the significant infectious disease emergency epidemic situation.

II. Core Principles

The safety of subjects and investigators shall be put in the paramount position. All measures taken in the clinical trial shall observe the principle of protecting the safety of subjects and study-related people.

We shall assess whether the epidemic situation will render it necessary to make an evidence change to the clinical trial protocol (for example, increase laboratory tests or operations). If yes, we shall initiate the work to revise the protocol, and if the protocol can't be revised, we shall suspend the implementation temporarily and wait until the epidemic situation comes to an end. Otherwise, we shall observe the original protocol in implementation, whenever possible. If no evident change is made to the trial procedures (for example, change the simple visit on the site to the visit on the phone), we can record the change in the trial procedures under such special situation as a protocol deviation and corresponding reason if the change doesn't affect subject interests and safety, and we shall continue to implement the original protocol after the epidemic ends.

III. Basic Strategy

1. If a hospital is located in a major epidemic-stricken region and designated to cure the disease and the clinical trial will affect the treatment of the infectious disease, we suggest suspending the clinical trial in progress. If a subject is already enrolled and remains at the follow-up stage and must receive a follow-up visit at the study institution, we suggest the investigator and the sponsor make a decision after discussion, and coordinate with a study site that participates in the same trial and is not designated to cure the disease for the purpose of performing the subsequent follow-up visit in the principle of proximity. In the transfer process, we suggest special persons (such as CRC) should coordinate and confirm the transfer step and take strict protective measure based on the needs, and the sponsor shall assist to provide appropriate transfer support such as follow-up visit appointment and provision of appropriate transportation subsidy.

2. When a designated treatment and care hospital not based in the major region visits a subject, the investigator shall, based on epidemic dynamics, discuss with the subject to determine whether an on-site visit is feasible after fully assessing the subject's benefits from the follow-up visit at the hospital and the exposure risk increased in the follow-up visit process. If the visit doesn't affect the epidemic treatment and the visit can't be changed to the treatment or follow-up visit off the site, the investigator can perform an assessment and continue the follow-up visit and medication of the subject while adequate protective measure is taken.

3. Parties concerned in clinical trials shall, whenever possible, count on the Internet, employ the information platform technology and implement remote collaborative office to fulfill the purpose of clinical trial management, reduce the flow of clinical trial-related people and reduce the disease spread risk.

IV. Work Implementation

Stated below are the general principles, and we suggest the sponsor and the investigator determine concrete requirements and measures at the specific trial level based on concrete trial protocol, characteristics of the trial drug, subject's situation and actual condition of the study site.

1. Attention to subjects

◢ We shall maintain a close contact with subjects in multiple ways (such as telephone, WeChat and other instant messaging services), keep a higher frequency than that required by the clinical trial protocol itself, trace health situations of subjects and remind subjects of the measures preventing the novel coronavirus.

◢ We shall confirm whether a subject has resided in or travelled to regions with a high incidence of the epidemic, or contacted groups who are confirmed or suspected of infection or visiting the fever clinic. When necessary, we shall remind the subject to isolate himself or herself or see a doctor in time.

2. Subject visit

◢ If patients are screened, the site shall check in detail whether a patient has resided in or traveled to the epidemic region, visited a fever clinic in the most recent period or had a close contact with confirmed patients or suspected patients, and perform the viral nucleic acid test to ensure the infection is excluded.

◢ Where necessary, we shall choose the remote visit, contact the subject through the phone, WeChat and other instant messaging services, trace relevant situation of the subject (such as health status, AE, concomitant drugs and compliance with trial drug), complete the visit content specified by the protocol allowing the remote visit, provide corresponding medical instruction and instruct the medication. We shall remind the subject to maintain an active contact with the study doctor and feedback his or her personal health status, medication and other information.

