一项在18岁及以上成人受试者中评价重组双组分新冠肺炎疫苗（CHO细胞）预防COVID-19的有效性、安全性及免疫原性的多中心、随机、双盲、安慰剂对照III期临床试验

A Multicenter, Randomized, Double-blind, Placebo-controlled Phase III Clinical Trial to Evaluate the Efficacy, Safety and Immunogenicity of the Recombinant Two-Component COVID-19 Vaccine (CHO Cells) in the Prevention of COVID-19 in Adult Subjects Aged 18 Years and Above

质量控制报告

Quality Control Report

申办方：江苏瑞科生物技术股份有限公司

Sponsor: Jiangsu Recbio Biotechnology Co., Ltd.

第三方质控单位：北京康信科威医药科技有限公司

Third-party quality control: Beijing Kangxin Kewei Medical Technology Co., Ltd.

实施现场：Research Center Eco-safety

Implementation site: Research Center Eco-safety

质控日期：2023 年 3 月 21—24 日

Date of quality control: March 21-24, 2023

保密声明

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项目名称 Project title	一项在 18 岁及以上成人受试者中评价重组双组分新冠肺炎疫苗（CHO 细胞）预防 COVID-19 的有效性、安全性及免疫原性的多中心、随机、双盲、安慰剂对照 III 期临床试验 A Multicenter, Randomized, Double-blind, Placebo-controlled Phase III Clinical Trial to Evaluate the Efficacy, Safety and Immunogenicity of the Recombinant Two-Component COVID-19 Vaccine (CHO Cells) in the Prevention of COVID-19 in Adult Subjects Aged 18 Years and Above
申办方 Sponsor	江苏瑞科生物技术股份有限公司 Jiangsu Recbio Biotechnology Co., Ltd.
方案版本/日期 Protocol version/date	1.0/2022 年 5 月 25 日 1.0/May 25, 2022
质控标准 Quality control criteria	ICH-GCP、GCP、临床研究方案、《中华人民共和国药品管理法》、《中华人民共和国疫苗管理法》、《药品注册核查要点和判定原则》、《疫苗临床试验质量管理指导原则（试行）》、《疫苗临床试验严重不良事件报告管理规定》 ICH-GCP, GCP, clinical study protocol, *Drug Administration Law of the People's Republic of China*, *Vaccine Administration Law of the People's Republic of China*, *Key Points of and Judgment Principles for Drug Registration Inspection*, *Good Clinical Practice for Vaccines (Trial)*, *Regulations on the Management of*

	Critical Adverse Event Reports in Vaccine Clinical Trials
质控范围 Scope of quality control	研究者文件夹质控（承担药物临床试验单位的合规性（设施设备））；知情同意书；源文件与原始记录（包括如日记卡、联系卡等；发生 SAE 需要住院资料包括出入院记录、病程记录、医嘱、各项实验室检查及影像相关检查记录等）的质控；CRF/EDC；生物样本管理；试验疫苗管理的；源数据的 HIS/LIS 溯源。 Quality control of investigator files (compliance of the facility undertaking the drug clinical trial (facilities and equipment)); informed consent form; quality control of source files and original records (including diary cards, contact cards, etc.; data of hospitalization required for SAEs, including admission and discharge records, medical records, medical orders, various laboratory tests, and imaging-related examination records, etc.); CRF/EDC; biological sample management; investigational vaccine management; HIS/LIS traceability of source data.
项目阶段 Project phase	准备□ 进行■ 完成□ In preparation□ In process■ Completed□
质控单位 Quality control facility	北京康信科威医药科技有限公司 Beijing Kangxin Kewei Medical Technology Co., Ltd.
质控性质 Nature of quality control	常规质控■ 有因质控□ Routine quality control ■ For-cause quality control □
质控员 Quality control personnel	孙久华、吴建超 Sun Jiuhua, Wu Jianchao

质控日期 Date of quality control	2023 年 3 月 21—24 日 March 21-24, 2023

二、质量控制问题的等级标准

II. Standards for Grades of Quality Control Issues

（一）**严重问题**：是指与药物 GCP 及相关法规要求有严重偏离的缺陷。

(I) Critical issues: Refer to deficiencies that critically deviate from the GCP for Pharmaceuticals and relevant regulatory requirements.

属于下列情形之一的为严重缺陷：

Any of the following situations is considered a critical deficiency:

- 受试者的安全和权益已受到或极可能受到严重损害；
- The safety and rights of the subjects have been or are highly likely to be severely damaged;
- 临床试验数据不可靠；
- The clinical trial data are unreliable;
- 在临床试验实施的不同环节存在多项重要缺陷，经综合分析表明质量保证体系不能正常运行；
- There are multiple significant deficiencies in different stages of clinical trial implementation, and comprehensive analysis shows that the quality assurance system cannot operate normally;
- 对以往的重要缺陷未及时整改或整改不到位。临床试验的质量控制和质量保

证体系存在严重缺陷。

- Past significant deficiencies have not been rectified promptly or properly. There are critical deficiencies in the quality control and quality assurance system of the clinical trial.

（二）**重点关注问题**：是指与药物 GCP 及相关法规要求有较大偏离的缺陷。

(II) Issues of intensive concern: Refer to deficiencies that greatly deviate from the GCP for Pharmaceuticals and relevant regulatory requirements.

属于下列情形之一的为主要缺陷：

Any of the following situations is considered a major deficiency:

- 与药物 GCP 要求有较大偏离，如不及时处理，将上升为严重缺陷；

- There is a great deviation from the GCP for Pharmaceuticals, which, if not dealt with promptly, will upgrade to a critical deficiency;

- 在临床试验实施中存在多项关联一般缺陷，经综合分析表明质量保证体系不能正常运行。

- There are multiple associated minor deficiencies in clinical trial implementation, and comprehensive analysis shows that the quality assurance system cannot operate normally;

（三）**一般问题**：是指偏离药物 GCP 及相关法规、指导原则或 SOP 的要求，但尚未达到严重缺陷和主要缺陷程度的缺陷。

(III) Minor issues: Refer to deficiencies that deviate from the GCP for Pharmaceuticals and relevant regulations, guidelines or SOP requirements, but do not

meet the criteria for critical deficiencies and major deficiencies.

