**Research on the Effects of the Global Static Management Policy against COVID-19 in 2022 on Clinical Trials in Shanghai**

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**Title page**

**What is known about subject?**

In order to against COVID-19, strict isolation measures had been put into effect. However, it’s not known how clinical trials suffered from global static management policy against this kind epidemic.

**What this study adds?**

The global static management policy against COVID-19 in Shanghai in 2022, caused serious effects on the local clinical trials. And the transformation to a new model of patient-centered by the means of the intelligent clinical trial system, might help clinical trials to cope with this kind of major public health events.

**Abstract:**

**Aims:** Toimprove the countermeasures of clinical trial institutions against major public health events such as COVID-19.

**Methods:** A questionnaire was created to investigate the effects of the global static management policy against COVID-19 on clinical trials in Shanghai in 2022. And the convenience sampling combined with snowball sampling were adopted to interview clinical research coordinators (CRC) and clinical research associates(CRA) on the platform of SOJUMP as well as WeChat.

**Results:** 156 valid questionnaires were collected, with an effective recovery rate of 93.98%. 98.07% of the respondents believed that the effects was severe. The extent of effects on different links of clinical trials was different (rank sum test P<0.01), being great on medication/follow-up (76.28% of significant effects), monitoring/audit (74.36%) and screening/admission (71.79%).The protocol deviations associated with out of visit window (experienced by 94.23% of respondents, during the static management policy), inspection (78.85%), medication (67.95%) and withdrawal (62.82%). And the interviewees reported 49.66% of the exclusion should blame the epidemic situation. The development of online-office or remote-ethics meetings alleviated the impact of lockdown policy on approval/ethics/contract and data cleaning/site closing. 90.98% of oral drugs could be sent by express delivery, but only 1.28% had the experience of online informed consent and remote inspection.

**Conclusions:** We shall speed up the application of the intelligent clinical trial system and remote monitoring system, realize the transformation to a new model of patient-centered clinical trial, and improve the ability to cope with major public health events such as COVID-19.

**Key Words**: COVID-19, Clinical Trial, Shanghai, Questionnaire, Static Management Policy

**Introduction**

Coronavirus Disease 2019 (COVID-19 for short) has spread throughout the world, mainly by means of droplets, contact and other ways[1] . The clinical drug trial refers to any systematic drug research in human body (healthy volunteers or patients), which is a necessary link for new drugs to be launched. In China, the clinical drug trial institutions are the body to protect the rights and interests of subjects. Institutions and research investigators need to identify risks and hidden dangers in time, strive to maximize the benefits of subjects and avoid harm as much as possible, and always put the safety, health and rights and interests of subjects in the first place [2] . In March 2022, COVID-19 situation in Shanghai was extremely severe, for which the country adopted strict lockdown measures. At the end of March, the whole city went into a state of static management successively. Due to the limited medical treatment of the subjects, visits and medication were affected, thus greatly affecting the clinical drug trials. By investigating the implement of clinical drug trials during the global static management for COVID-19 from March to June, 2022, the paper probed into the scope and extent of effects, and the corresponding measures, and collected relevant suggestions and opinions, to protect the legitimate rights and interests of subjects in the event of similar major public health events, safeguard the scientific and standardized clinical trials, and provide reference and guidance for the future informatized development of clinical trials.

**1.Methods**

**1.1 Respondents**: The participating Clinical Research Associates (CRAs) and Clinical Research Coordinators (CRCs) in Shanghai Clinical Research Center from March to June, 2022.

**1.2 Questionnaire Design:** With reference to the literature of clinical trials and research during COVID-19 [3-5], the draft of the questionnaire was firstly made for further distribution in a small scale, and then the opinions of senior CRCs and CRAs were adopted for further revision, and in the end, the formal questionnaire was finalized. Through the reliability analysis of SPSS25.0, the value of Cronbach’s alpha, α (or coefficient alpha), was 0.617, and the reliability level was satisfactory (>0.6).This questionnaire includes three aspects: Basic information, effects, and countermeasures, as shown in Table 1.