◢ When it is genuinely necessary to perform relevant examination, we shall observe the principle of proximity, and suggest the patient receive normal examinations at the local community health institution. When it is necessary to perform a special examination, a subject residing in the local urban area in the domicile of the study site can visit the study site and receive relevant examination, and if the subject doesn't reside in the urban area in the domicile of the study site, the following priorities shall apply, while the principle of proximity is observed: Other hospitals participating in the same clinical trial (avoid designated medical service hospitals) and other hospitals with GCP qualifications, or go to other hospitals that can meet the examination need, when both of the preceding options are unavailable.

◢ If the clinical trial protocol requires the central laboratory perform an examination item but it is truly difficult to do it, we can use a local laboratory to perform the examination.

◢ If it is genuinely incapable to complete a special examination item at present, we can treat it as a super window or data absence item and perform a supplementary examination as soon as possible when conditions allow or the epidemic ends. Moreover, we shall record and explain it as corresponding protocol deviation (PD) to facilitate the audit.

◢ When a subject is transferred from a major epidemic region or designated treatment hospital to another site for follow-up visit, the investigator of the original study site shall communicate with the investigator of the site actually performing the follow-up visit, and elaborate the disease situation and therapeutic process of the subject and give necessary suggestions if possible.

◢ We shall register and record any subject who visits the hospital so that the subject will be traceable in future.

3. Study drug

If a subject can't return to the study site or go to other suitable hospitals to receive the follow-up visit and relevant necessary examination, the investigator shall reach a consensus with the medical expert of the sponsor and decide whether the subject can directly enter the drug treatment next stage in line with the concrete trial protocol and drug characteristics.

★ Study drug usable outside the hospital

◢ After communication and confirmation with the sponsor, if the local posting condition meets the drug storage requirement and the subject can use the trial drug on one's own, such as most of oral drugs, insulin, hypodermic injection preparations and external drugs, the drug can be posted by an express delivery company with the transport qualification. The investigator/CRC shall pay attention to and communicate with the subject, and keep relevant record.

★ Study drug unusable outside the hospital

◢ If the study drug, such as psychotropic, toxic, narcotic or radioactive drug or the injection that requires injection or transfusion, can't be used outside the hospital, or the subject chooses to receive the medication at the study site, we shall contact the subject through the Internet platform or other channels in advance, make an appointment with the subject, confirm the personal health status of the subject satisfies the requirement for a visit to the site, and remind the subject to take effective personal protective measure and arrive on time.

◢ The study site shall arrange an independent clean area (or far away from the infected area) for the subject to receive a follow-up visit and medication. If a subject needs to be hospitalized for the follow-up visit, the study site shall, whenever possible, arrange an independent sickroom to hospitalize and visit the subject for the purpose of avoiding cross infection. The follow-up visit area or sickroom shall be often ventilated and sterilized at regular intervals.

◢ We shall reasonably reserve the time to avoid a concentrated visit of subjects and prevent cross infection.

4. Safety information

◢ We shall collect complication and medication data of the subject in detail, and in particular, if the subject may use the drug related to the prevention and control of the novel coronavirus pneumonia, we shall remind the subject to save relevant diagnosis, therapy and medication record and take the record back to the study site for filing when conditions allow or the epidemic ends.

◢ The investigator shall judge whether a patient suspected of novel coronavirus infection has an SAE. In general, if a patient is suspected of catching the novel coronavirus pneumonia and isolated at home, the subject will not be seen as a severe adverse event, but a subject who needs to be isolated and observed at the hospital shall be reported as an SAE. The adequacy of medical resources varies from one region to another and medical measures received by subjects are not totally the same. Therefore, some regions require that people suspected of infection with mild symptoms should be isolated and observed at the hospital (which shall be reported as a SAE), but some regions suggest people suspected of infection with severer symptoms take the isolation measure at home (which will not be reported as a SAE).

◢ When any SAE occurs, we shall remind the subject to receive the therapy in the principle of proximity in time. When necessary, the study doctor shall communicate

with the receiving doctor about the subject's participation in the clinical trial and assist the receiving doctor to treat the subject.