三、质控内容

III. Content of Quality Control

1、临床试验资质或资料的合规性

1. Compliance of Clinical Trial Qualification or Materials

包括但不限于临床试验单位承担药物临床试验的条件与合规性；委托合同和职责；伦理审查批件及记录的原始性及完整性，伦理审查相关资料（质控全部上报伦理相关资料，包括但不限于知情同意书、SAE、方案违背等上报伦理记录及回执）；试验相关人员（资质、授权分工、培训等质控所有参与项目相关人员资质、授权分工、培训的完整性；重点质控新增授权人员合规性）。

Including but not limited to the conditions and compliance of the facility undertaking the clinical trial; entrustment contract and responsibilities; originality and integrity of ethical review approvals and records, as well as ethical review-related materials (all ethics-related materials submitted for quality control, including but not limited to informed consent forms, SAEs, protocol violations, and other ethical submission records and acknowledgement of receipt); trial-related personnel (completeness of qualifications, authorized division of labor, and training of personnel involved in qualification, authorized division of labor, training, and other quality control of the project; compliance of newly authorized personnel for intensive quality control).

2、临床试验存档文件管理

2. Management of Archived Clinical Trial Documents

包括但不限于研究前期文件：研究现场概况（如有）、招募计划、伦理、应急预案、研究单位资质证明等；研究者资料和培训（研究者资料（包括分工授权表、GCP 培训、岗位培训记录）、项目启动培训及会议记录、其他培训记录）、签名样章；疫苗管理（出入库、运输（温度监控）、分发登记、使用记录（空瓶/空盒、备份疫苗）、冷链管理/冷链破坏、疫苗储存温度记录、湿度记录、回收、销毁记录（生物废弃物品处置记录等）；生物样本管理（采集、处理、储存（储存温度、存放地点）、运输及冷链、接收（生物废弃物处置记录等）；受试者管理文件（鉴认代码表、随机分配表）；设备设施管理。（校验、维修保养记录）。

Including but not limited to preliminary study documents: overview of the study site (if any), recruitment plan, ethics, emergency plan, qualification certificate of the study facility, etc; investigator materials and training (investigator materials (including division of labor authorization form, GCP training, job training records), project initiation training and meeting minutes, and other training records), sample signature seal; vaccine management (warehousing-in and warehousing-out, transportation (temperature monitoring), distribution registration, usage records (empty bottles/boxes, backup vaccines), cold chain management/cold chain destruction, vaccine storage temperature records, humidity records, recovery and destruction records (biological waste disposal records, etc.); biological sample management (collection, processing and storage (storage temperature, storage location), transportation and cold chain, reception (biological waste disposal records, etc.); subject management documents (identification code table, randomization table); equipment and facility management (calibration, repair and maintenance records).

3、临床试验实施

3. Clinical Trial Implementation

包括但不限于：试验方案执行的依从性。试验流程实施。临床试验流水号登记；受试者知情同意书签署及过程；筛选、体检、入组、疫苗接种、留观记录、日记卡、联系卡、随访记录、SAE 报告、方案违背、急性过敏反应合并用药、安全性和不良事件的记录等其他试验相关原始数据及原始记录的检查和溯源。

Including but not limited to: compliance of trial protocol execution, trial process implementation, clinical trial serial number registration; the subject's informed consent form signing and process; examination and traceability of screening, physical examination, enrollment, vaccination, observation records, diary cards, contact cards, follow-up records, SAE reports, protocol violations, concomitant medications for acute allergic reactions, safety and adverse event records, and other trial-related raw data and original records.

四、发现问题

IV. Issues Found

1、严重问题 0 项

1. Critical Issues: 0

2、重点关注问题 2 项

2. Issues of Intensive Concern: 2

问题 1 **Issue 1**	入排问题 **Inclusion and exclusion issue**
问题描述 **Issue description**	排除标准 **5:** 有严重过敏性疾病史或可能因 **ReCOV** 中任何成分而加重的过敏反应史，如过敏性休克、过敏性喉头水肿、过敏性紫癜、血小板减少性紫癜、局部过敏坏死反应，或既往对任何疫苗或药物的严重不良反应史，如过敏、荨麻疹、湿疹、呼吸困难和

	血管神经性水肿。 **Exclusion criterion 5: Those with a history of severe allergic diseases or allergic reactions that may worsen due to any component of ReCOV, such as allergic shock, allergic laryngeal edema, allergic purpura, thrombocytopenic purpura, local allergic necrosis reactions, or a history of severe adverse reactions to any vaccine or drug, such as allergy, urticaria, eczema, dyspnea, and angioneurotic edema.** ➢ 筛选号 301400244 受试者，《访视记录本》记录对阿莫西林克拉维甲酸过敏，表现为全身多处红斑；对夫沙芬净过敏，表现为窒息。符合排除标准 5。 ➢ Subject with screening number 301400244: It was recorded in the *Visit Record Book* that the subject was allergic to amoxicillin and clavulanate potassium, manifested as multiple erythema throughout the body, and allergic to fusafungine, manifested as suffocation, and met exclusion criterion 5.
整改措施 **Rectification measures**	加强对研究者的培训，严把入选/排除标准关。 Strengthen the training of investigators and strictly control the inclusion/exclusion criteria.