**Table 1 Topics**

|  |  |
| --- | --- |
| **Classification** | **Title** |
| I. Basic Information | 1. Role (CRC/CRA) |
| 2. Number of Clinical Research Sites in Shanghai |
| 3. Trial Type |
| 4. Number of Trials |
| 5.Trial Status |
| II. Effects on the Clinical Trial Items | 6. Overall Extent of Effects |
| 7. Effects on Approval/Ethics/Contract/Screening for Admission/Medication and Follow-up/Monitoring and Audit/Site Closing. |
| 8. Reasons Why the Subjects Could Not Visit the Research Center |
| 9. Reasons Why the Subjects Are Excluded |
| 10. Reasons for Protocol Violation |
| 11. Change in the Incidence Rate of Severe Adverse Events |
| III. Countermeasures | 12. Online Approval and Ethics Review |
| 13. Online Informed Consent |
| 14. Remote Monitoring |
| 15. Way to Get the Trial Drugs |
| 16. Visit and Inspection |
| 17. Comments and Suggestions |

**1.3 Survey Methodology**: The questionnaire was firstly developed by virtue of SOJUMP, and then forwarded to the work group of WeChat for the further completion in an anonymous way by means of snowballing , during the period from August 8 to August 14, 2022. Besides the on-line relay of the questionnaire link, the QR code of SOJUMP was posted at the reception position of the site office for the visiting staff to answer and relay.

**1.4 Analysis Method**: (1) Investigate the extent of effects of COVID-19 in Shanghai on clinical trials, the differences in the extent of effects on different segments, and the relationship between the extent of effects and the identity of respondents and the numbers of respondents’ items and sites. (2) The correlation between the reason for exclusion, violation, out of visit window, and delayed medication and the epidemic was analyzed. (3) Seek relevant strategies.

**1.5 Statistical Processing:** SPSS25.0 statistical software was used to process the data, and the count data were expressed as rate (%). The χ2 test was conducted for row × column crosstab, and the rank sum test was used for graded data (Mann-Whitney U test for two samples), and it was considered as having a statistical difference in case of *P*<0.05.

**2. Results**

**2.1 Extent of Effects**

A total of 166 questionnaires were collected, with 156 valid questionnaires, and the effective recovery rate was 93.98%, of which 10 invalid papers were from non-Shanghai places, the basic information of the investigated personnel and clinical trial programs they charging, is shown in Table 1. As of August 2022, there were 67 clinical research sites with registered addresses in Shanghai on the “filing platform” of the National Medical Products Administration’s drug clinical trial institutions, of which 18 major sites, who undertook more than 90% of total clinical trial items in Shanghai, were covered by the data in the research. 86 respondents deemed the effects of the static management policy against the epidemic on clinical trials as “serious” (55.13%), 67 as “fair” (42.94%), and 3 as “not applications” (1.92%). The selection on severity was not associated with the role of respondents in the experiment, the number of responsible sites, item status, and the type and quantity of items undertaken, as shown in Table 2. The extent to which different links are affected was different (rank sum test, P<0.01), as shown in Table 3.

**Table 2 Basic Situation and Extent of Effects**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Basic Situation** | **Options** | **Number of Cases** | **Composition ratio (**%) | **Extent of Effects** | | | | |
| **Significant Effects** | **Average Effects** | **NA** | **Statistics\*** | *P* Value |
| Division of Labor | CRC | 64 | 41.03 | 33 (59.38)# | 26 (40.63) | 0 (0.00) | 2,693.000 | 0.297 |
| CRA | 92 | 58.97 | 43 (52.17) | 40 (44.57) | 3 (3.26) |
| Number of Sites in Shanghai | 1 | 37 | 23.72 | 20 (54.05) | 17 (45.95) | 0 (0.00) | 2.320 | 0.314 |
| 2 | 36 | 23.08 | 15 (41.67) | 21 (58.33) | 0 (0.00) |
| 3 | 29 | 18.59 | 18 (62.07) | 10 (34.48) | 1 (3.45) |
| 4 | 25 | 16.03 | 12 (48.00) | 11 (44.00) | 2 (8.00) |
| 5 Or above | 29 | 18.59 | 21 (72.41) | 8 (27.59) | 0 (0.00) |
| Status | Approval/ethics/Contract/Conclusion | 34 | 21.79 | 16 (47.06) | 17 (50.50) | 1 (2.94) | 1,852.000 | 0.272 |
|  | Screening for Admission /medication/follow-up | 122 | 78.21 | 70 (57.38) | 50 (40.98) | 2 (1.64) |
| Item Type | Drug Phase I | 52 | 33.33 | 32(61.54) | 18(34.62) | 2(3.85) | 1.753 | 0.416 |
| Drug Phases II-IV | 90 | 57.69 | 52(57.78) | 37(41.11) | 1(1.11) |
| Medical Device | 14 | 8.97 | 9(64.29) | 5(35.71) | 0(0.00) |
| Reagent for Clinical Diagnosis | 5 | 3.21 | 5(100.00) | 0(0.00) | 0(0.00) |
| Number of Items | 1 | 42 | 26.92 | 21(50.00) | 20(47.62) | 1(2.38) | 4.915 | 0.426 |
| 2 | 39 | 25.00 | 23(58.97) | 15(38.46) | 1(2.56) |
| 3 | 24 | 15.38 | 13(54.17) | 11(45.83) | 0(0.00) |
| 4 | 3 | 1.92 | 2(66.67) | 1(33.33) | 0(0.00) |
| 5 Or above | 14 | 8.97 | 11(78.57) | 3(21.43) | 0(0.00) |