5. Clinical supervision

Supervision is an important quality assurance measure for clinical trial, and we can combine on-site supervision and centric supervision and reduce the frequency at which supervisors go to the site.

◢The site shall adopt the supervision based on the risk management principle, reduce the on-site supervision frequency and take effective protection measures.

◢ We should count on the Internet, employ the information platform technology, and assess whether to increase the central supervision frequency and adjust the centric supervision strategy when necessary in combination of detailed operation guide as well as timely training, communication and instruction for investigators.

◢ We shall supervisor subject compliance, SAE, major therapeutic effect and safety assessment indicators.

◢ Any on-site supervision activity of the supervisor shall be registered and put on record. When conditions allow, we suggest the hospital build a uniform registration platform to facilitate timely trace when necessary.

6. Contract approval

◢ If the study remains at the startup stage (such as a study that comes at the ethical review/contract review stage), we can make full use of modern information technologies to continue relevant review or discussion and reduce unnecessary late start caused by the epidemic.

◢ If a study is ongoing and necessary to revise the operating process for the need epidemic response, which will lead to a contract supplement, we can observe the principle of "ex-post contract" on an as-needed basis, and different parties can negotiate to revise the process earlier than the contract supplement.

7. Other processes and approvals

◢ The sponsor can complete the work to submit, review and accept various clinical trial applications and documents on the Internet platform. For example, when the sponsor submits an application to file the document update, related person of the

sponsor can submit it online, the staff of the study institution can review it online and accept or approve it online after confirmation.

◢ If the process involves the approval by multiple parties, we can count on the Internet platform to establish the online approval process.

8. Response to loss to follow-up and dropout

◢ Considering the need to control the epidemic, it is likely that many PD events will happen, and the investigators should keep an adequate record and explanation. At the same time, all parties shall make a concerted effort and take corresponding measure, such as the application of information technology method, with the purpose of trying to collect trial-related data and information as much as possible and reduce the dropouts.

◢ When it is impossible to complete the visit for an actual reason, the investigator shall communicate with the sponsor, and may temporarily not see the patient as a dropout, but treat the patient as missing follow-up visit. If the data of a patient are missing, the investigator can discuss the application of such data based on the opinions of statistical experts and clinical experts in a concentrated manner at the data review stage (blind review).

9. Supply management

The study site shall confirm in time whether trial supplies have been contaminated and handle the supplies properly. Trial supplies include but are not limited to the trial drug, trial-related documents, other facilities/equipment (such as centrifugal machine) and supplies. If the supply has been contaminated, it shall be immediately isolated. If the supply is usable after sterilization, the site shall immediately take appropriate sterilization measure, and if the supply is no longer usable after sterilization, the site shall communicate with the sponsor about subsequent affairs.

The aforesaid operation processes shall be recorded in detail, and a communication report on the communication with the sponsor shall also be prepared, filed and saved.

V. Ethical review

Ethical review is one of the core measures to protect subject rights and interests. However, we shall not change the principles and standards for ethical review and ensure the Ethics Committee will perform its responsibilities in relation to subject

protection. The Ethics Committee shall work in the principle of protecting the subject safety and welfare and assess various affairs in a comprehensive manner based on medical resources, supply support and other factors in the particular period.

General ethical review meetings can be suspended and postponed. When it is necessary to hold a review meeting for any special reason, the Ethics Committee shall make full use of various information technologies to flexibly arrange the meeting form. For example, the committee can hold a meeting in the form of Internet video conference that meets relevant requirements, and take corresponding meeting record.

New protocol, amendment and other review documents shall be submitted in the form of electronic document. If the Ethics Committee must keep paper documents, it can be supplemented after the epidemic ends and the documents shall be checked carefully. Ethical letter, notification letter, comment letter and other documents can temporarily be transmitted in the form of electronic document, unless the sponsor/investigator must immediately obtain paper documents for special reason.