问题 2 **Issue 2**	**采样问题** **Sampling issue**
问题描述 **Issue description**	● 本中心自 2022 年 12 月 14 日起，有疑似 COVID-19 的受试者需要采集拭子检测 RT-PCR 时，现场同时采集两份拭子。先采集一份两侧鼻咽拭子备用（国家实验室检测样本），后采集一份口咽+鼻咽拭子（当地实验室检测样本）。先送检口咽+鼻咽拭子在当地实验室检测 RT-PCR，结果为阴性时不需把两侧鼻咽拭子备用样本送往国家实验室检测；如当地实验室检测结果为阳性则把两侧鼻咽拭子备用样本送往国家实验室检测。**问题：**同时采集两份拭子

	时，后采集的拭子中 SARS-CoV-2 病毒载量比先采集样本的低，当把后采集样本在当地实验室检测 RT-PCR 以明确该受试者是否是 COVID-19 时，若 RT-PCR 结果为阴性，不把先采集的两侧鼻咽拭子送国家实验室检测，可能存在漏诊的情况。 ● Starting from December 14, 2022, when swabs need to be collected from subjects suspected of COVID-19 for RT-PCR testing, two swabs will be collected on the spot simultaneously. First, collect a set of bilateral nasopharyngeal swabs for backup (sample for national laboratory testing), and then collect a set of oral + nasopharyngeal swabs (sample for local laboratory testing). First, send the oral + nasopharyngeal swabs for RT-PCR testing in the local laboratory. If the result is negative, there is no need to send the backup samples of bilateral nasopharyngeal swabs to the national laboratory for testing; if the local laboratory test results are positive, send the backup samples of bilateral nasopharyngeal swabs to the national laboratory for testing. Issue: After two sets of swabs are collected, the SARS-CoV-2 virus load in the later collected swabs is lower than that in the first collected sample. When the later collected sample is tested in the local laboratory for RT-PCR to determine whether the subject has COVID-19, if the RT-PCR result is negative and the first collected nasopharyngeal swabs are not sent to the national laboratory for testing, there may be missed diagnosis. ➢ 筛选号 301400114 受试者，2023 年 1 月 11 日出现疑似 COVID-19 相关症状，1 月 13 日、1 月 15 日两次在当地实验室检测 RT-PCR 均为阴性，未送先采集的两侧鼻咽样本至国家实验室检测。 ➢ Subject with screening number 301400114 presented with suspected COVID-19-related symptoms on January 11, 2023, and two

	RT-PCR tests on January 13 and January 15 in the local laboratory were both negative. The first collected bilateral nasopharyngeal samples were not sent to the national laboratory for testing. ➢ 筛选号 301400102 受试者，2022 年 12 月 15 日出现疑似 COVID-19 相关症状，12 月 16 日在当地实验室检测 RT-PCR 均为阴性，未送先采集的两侧鼻咽样本至国家实验室检测。 ➢ Subject with screening number 301400102 presented with suspected COVID-19-related symptoms on December 15, 2022, and the RT-PCR test on December 16 in the local laboratory was negative. The first collected bilateral nasopharyngeal samples were not sent to the national laboratory for testing.
整改措施 **Rectification measures**	按项目要求进行 RT-PCR 采集。 Perform RT-PCR collection as required by the project.

3、一般问题 11 项

3. Minor Issues: 11

问题 1 **Issue 1**	不良事件相关问题 **Adverse event-related issue**
问题描述 **Issue description**	● **漏记 AE** ● **Missed recording of AEs** ➢ 筛选号 301400223 受试者， 2023 年 1 月 13 日接种第 2 剂试验疫苗，日记卡记录 1 月 14 日-14 日头痛，不良事件表及 EDC 未记录该不良事件，请核实。 ➢ Subject with screening number 301400223 received the second dose of the investigational vaccine on January 13, 2023, the diary card recorded headache on January 14-14, while the adverse event form and EDC did not record this adverse event. Please verify.

	➢ 筛选号 301400158 受试者，2022 年 11 月 27 日接种第 1 剂试验疫苗，12 月 12 日进行每周电话随访获知出现疲劳症状，不良事件表及 EDC 未记录。类似情况还见于筛选号 301400017 受试者每周电话随访记录 12 月 19 日获知发生头晕、2023 年 1 月 19 日获知发生乏力、头痛；筛选号 301400223 受试者每周电话随访记录 2023 年 2 月 10 日获知疲劳，未见记录在不良事件表，请研究者核实是否存在漏记的可能。 ➢ Subject with screening number 301400158 received the first dose of the investigational vaccine on November 27, 2022. On December 12, during weekly telephone follow-up, it was learnt that the subject experienced fatigue, but the adverse event form and EDC did not record it. Similar situations were also seen in subject with screening number 301400017 (as shown by the weekly telephone follow-up record, it was learnt that the subject experienced dizziness on December 19 and asthenia and headache on January 19, 2023) and subject with screening number 301400223 (as shown by the weekly telephone follow-up record, it was learnt that the subject experienced fatigue on February 10, 2023, but it was not recorded in the adverse event form). The investigator was requested to verify whether there was a possibility of missed recording. ● 不良事件严重程度判定问题 ● **Issue about determining the severity of adverse events** ➢ 筛选号 301400017 受试者，第 2 次访视日记卡记录自接种后第 1 天至 5 天出现注射局部发红，最大直径为 5.5cm，研究者判定严重程度为 1 级。按照《预防用疫苗临床试验不良事件分级指导原则》注射局部发红 1 级：直径 2.5-＜5cm；2 级：直径 5-＜10cm，故应判定 2 级。类似情况还见于筛选号 301400098 受试者。 ➢ Subject with screening number 301400017: The Visit 2 diary card