Notes: \* Regarding the statistics of rank sum test, the Mann-Whitney U test was adopted for two independent samples, while the Kruskal-Wallis H test for multiple independent samples.

#Among the 64 CRCs researched, the number of those who chose “significant effects” was 33, and the percentage was 33/64=59.38%.

Table 3 Extent of Effects on Different Links

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Link** | **Significant Effects** | **General Effects** | **NA** | **Kruskal-Wallis H** | ***P* Value** |
| Approval/Ethics/Contract | 75(48.08) | 68(43.59) | 13(8.33) | 37.386 | 0.000 |
| Screening for Admission | 112(71.79) | 34(21.79) | 10(6.41) |
| Medication/follow-up | 119(76.28) | 34(21.79) | 3(1.92) |
| Monitoring/Audit | 116(74.36) | 35(22.44) | 5(3.21) |
| Data Cleaning/Site Closing | 107(68.59 | 42(26.92) | 7(4.49) |
| **Overall** | 86 | 67 | 3 |

**2.2 Reasons for Effects**

The reasons for an inability to visit the research centers lied in different geographical lockdowns or inconvenience of transportation, as shown in Table 4. 98.08% constituted a protocol violation, as shown in Table 5. The reasons why the subjects were excluded generally included, the disease progression, voluntary exclusion or absence or noncompliance of the subjects themselves, and serious adverse reactions, etc. The research results showed that the percentage of exclusion due to a failed inspection/medication research by virtue of epidemic policy was 49.66% ± 32.66%. However, 74.59% believed that the number of SAEs was not higher than that before the outbreak.

**Table 4 Lockdown Reasons for an Inability to Visit the Site**

|  |  |  |
| --- | --- | --- |
| **Reasons for an Inability to Visit the Site** | **Number of Cases** | **Percentage (%)** |
| The residential area of the subject had been locked down. | 139 | 89.10 |
| The research site had been locked down. | 130 | 83.33 |
| The subject was at the non-local place and could not return to Shanghai. | 123 | 78.85 |
| The subject was in Shanghai, but there was no available transportation to visit the research center. | 98 | 62.82 |

**Table 5 Reasons for Violation**

|  |  |  |
| --- | --- | --- |
| **Reason for Violation** | **Number of Cases** | **Percentage (%)** |
| Associated with out of visit window, such as the delayed time of visit or certain inspection procedures delayed. | 147 | 94.23 |
| Associated with inspection, e.g., tests not done or incomplete, etc. | 123 | 78.85 |
| Associated with medication, e.g. an inability to obtain drugs, etc. | 106 | 67.95 |
| Violation such as the subject’s drop-out/loss to follow-up. | 98 | 62.82 |

**2.3 Solutions**

2.3.1 Trial Drugs/Inspection

The access to drugs and inspections is shown in Table 6. In addition, for access to oral drugs, 60.66% of the respondents indicated that the oral drugs for the subjects were sent via courier, 23.77% were both courier and personal take-over, 9.02% were personal take-over by the patients only, and the remaining 6.55% were non-accessible or otherwise non-applicable.

**Table 6 Access to Trial Drugs/Follow-up Inspections (Number of Cases/Percentage %)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Research Coverage | The Research Site | Other Research Site | Warehouse | Local Medical Unit | Telephone Follow-up |
| Oral Drug | 92 (75.41%) | 47 (38.52%) | 48 (39.34%) | NA | NA |
| Injectable Drug | 76 (62.30%) | 39 (31.97%) | NA | 26 (21.31%) | NA |
| Inspection | 88 (72.13%) | 76 (62.30%) | NA | 59 (48.36%) | 79 (64.75%) |

2.3.2 Information System: Of the respondents, 80.13% had participated in the online approval/ethic meetings, but only 1.28% had the experience of online informed consent and remote inspection. 82.69% indicated that monitoring/audit had to be postponed, 10.26% had relevant experience with remote monitoring, and only 7.05% could do the job on site.