1. Review method

◢ The Ethics Committee shall apply different review methods fully and flexibly while observing the Measures for the Ethical Review of Biomedical Research Involving Humans and the Guiding Principles for Ethical Review of Drug Clinical Trial.

◢ If a new drug, new apparatus or diagnostic reagent is developed or necessary clinical trial is implemented to prevent and control the current epidemic, the Ethics Committee shall quickly respond, take the form of urgent meeting review, effectively use the information platform to complete the review online within the given time, and transmit the review comment and review result as soon as possible.

◢ If the trial protocol, informed consent form and other documents are revised as a result of the epidemic situation, the Ethics Committee shall, whenever possible, apply the expedited review method to increase the review frequency if the increased benefit is higher than the risk after the principal reviewer of the committee fully assesses the risk-benefit ratio. If the principal reviewer thinks the continuing review, closure review and suspension/termination review will not affect the subject right and interest after assessment, the Ethics Committee can take the form of expedited review.

2. Ethical review about SAE

◢ The investigator shall report an SAE occurring at the site to the Ethics Committee in a timely manner. The Ethics Committee shall collaborate with the drug clinical trial institution and the scientific research management department to fully trace the working progress of the study team. If the epidemic situation makes the study team no longer capable to conduct the study, the Ethics Committee shall fully coordinate the sponsor, CRO and other parties to provide necessary working support, such as follow-up visit on the phone to avoid missing the identification and reporting of SAEs occurring at the site. When reviewing an SAE occurring at the site and finding the SAE is obviously a result of the epidemic situation, the Ethics Committee can take the form of expedited review, but shall pay attention to assessing the relationship between the study and the epidemic situation.

3. Ethical review about PD

◢ When handling a patient with potential loss to follow-up or dropout, the investigator shall first consider the case from the perspective of the subject's safety, and if the subject can't suspend/terminate the therapy based on the need to treat the disease, the investigator shall coordinate clinical resources to assure the treatment to the biggest extent. If a trial procedure that doesn't affect the subject safety but may affect the accuracy and integrity of trial data, we suggest the investigator should consider delaying the processing and record it as PD. When reviewing such PD events, the Ethics Committee shall not judge it as an implementation issue of the investigator and thus require the investigator to receive additional GCP training, but shall pay attention to whether the subject safety and related data are properly handled during the follow-up visit later.

VI. Protection against Epidemic Situation

During the epidemic, we shall take adequate measures to protect clinical trial-related people, particularly people of the study site who have to receive subjects, sponsors or other trial participants, including study doctors and people of the clinical trial institution office, the Ethics Committee and the trial pharmacy.

1. The sponsor, the CRO, the SMO or other clinical trial participants shall, whenever possible, rely on the Internet technology and apply information platforms and other channels to do relevant work in collaboration, and avoid working on the site of the study site.

2. When it is necessary to go to the study site, we shall make an appointment in advance, confirm whether a person going to the study site has resided in or travelled to regions with a high incidence of the epidemic, or contacted groups who are infected or suspected of infection or visited the fever clinic within 14 days, and register the

record to facilitate future trace. Before the epidemic ends, we shall forbid a person who has resided in or travelled to regions with a high incidence of the epidemic, or visited the fever clinic or has contacted patients who are confirmed to have an infection within 14 days to visit the study site.

3. Before going to the study site, the subject or other trial-related people shall take adequate protective measures, wear the mask, move in the movement area designated by the hospital, and regularly measure the temperature in accordance with the hospital's requirement for epidemic prevention and control. The person shall avoid walking in the fever clinic area or suspected patient screening area of the hospital and reduce the scope of activity in the hospital to the biggest extent.

4. When a subject or other trial personnel visits the site, personnel of the study site, including study doctors and personnel of the clinical trial institution office, the Ethics Committee and the trial pharmacy, shall first confirm whether the visitor has no fever and has not resided in or travelled to regions with a high incidence of the epidemic, or contacted patients who are confirmed to have an infection or visited the fever clinic within 14 days and identified the visitor as non-infected or suspicious infected. At the same time, they shall take adequate personal protective measures, wear the mask, and change the gown according to the specified usable time. If there is no labelled suggestion, we suggest changing the gown no more than 4 hours. When the mask gets wet or gets contaminated with droplet, blood or body fluid, it shall be replaced in time.