	recorded that the subject experienced injection site redness, up to 5.5 cm in diameter on Days 1-5 after vaccination, and the investigator judged the severity as grade 1. In the *Guidelines for the Classification of Adverse Events in Clinical Trials of Preventive Vaccines*, grade 1 injection site redness: diameter 2.5-<5 cm; grade 2: 5-<10 cm, the event should be determined as grade 2. Similar situations were also seen in subject with screening number 301400098. ➢ 筛选号 301400017 受试者，2022 年 12 月 12 日接种第 2 剂试验疫苗，日记卡记录接种后第 1 天至 6 天出现注射局部肿胀，每天最大直径依次为 5、4、3、2.5、2、1cm，研究者判定严重程度为 1 级。按照《预防用疫苗临床试验不良事件分级指导原则》注射局部肿胀 1 级：直径 2.5-＜5cm；2 级：直径 5-＜10cm，故应判定 2 级。另外，该 AE 结束时间记录为 12 月 18 日（第 6 天），应为 12 月 16 日。 ➢ Subject with screening number 301400017 received the second dose of the investigational vaccine on December 12, 2022, and the diary card recorded that the subject experienced injection site swelling on Days 1-6 after vaccination, with a diameter of 5, 4, 3, 2.5, 2 and 1 cm respectively, and the investigator judged the severity as grade 1. In the *Guidelines for the Classification of Adverse Events in Clinical Trials of Preventive Vaccines*, grade 1 injection site swelling: diameter 2.5-<5 cm; grade 2: 5-<10 cm, the event should be determined as grade 2. In addition, the AE end time was recorded as December 18 (Day 6), which should actually be December 16. ➢ 筛选号 301400114 受试者，2023 年 1 月 11 日出现发热、肌痛、头痛、咽痛等症状，不良事件表记录 AE：急性呼吸道病毒感染，起止时间 1 月 11 日-21 日，药物治疗，严重程度为 1 级。判定为 2 级更合理。**备注：**《预防用疫苗临床试验不良事件分级》中其它

	不良事件 1 级：短时或轻微不适，不影响活动，无需治疗；2 级：轻度或中度活动受限，可能需要就诊、不需或仅需轻度治疗。 ➢ Subject with screening number 301400114 experienced symptoms such as fever, myalgia, headache and sore throat on January 11, 2023, and the adverse event form recorded an AE: acute respiratory virus infection, the start and end time was January 11-21, drug treatment, grade 1 in severity. It would be more reasonable to judge the event as grade 2. **Note:** In the *Guidelines for the Classification of Adverse Events in Clinical Trials of Preventive Vaccines*, grade 1 other adverse events: transient or mild discomfort, not affecting activity and not requiring treatment; grade 2: mild or moderate activity restriction, which may require medical attention, not require or only require mild treatment. ➢ 筛选号 301400305 受试者，2023 年 2 月 6 日接种第 3 剂试验疫苗，日记卡记录 2 月 6 日至 8 日出现注射局部硬结，最大直径 5CM；研究者判定 1 级。根据《预防用疫苗临床试验不良事件分级指导原则》注射局部硬结 2 级：直径 5-<10CM，此不良事件严重程度应判定 2 级。类似情况还见于筛选号 301400158 受试者。 ➢ Subject with screening number received the third dose of the investigational vaccine on February 6, 2023, and the diary card recorded injection site induration on February 6-8, up to 5 cm in diameter, which was judged as grade 1 by the investigator. In the *Guidelines for the Classification of Adverse Events in Clinical Trials of Preventive Vaccines*, grade 2 injection site induration: diameter 5-<10 cm, the severity of this event should be determined as grade 2. Similar situations were also seen in subject with screening number 301400158. ➢ 筛选号 301400071 受试者，2023 年 1 月 9 日接种第 3 剂试验

	疫苗，日记卡记录 1 月 10 日出现注射局部硬结，最大 10CM。研究者判定严重程度 2 级。根据《预防用疫苗临床试验不良事件分级指导原则》注射局部硬结 3 级：直径≥10CM 或面积≥100cm^2。此不良事件严重程度应为 3 级。 ➢ Subject with screening number 301400071 received the third dose of the investigational vaccine on January 9, 2023. The diary card recorded injection site induration on January 10, up to 10 cm in diameter, and the severity was judged as grade 2 by the investigator. In the *Guidelines for the Classification of Adverse Events in Clinical Trials of Preventive Vaccines*, grade 3 injection site induration: diameter ≥ 10 cm or area ≥100 cm^2, the severity of this event should be grade 3. ● 不良事件记录问题 ● **Adverse event recording issue** ➢ 筛选号 301400017 受试者，2022 年 12 月 12 日接种第 2 剂试验疫苗，日记卡记录 12 月 13 日-18 日出现不良事件-蜂窝组织炎，研究者记录在不良事件表中，后又在不良事件表上记录“进行了重新判定”并将此不良事件划线删除。建议：删除受试者记录的不良事件，应记录理由，如经核实受试者只出现注射局部红、肿、痛，理解错误为蜂窝组织炎等等。 ➢ Subject with screening number 301400017 received the second dose of the investigational vaccine on December 12, 2022, and the diary card recorded an adverse event—cellulitis on December 13-18. The investigator recorded it in the adverse event form, and later recorded “re-determination was performed” in the adverse event form and crossed out this adverse event. Recommendation: The reason for deleting adverse events recorded by the subject should be recorded, such as “after verification, the subject only had injection site redness,