2.3.3 Comments and Suggestions: Out of 156 valid questionnaires, 56 comments were returned, as shown in Table 7.

**Table 7 Comments and Suggestions for Conducting Clinical Trials under COVID-19 Policy**

|  |  |
| --- | --- |
| **Comments and Suggestions** | **Number of cases (percentage %)** |
| Remote Monitoring System | 16 (28.57%) |
| Extranet Transmission of Information & Online Approval/Ethic Meeting | 12 (21.43%) |
| Available Monitoring on Site, with Clear Reception Policy. | 8 (14.29%) |
| Green Channel for Clinical Trials during the Outbreak | 6 (10.71%) |
| Intelligent Clinical Trial & Online Medical Records | 6 (10.71%) |
| Medication by Other Medical Institution (Injectable Drugs) & Oral Drugs Sent | 6 (10.71%) |
| SMO Providing CRCs to Assist in the Daily Epidemic Registration and Management | 2 (3.57%) |

**3 Discussion**

**3.1 Effect Analysis**

The literature research revealed that the participation of medical staff in fighting against COVID-19 or their isolation caused a shortage of health care resources, and coupled with the prevailing lockdown and isolation policy, the clinical trial work in many sites was almost semi-suspended at the beginning of the outbreak in 2020, and the clinical trial progress was therefore greatly affected (68.24%) [6] . Reviewing the literature, the effects of COVID-19 on clinical research were specifically demonstrated in [3-4] : clinical trial approval, ethical review meetings and trial item initiation were suspended; the face-to-face informed consent with the subject was limited, screening for admission progressed slowly, and the subject was unable to visit on schedule or delayed in follow-up to ensure the efficacy assessment and safety appraisal, thus resulting in protocol violation; item quality control, audit, monitor and conclusion were all in trouble. All these have significant effects on the quality of clinical trials and the rights and interests of subjects. Compared with device and diagnostic reagent clinical trials, drug clinical trials suffered a greater effect, with non-oral drug clinical trials much more than oral drugs, and oncology patients were more dependent on the treatment and much more greatly affected [6] .

The lockdown policy against COVID-19 in Shanghai in the first half of 2022 was different from the former policy against the epidemic. Since March 28, Pudong and Puxi had initiated the global static management successively and maintained it till May 31, totally two months of fully-covered management and control which had significant effects on clinical trials. 98.07% of the respondents in the research believed that the effect was severe (55.13% believed that the effect was very severe), regardless of the role of the respondent, or the phase, the type, or the number of the clinical trial items. In addition, the isolation control measures such as residential area lock-down, hospital lock-down, and traffic control had a great effect on medication/follow-up, monitoring/audit, and screening for admission, with the percentage of significant effects all >70%, thus resulting in a percentage of exclusion at nearly 50% by virtue of epidemic policy due to the frequent violations such as incomplete inspections, inaccessible drugs, and the subject’s drop-out. On the contrary, the effects on the pre-initiation and closing items were less thanks to the extensive implementation of online approval/ethic meetings, but the effects on screening for admission and inspection/audit were significant because online informed consent and remote monitoring were very limited.

**3.2 Domestic and International Policies**

Article 49 of the new version of GCP (by NMPA, 2020) proposed that, under the centralized monitoring, the data trend may be identified by applying the statistical analysis, including the scope and consistency of data within and between different clinical trial institutions, and may analyze the characteristics and quality of data, which was beneficial for selecting the monitoring sites and procedures [2] . On July 14, 2020, the Center for Drug appraisal of NMPA released the Guidelines for the Management of Drug Clinical Trials During COVID-19 Epidemic (Trial) [7], emphasizing the subject-centered clinical trials with the help of intelligent clinical trial management platforms and remote communication technologies. On March 26, 2021, Center for Drug Evaluation, NMPA, held a workshop on remote intelligent clinical trials, where in-depth exchanges were communicated on such hot issues as patient recruitment, remote visit, electronic source data, remote monitoring and safety information management of remote intelligent clinical trials, and scientific strategies for safety supervision of remote intelligent clinical trials were preliminary discussed. On August 9, 2022, Center for Drug Evaluation released the “Technical Guidelines for the Implementation of Patient-Centered Clinical Trials” for public comments [8], proposing the model of Decentralized Clinical Trial (DCT), an optional novel model for clinical trials being patient-centered and not limited to the traditional sites for the implementation of clinical trials, such as visiting the subject’s home or other medical institution near the subject’s residence, telephone or video visits, etc.; Internet platform recruitment, the intelligent recruitment based on big data of patient information; Electronic or remote informed consent; for some drugs that can be administered orally or can be administered at home, direct-to-patient (DTP) could be considered. for the drugs that can be administered orally or can be self-administered at home, the Direct to Patient (DTP) approach could be considered, whereby the drug for research would be delivered directly to the subject and the remaining drug be collected after the subject has administered the drug according to the protocol; for the drugs that require the help from healthcare professionals, such as intravenous infusions, the DTP approach combined with home visits could be used to administer the treatment at the subject’s home under certain circumstances; and patient experience data should be collected with the application of digital health technologies, etc.