5. When going to work at the study site, all trial-related personnel shall take adequate protective measures in line with the hospital's protective requirements for different areas with low, medium and high risks.

VII. Communication among Different Parties

During the epidemic, all clinical trial participants shall maintain close communication, and can employ multiple channels, including information technology and Internet platform, to communicate information in time and ensure all parties understand the actual progress of the trial in a real-time manner and at the same frequency.

1. The investigator shall strive to ensure the subject can notify the investigator of the disease development and medication data in a timely manner.

2. After knowing the subject's actual condition, the investigator shall provide a medical instruction in time.

3. Other clinical trial participants, such as sponsor, CRO or SMO, can employ multiple paths, including information platform, to track the progress of the clinical trial in time and feed it back to the study site.

4. The clinical trial quality management parties can employ multiple paths, including information platform, to track the implementation progress of the clinical trial in time and feedback potential quality risks to related parties in time.

5. When communication is required but on-site communication is impossible, all parties shall communicate in time on the phone or through the net meeting, and keep a record.

VIII. Documents & Records

During the epidemic, we shall record all relevant normal operations of the clinical trial in detail, and save the same completely. All parties involved in the clinical trial shall, whenever possible, employ multiple channels, including information technology and Internet platform, feedback related information in time so that all parties are informed of the subject's status and the trial progress in time and take corresponding actions in time when necessary.

1. We shall record the communication with the subject in detail, prepare a written report on every communication event, including time, channel and content of communication, and feedback the information to clinical trial-related parties in a timely manner.

2. When a subject attends a remote follow-up visit, we shall record in detail the background, method and content of the follow-up visit, including the subject's feedback and the investigator's medical measure for the subject. In particular, we shall pay attention to the AE and combined medication of the subject during the period, keep a record in detail and put it on file.

3. When a subject attends a follow-up visit outside the study site, the study doctor shall directly communicate with the doctor who performs the visit at that time, explain the subject's participation in the clinical trial in detail, and state various requirements for the follow-up visit in order for the receiving doctor to perform the follow-up visit in line with the requirements set forth by the clinical trial protocol. At the same time, the investigator shall remind the subject to collect and save complete records. When conditions allow, the investigator shall ask the subject to feed back the data on the follow-up visit at other hospitals to the investigator so that the investigator will know the subject's situation or take necessary action. After the epidemic ends, the subject shall bring all relevant complete documents and records to the study site for filing.

4. When it is necessary to post the drug products to the subject, the trial drug manager shall record the background data in detail, state the necessity to post the drug, and prepare a written document to confirm the qualification of the carrier and the compliance of transport conditions. At the same time, the manager shall record in detail the drug number (if applicable), batch number specification, quantity and transport document number of the posted drug, and provide the administration method and matters requiring attention. When receiving the drug, the subject shall sign a written receipt and send it back in time to the trial drug manager for saving and filing. For the drug or package to be returned, the investigator shall remind the subject to keep it as intact, and consider the collection method and frequency based on the specific situation.

5. The investigator shall remind the subject to contact the investigator at the first opportunity in case of an AE or SAE, record the AE/SAE data of the subject in detail according to the requirements of the clinical trial protocol, and report it based on relevant process. Meanwhile, the investigator shall pay particular attention to reporting the SAE. When the treatment outside of the study site is involved, the investigator shall remind the subject to collect and save complete records, including medication records. If possible, the investigator shall ask the subject to feed back the data on the follow-up visit at other hospitals to the investigator so that the investigator will know the subject's situation or take corresponding action when necessary. After the epidemic ends, the subject shall bring all relevant complete documents and records to the study site for filing. This will facilitate the audit.

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