	swelling and pain, but it was misunderstood as cellulitis". ➢ 筛选号 301400211 受试者，2022 年 12 月 16 日接种第 1 剂试验疫苗，日记卡记录征集期未出现注射局部疼痛，而不良事件表于 2023 年 2 月 14 日记录了不良事件—注射局部疼痛，起止时间 12 月 17 日至 12 月 29 日。经核实，12 月 23 日进行每周电话访视时获知此 AE，受试者未记录在日记卡上。建议研究者应将电话访视获知内容记录在《访视记录本》上作为原始记录（因每周随访表备注栏对不良事件的记录不全，如相关性、严重程度等未记录）。类似情况还见于筛选号 301400336、301400045 受试者。 ➢ Subject with screening number 301400211 received the first dose of the investigational vaccine on December 16, 2022. The diary card recorded that the subject did not experience injection site pain during the solicitation period, while the adverse event form recorded an adverse event—injection site pain on February 14, 2023, and the start and end time was December 17-29. After verification, this AE was learnt during the weekly telephone visit on December 23, and the subject did not record it in the diary card. The investigator is advised to record the content learnt through telephone visits in the *Visit Record Book* as original record (as the "remarks" column of the weekly follow-up form does not record adverse events completely. For example, correlation and severity are not recorded). Similar situations were also found in subjects with screening numbers 301400336 and 301400045. ➢ 筛选号 301400244 受试者，2022 年 12 月 17 日接种第 1 剂试验疫苗。日记卡记录 12 月 17 日-12 月 21 日注射局部疼痛、硬结、肿胀，12 月 17 日-17 日头痛，2023 年 1 月 13 日-15 日注射局部疼痛、硬结、肿胀，1 月 14 日-14 日注射局部发红，1 月 13 日-17 日疲劳。不良事件表及 EDC 记录注射局部疼痛的起止时间是 12

	月 17 日-12 月 21 日，其余不良事件的停止日期均记录为日记卡停止日期的第 2 天。不良事件停止日期记录不一致。类似情况还见于筛选号 301400017、301400251、301400305、301400268 受试者。 ➢ Subject with screening number 301400244 received the first dose of the investigational vaccine on December 17, 2022. The diary card recorded injection site pain, induration and swelling on December 17-21, headache on December 17-17, injection site pain, induration and swelling on January 13-15, 2023, injection site redness on January 14-14, and fatigue on January 13-17. The adverse event form and EDC recorded that the start and end time of injection site pain was December 17-21, while the stop date of all other adverse events was recorded as the next day of the stop date in the diary card. The adverse event stop date records were inconsistent. Similar situations were also seen in subjects with screening numbers 301400017, 301400251, 301400305 and 301400268. ➢ 筛选号 301400098 受试者，2022 年 12 月 16 日接种第 2 剂试验疫苗，日记卡记录接种 30 分钟内出现注射局部发红，直径 1cm，不良事件表记录为严重程度 1 级。按照《预防用疫苗临床试验不良事件分级指导原则》注射局部发红 1 级：直径 2.5-＜5cm。未达 1 级，不用记录不良事件。 ➢ Subject with screening number 301400098 received the second dose of the investigational vaccine on December 16, 2022. The diary card recorded that the subject experienced injection site redness within 30 minutes after vaccination, 1 cm in diameter. The adverse event form recorded the severity as grade 1. In the *Guidelines for the Classification of Adverse Events in Clinical Trials of Preventive Vaccines*, grade 1 injection site redness: diameter 2.5-< 5 cm. The event did not reach grade 1, so it should not have been recorded as an

	adverse event. ➢ 筛选号 301400071 受试者，2022 年 11 月 25 日接种第 1 剂试验疫苗，11 月 26 日-12 月 2 日失眠，记录为不良事件，严重程度 1 级。12 月 19 日接种第 2 剂试验疫苗，受试者在日记卡记录 12 月 19 日出现“失眠”，严重程度 3 级，治疗情况为 2（药物治疗），研究者将治疗情况修改为 1（未治疗），记录：失眠为长期间歇病史和试验无关判定，严重程度为 0 级，治疗 1，未记录为不良事件。研究者修改受试者记录的治疗情况，应记录核实的经过，并应该让受试者签名及日期。若入组前有失眠病史，入组后失眠进行了药物干预，治疗情况发生变化，也应记录为不良事件。 ➢ Subject with screening number 301400071 received the first dose of the investigational vaccine on November 25, 2022, and had insomnia from November 26 to December 2, which was recorded as an adverse event, grade 1 in severity. The subject received the second dose of the investigational vaccine on December 19, and recorded “insomnia” in the diary card on December 19, grade 3 in severity. Treatment status was 2 (drug treatment). The investigator modified the treatment status to 1 (no treatment), and recorded the determination that the insomnia was a long-term intermittent medical history and not related to the trial, the severity was 0, treatment status was 1, and did not record it as an adverse event. Before modifying the treatment recorded by the subject, the investigator should record the verification process, and ask the subject to sign and date it. If the subject had a history of insomnia before enrollment, and received drug intervention after enrollment, the treatment changed, and it should also be recorded as an adverse event. ● 不良事件相关性判定问题 ● **Issue about determining the correlation of adverse events**

	➢ 筛选号 301400017 受试者，2022 年 12 月 12 日接种第 2 剂试验疫苗，日记卡记录 12 月 13 日出现咳嗽，相关性判定为可能无关。咳嗽是接种本试验疫苗已知的潜在风险，且未注明是否由其它疾病导致的可能，判定可能无关依据不充分。 ➢ Subject with screening number 301400017 received the second dose of the investigational vaccine on December 12, 2022. The diary card recorded that the subject experienced cough on December 13, and the correlation was determined to be unlikely related. Cough was a known potential risk of vaccination of the investigational vaccine, and it was not indicated whether it may be caused by other diseases. The basis for judging "unlikely related" was insufficient. ➢ 筛选号 301400017 受试者，2022 年 11 月 19 日接种第 1 剂试验疫苗，日记卡记录 11 月 19 日-19 日疲劳，判定很可能有关，11 月 22 日-23 日关节痛，判定很可能有关；12 月 12 日接种第 2 剂试验疫苗，日记卡记录 12 月 13 日-13 日疲劳，判定可能有关，12 月 15 日-16 日关节痛，判定可能有关，按照方案相关性判定原则，重复接种再次出现疲劳、关节痛，判定肯定有关更合理。 ➢ Subject with screening number 301400017 received the first dose of the investigational vaccine on November 19, 2022. The diary card recorded that the subject experienced fatigue on November 19-19 (which was determined to be probably related) and arthralgia on November 22-23 (which was determined to be probably related). The subject received the second dose of the investigational vaccine on December 13. The diary card recorded that the subject experienced fatigue on December 13-13 (which was determined to be possibly related) and arthralgia on December 15-16 (which was determined to be possibly related). According to the correlation determination principle in the protocol, since fatigue and arthralgia recurred after