In March 2020, the European Medicines Agency (EMA) issued guidance [9] that provides for a series of responses to simplify or replace clinical trial procedures, such as home visits for those subjects who cannot visit the institution, and recommends the use of communication devices or other electronic medical technologies for remote visits. In August 2021, the U.S. Food and Drug Administration (FDA) revised the Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency [10], and the appendix thereto clarifies the response measures for protecting subjects and managing clinical trials during an epidemic in a question-and-answer format, including remote informed consent, drug distribution by mail, remote visits, remote clinical outcomes appraisal, remote monitoring, etc. Compared to Europe, the U.S. guidelines provide more detailed and operational alternative processes for trials, such as remote informed consent, where a photo of the signed informed consent can be transmitted to trial staff, or via telephone recording or video conferencing, and apply not only during COVID-19, but also to clinical trials and other public health emergencies[3] .

**3.3 Response Measures**

The literature report indicated [3-4, 7, 11-13] that, more and more clinical research centers are practicing patient-centered clinical research procedures: improving the non-face-to-face informed consent process by using electronic informed consent via mail or telephone, etc.; using alternative visiting or appraisal methods, such as visiting the nearest medical institution or other research site, holding video conferences for remote visit, or conducting a community visit at subject’s home; trial drugs direct to patient by mail; the use of digital technology for clinical trial data collection or management through integrated clinical research platforms, electronic health source data collection, linkable device data monitoring, and remote intelligent systems.

Jiang Yun et. al. [4] categorized and managed visits according to whether oncology subjects needed intravenous drug administration, whether the visit required only safety check or efficacy appraisal, whether the visit required intensive blood collection, and whether the visit could be done by telephone. The nearby visits, return to hospital, and telephone visits were performed, respectively, and it was found that the difference between return to hospital and visit completion rate was not statistically significant (*P*=0.472).

Besides, in addition to adopting new technologies and ideas, we can also keep up with the times in terms of management mechanisms, such as issuing timely notices and guidelines for clinical trial implement by management office at clinical trial sites, streamlining workflow, and initiating online offices or meetings. Supervision should be strengthened to appraise clinical trial research group for researcher isolation and support, rationalize institutional project quality control, and provide regular feedback and timely handling of clinical trial drug dispatch, subject safety information, violations, and many other practical work issues [6] .

**3.4 Problems and Outlook**

In addition to COVID-19, major public health emergencies may significantly affect the implement of clinical trials, clinical research should be transformed from the traditional “institution-centered” clinical research model to a new “patient-centered” model by means of information technology [7, 13-15] .

Clinical trial data sharing is an inevitable trend to promote the development of clinical trials, and to improve the quality of clinical trials worldwide [15-16] . However, if data management and statistical analysis are to be managed electronically, it is necessary to solve the problems of system segmentation and information system silos that exist for various electronic source data, to achieve interoperability of electronic clinical data resources across institutions, regions, and fields , and to establish a unified clinical data standard system before study implementation as much as possible to avoid additional data mapping efforts to improve data quality [14] .

In addition, it has been suggested [5, 11] that cross-site visits or visits to the nearest medical institution is an issue that requires a balance between scientific and ethical aspects. Visit protocols need to be evaluated and approved by the ethics committee before implementation. The staff conducting remote visits should be trained before the real-time video-conferencing visits. That procedures should be properly provided to maintain the privacy of subjects. Consideration also needs to be given to whether blinding of the experimental design will be compromised, and the issues such as the feasibility of a randomized talk system, but the trial design itself should not deprive subjects of the opportunity to potentially continue to receive the benefits of the trial drug treatment.

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