	re-vaccination, it would be more reasonable to determine them as "definitely related". ➢ 筛选号 301400017 受试者，2022 年 12 月 12 日接种第 2 剂试验疫苗，12 月 13 日-13 日出现便秘、吞咽困难，相关性判定为可能无关。便秘、吞咽困难是本试验疫苗的征集性不良事件，接种后第 1 天即出现，判定可能无关未注明依据。 ➢ Subject with screening number 301400017 received the second dose of the investigational vaccine on December 12 and experienced constipation and dysphagia on December 13-13, and the correlation was determined to be unlikely related. Constipation and dysphagia were solicited adverse events for the investigational vaccine and occurred on Day 1 after vaccination, but the basis for determining them as "unlikely related" was not specified. ➢ 筛选号 301400449 受试者，2023 年 1 月 14 日接种第 1 剂试验疫苗，1 月 15 日出现头痛、肌痛消失后于 1 月 20 日再次出现头痛和肌痛，判定可能无关，征集期内（接种后第 6 天）征集性不良反应判定可能无关未注明依据。 ➢ Subject with screening number 301400449 received the first dose of the investigational vaccine on January 14, 2023, and experienced headache and myalgia on January 15, which disappeared and recurred on January 20, but were determined to be unlikely related. The basis for determining solicited adverse reactions within the solicitation period (Day 6 after vaccination) as "unlikely related" was not specified. ➢ 筛选号 301400088 受试者，2022 年 11 月 25 日接种第 1 剂试验疫苗，12 月 1 日-1 日（接种后第 6 天）出现头痛，判定可能无关。头痛是接种本试验疫苗已知的潜在风险，征集期内出现头痛，且未注明是否由其它疾病导致的可能，判定可能无关依据不充分。

	➢ Subject with screening number 301400088 received the first dose of the investigational vaccine on November 25, 2022, and experienced headache on December 1-1 (Day 6 after vaccination), which was determined to be unlikely related. Headache was a known potential risk of vaccination of the investigational vaccine and occurred during the solicitation period, and it was not indicated whether it may be caused by other diseases. The basis for judging "unlikely related" was insufficient.
整改措施 Rectification measures	认真核对研判并记录，确保研究者判定、转录及 EDC 录入的一致性。 Carefully verify the investigator's judgment and record it to ensure that the investigator's judgment, transcription and EDC entry were consistent.

问题 2 Issue 2	**EDC 录入问题 EDC entry issue**
问题描述 Issue description	● 筛选号 301400098 受试者，第 2 次访视日记卡记录 11 月 25 日-12 月 2 日出现注射局部硬结，最大直径 5cm，不良事件表记录严重程度为 2 级，EDC 录入为 1 级。 ● Subject with screening number 301400098: The Visit 2 diary card recorded that the subject experienced injection site induration from November 25 to December 2, up to 5 cm in diameter. The adverse event form recorded the severity as grade 2, while the EDC entry was grade 1. ● 筛选号 3014000251 受试者，2022 年 12 月 17 日接种第 1 剂试验疫苗，不良事件表记录 12 月 18 日-19 日肌痛，EDC 录入停止时间为 18 日；12 月 17 日-20 日注射部位瘙痒，EDC 录入停止时间为 19 日。 ● Subject with screening number 3014000251 received the first

	dose of the investigational vaccine on December 17, 2022. The adverse event form recorded myalgia on December 8-19, while the EDC entry showed that the end time was December 18; for injection site itching on December 17-20, the EDC entry showed that the end time was December 19. ● 筛选号301400071受试者，2022年12月19日接种第2剂试验疫苗，日记卡记录12月26日出现咳嗽，相关性判定为可能有关；2023年1月23日研究者填写不良事件表对 咳嗽判定 大概率有关，EDC仍为可能有关。 ● Subject with screening number 301400071 received the second dose of the investigational vaccine on December 19, 2022. The diary card recorded that the subject experienced cough on December 26, and the correlation was determined to be possibly related. On January 23, 2023 when filling out the adverse event form, the investigator judged cough as highly likely to be related, but EDC entry was still "possibly related". ● 筛选号301400305受试者，2022年12月18日接种第1剂试验疫苗，日记卡记录12月19日至23日出现肿胀不良事件表记录严重程度为2级。EDC录入为1级，录入错误。 ● Subject with screening number 301400305 received the first dose of the investigational vaccine on December 18, 2022. The diary card recorded that the subject experienced swelling from December 19 to December 23, and the adverse event form recorded the severity as grade 2, while the EDC entry was grade 1, which was an entry error. ● 筛选号 301400305 受试者，2022 年 12 月 18 日接种第 1 剂试验疫苗，日记卡记录 12 月 19 日至 22 日出现疲劳，不良事件表记录严重程度为 2 级。EDC 录入为 1 级，录入错误。 ● Subject with screening number 301400305 received the first dose

	of the investigational vaccine on December 18, 2022. The diary card recorded that the subject experienced fatigue from December 19 to December 22, and the adverse event form recorded the severity as grade 2, while the EDC entry was grade 1, which was an entry error. ● 筛选号 301400196 受试者，2022 年 12 月 16 日接种第 1 剂试验疫苗， 12 月 16 日至 19 日出现注射部位疼痛，研究者填写不良事件表记录该 AE 的结束时间 12 月 19 日，EDC 录入结束时间为 2022 年 12 月 18 日。 ● Subject with screening number 301400196 received the first dose of the investigational vaccine on December 16, 2022, and experienced injection site pain from December 16 to December 19. The investigator recorded the AE end time as December 19 when filling out the adverse event form, while the end time entered in the EDC was December 18, 2022.
整改措施 Rectification measures	EDC 录入及时准确。 EDC entry should be timely and accurate.

问题 3 Issue 3	**不良事件表与日记卡记录不一致 Inconsistency between the adverse event form and diary card records**
问题描述 Issue description	● 筛选号 301400098 受试者，2022 年 11 月 25 日接种第 1 剂试验疫苗，受试者在日记卡记录 11 月 25 日-12 月 2 日出现疲劳，严重程度 1 级。不良事件表记录严重程度 2 级。 ● Subject with screening number 301400098 received the first dose of the investigational vaccine on November 25, 2022. The subject recorded fatigue from November 25 to December 2 in the diary card, grade 1 in severity. The adverse event form recorded severity as grade 2.

	● 筛选号 301400399 受试者，2023 年 2 月 8 日接种第 3 剂试验疫苗，日记卡记录 2 月 14 日至 15 日出现“焦虑”，严重程度 2 级，不良事件表与 EDC 记录该不良事件严重程度为 1 级。 ● Subject with screening number 301400399 received the third dose of the investigational vaccine on February 8, 2023. The diary card recorded “anxiety” from February 14 to February 15, grade 2 in severity. The adverse event form and EDC recorded the severity of the adverse event as grade 1.
整改措施 Rectification measures	仔细核对确保记录准确。 Carefully check to ensure that the records are accurate.

问题 4 Issue 4	**COVID-19 病例分类问题 COVID-19 case classification issue**
问题描述 Issue description	**方案规定研究者根据 NMPA 于 2022 年 3 月 15 日发布的最新《COVID-19 诊断和治疗方案（试行第 9 版）》对 COVID-19 病例进行分类。其中轻型：临床症状轻微，影像学未见肺炎表现；普通型：有发热、呼吸道症状等，影像学可见肺炎表现。**筛选号 301400244 受试者，2023 年 2 月 3 日接种第 3 剂试验疫苗。2 月 19 日出现发热、寒颤、咳嗽、鼻塞， RT-PCR 结果阳性，诊断 COVID-19。未进行影像学检查就临床分型为轻型。建议研究者记录体格检查结果（重点是肺部），以支持不进行影像学检查。对于有明显临床症状的，如咳嗽、发热持续时间较长，建议进行影像学检查，为病例严重程度评级提供充分依据。类似情况还见于筛选号 301400117 受试者。 **The protocol stipulates that investigators should classify COVID-19 cases according to the latest *COVID-19 Diagnosis and***

	Treatment Protocol (Trial Version 9) **released by the NMPA on March 15, 2022, wherein mild: mild clinical symptoms, no signs of pneumonia on imaging; moderate: with fever and respiratory symptoms, etc., and signs of pneumonia on imaging.** Subject with screening number 301400244 received the third dose of the investigational vaccine on February 3, 2023, and experienced fever, chills, cough and nasal obstruction on February 9. The RT-PCR result was positive, and the subject was diagnosed with COVID-19, and clinically classified as mild without imaging examinations. It is recommended that investigators record the results of physical examination (focusing on lungs) to support the exemption of imaging examination. For patients with significant clinical symptoms, such as cough and fever, which last for a long time, it is recommended to perform imaging examination to provide sufficient basis for the severity grading of the case. Similar situations were also seen in subject with screening number 301400117.
整改措施 **Rectification measures**	依据《COVID-19 诊断和治疗方案（试行第 9 版）》标准，通过必要的技术手段，准确进行临床分型。 According to the *COVID-19 Diagnosis and Treatment Protocol (Trial Version 9)*, perform accurate clinical classification through necessary technical means.

问题 5 **Issue 5**	记录问题 **Recording issue**

问题描述 **Issue description**	● 筛选号 301400122 受试者，2022 年 12 月 20 日接种第 2 剂试验疫苗，《访视记录表》第 3 次访视中延迟接种说明中，记录下次接种时间：2022 年 1 月 24 日。记录错误，应写 2023 年 1 月 24 日。 ● Subject with screening number 301400122 received the second dose of the investigational vaccine on December 20, 2022. In the explanation for delayed vaccination at Visit 3 in the *Visit Record Book*, the time of the next vaccination was recorded as January 24, 2022, which was a mistake. It should be January 24, 2023. ● **筛选号 301400244 受试者，COVID-19 病例评估表中记录国家实验室的 RT-PCR 报告，其样本勾选送至"当地实验室"，请核对。** ● **Subject with screening number 301400244: The national laboratory's RT-PCR report was recorded in the COVID-19 case assessment form, but "sent to the local laboratory" was checked for the sample. Please verify.** ● 筛选号 301400117 受试者，2022 年 12 月 21 日出现疑似 COVID-19 相关症状，12 月 23 日当地实验室 RT-PCR 阳性后送样本至国家实验室。COVID-19 病例评估表记录送国家实验室的样本为口咽+鼻咽拭子，与本试验要求的采样方式不符，请核实。 ● Subject with screening number 301400117 presented with suspected COVID-19-related symptoms on December 21, 2022, and the samples were sent to the national laboratory after the RT-PCR result in the local laboratory was positive on December 23. The COVID-19 case assessment form recorded that the samples sent to the national laboratory were oral + nasopharyngeal swabs, which did not conform to the sampling method required for the trial. Please verify. ● 筛选号 301400062 受试者，V3（2022 年 12 月 16 日）接种第 2 剂试验疫苗，《访视记录本》中记录预约的 V4 日期为 2023 年 1

	月 14 日，依据方案要求 V4（V3+21 天）到访日期应为 2023 年 1 月 6 日，为何准确到超窗日期 2023 年 1 月 14 日，请合理解释。 ● Subject with screening number 301400062 received the second dose of the investigational vaccine at Visit 3 (December 16, 2022). The appointed V4 date recorded in the *Visit Record Book* was January 14, 2023. According to the protocol requirement, the V4 (V3 + 21 days) date should be January 6, 2023. Why was the date accurately determined to be January 14, 2023 beyond the window? Please give a reasonable explanation.
整改措施 **Rectification measures**	确保研究资料记录的及时性、准确性、完整性。 Ensure the timeliness, accuracy and completeness of study data records.

问题 6 **Issue 6**	**日记卡问题** **Diary card issue**
问题描述 **Issue description**	● 筛选号 301400211 受试者，2022 年 12 月 16 日接种第 1 剂试验疫苗，日记卡记录自 12 月 16 日至 23 日每日体温均为 36.6℃，连续 7 天体温一致，请研究者与受试者核实确认是否为实测体温。 ● Subject with screening number 301400211 received the first dose of the investigational vaccine on December 16, 2022. The diary card recorded the body temperature everyday from December 16 to December 23 was all 36.6 ℃, consistent for 7 consecutive 7 days. The investigator is requested to verify and confirm with the investigator whether the body temperature was actually measured body temperature. ● 筛选号 301400449 受试者，访视 3 日记卡（非征集）联系电话未填写。 ● Subject with screening number 301400449: The contact number in the Visit 3 diary card (unsolicited) was not filled in.

	● 筛选号301400090受试者，第3次访视时未发放新的日记卡（非征集），仍用第2次访视的日记卡（非征集）记录至第3剂接种前发生的非征集性不良事件。类似情况还见于筛选号301400084、301400132、301400017、301400251、301400114、301400045、301400058、301400268、301400088受试者。**方案要求：**访视3需完成以下事项：回收首剂接种后7天内的征集性不良事件的日记卡和首剂接种后至第2剂接种前发生的非征集性不良事件的日记卡。发放新的受试者日记卡用于记录第2剂接种后7天内发生的征集性不良事件和至第3剂接种前发生的非征集性不良事件。 ● Subject with screening number 301400090: No new diary card was distributed at Visit 3 (unsolicited), and the subject was still using the Visit 2 diary card (unsolicited) to record unsolicited adverse events that occurred before the third dose of vaccination. Similar subjects were also seen in subjects with screening numbers 301400084, 301400132, 301400017, 301400251, 301400114, 301400045, 301400058, 301400268 and 301400088. **Protocol requirement:** the following items should be completed at Visit 3: the diary card on solicited adverse events within 7 days after the first vaccination and diary card on unsolicited adverse events that occur after the first dose and after the second dose of vaccination should be recovered, and a new subject diary card should be distributed to record solicited adverse events that occur within 7 days after the second dose of vaccination and unsolicited adverse events that occur before the third dose of vaccination.
整改措施 Rectification measures	教育受试者按要求填写日记卡，提高研究者审核日记卡质量。 Educate subjects to fill out diary cards as required, and improve the quality of the investigator's review of diary cards.

问题 7	**资料问题**

issue 7	Data issue
问题描述 Issue description	筛选号 301400130 受试者，2022 年 11 月 26 日参加筛选，当天采集核酸，核酸报告中样本采集时间为：2004 年 8 月 26 日 16：12，请核实。 Subject with screening number 301400130 participated in screening on November 26, 2022, and nuclear acid sampling was performed on the same day. The sample collection time was 16:12 on August 26, 2004 in the nuclear acid report. Please verify.
整改措施 Rectification measures	收集检测报告。 Collect the test report.
问题 8 Issue 8	修改问题 Modification issue
问题描述 Issue description	● 筛选号 301400058 受试者，2022 年 11 月 20 日 18：37 接种第 1 剂试验疫苗，访视记录本记录在中心结束观察的时间为 19：05，修改为 19：07。修改前不满足观察 30 分钟的要求，修改后满足观察 30 分钟的要求，建议备注修改理由。 ● Subject with screening number 301400058 received the first dose of the investigational vaccine at 18:37 on November 20, 2022. The *Visit Record Book* recorded that the end time of observation at this site was 19:05, which was modified to 19:07. It did not meet the requirement for 30-minute observation before modification, and met the requirement after modification. It is recommended to specify the reason for modification. ● 筛选号 301400268 受试者，知情同意书“是否同意进入免疫亚组”处由是改为否，无修改人签名及日期。 ● Subject with screening number 301400268: In the informed consent form, “Yes” was changed to “No” for “whether you agree to

	enter the immunogenicity subgroup" in the informed consent form, but there was no signature or date of the modifier.
整改措施 **Rectification measures**	加强对研究者培训，按要求进行规范修改。 Strengthen training of investigators, and standardized modifications as required.

问题 9 **Issue 9**	溯源问题 **Traceability issue**
问题描述 **Issue description**	● 本现场尿妊娠试验均未留存检测结果照片。 ● No photos of urine pregnancy test results were retained at this site. ● 本中心自筛选号 301400160 之前入组的受试者未留存快速抗原检测结果照片。 ● The photos of rapid antigen test results of subjects enrolled before screening number 301400160 at this site were not retained.
整改措施 **Rectification measures**	按要求落实拍照，妥善留存。 Take photos as required, and properly retain the photos.

问题 10 **Issue 10**	文件夹问题 **Files issue**
问题描述 **Issue description**	● **疫苗管理问题。**有俄罗斯配送公司到3014中心的运输记录，没有看到中国到俄罗斯疫苗派送公司的记录。 ● **Vaccine management issue.** There were records of transportation from the Russian distribution company to Site 3014, but no records of transportation from China to the Russian vaccine distribution company were found. ● **无CRO营业执照。** ● **There was no CRO's business license.**

整改措施 **Rectification measures**	收集补充资料。 Collect supplementary data.

质控签署页

Quality Control Signature Page

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