China DCT Regulation and Implementation[1]

Authors: Aaron GU | Pengfei YOU | Duzhiyun ZHENG | Fengqi YU[2]

The concept of "patient-centered" has become the core guiding principle in current research and development ("**R&D**") of drugs. "Patient-centered" drug R&D refers to the process of drug discovery, design, implementation and decision-making based on the patient's point of view, with the aim of efficiently developing clinically valuable drugs that better meet the needs of patients. Decentralized Clinical Trials ("**DCT**") are a new type of clinical trial that embodies the "patient-centered" concept, providing new solutions and motivation for drug R&D activities for marketing registration purposes. According to the *latest Technical Guidelines for the Implementation of Patient-Centered Drug Clinical Trials (for Trial Implementation)* ("*Technical Guidelines for Implementation")* released by the Center for Drug Evaluation ("**CDE**") of the National Medical Products Administration ("**NMPA**") on July 27, 2023, DCT refers to a new patient-centered clinical trial model, the implementation of which is not limited to the traditional on-site clinical trials. In simple terms, usually, DCT would be conducted using telemedicine as well as mobile or local medical care, allowing clinical trials to take place remotely while the subjects can remain at home.

Compared with traditional on-site clinical trials, DCT has several advantages. For instance, it significantly reduces the burden on the subjects, enabling them to participate even if they cannot visit the site in person. It also enhances the representativeness of the subjects and breaks the traditional limitations on the frequency of subject visits, thus gathering more comprehensive clinical data. Furthermore, DCT may reduce the errors caused by human intervention or data transcription, thus improving the quality of clinical trials. However, due to uncertainties such as the complexity of the new processes and technology operations, the practice of DCT may also present challenges such as the uniformity of clinical trial evaluation standards, data integrity, comparability of results, and operational standardization, etc.

DCT has already been practiced in some Western countries. As early as June 2011, Pfizer announced its first "virtual" clinical trial, aiming at conducting the first-ever randomized clinical trial under an investigational new drug ("**IND**") application that manages study participation entirely using electronic tools

[1] For the Chinese version, please click 《*汉坤 • 观点 | 中国DCT(去中心化临床试验)的实施与监管*》.

[2] Leyi Wang and Shuwen Sun have contributions to this article.

and allows patients to participate in the clinical trial regardless of their proximity to clinical sites[3]. The outbreak of the COVID-19 pandemic in early 2020 posed significant challenges to global drug clinical trials, but it also accelerated the rapid development of DCT. To address issues related to the conduction of clinical trials during the pandemic, the US Food and Drug Administration ("**FDA**") released the *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards* in March 2020, providing regulatory guidance for issues such as electronic signatures and remote monitoring in the conduction of DCT. Recently, the FDA also issued a draft guidance titled Decentralized Clinical Trials for Drugs, Biological Products, and Devices, which specifically focused on the compliance issues for implementing DCT. Moreover, some countries and regions such as the European Union, Canada, Denmark, and Sweden have also issued DCT-related guidance documents.

In China, although the practices are not yet abundant, the industry has been actively exploring the implementation of DCT in recent years. For example, in 2022, an expert consensus on the conduction of remote intelligent clinical trials was released to provide references for exploring DCT compliance in China. The development of DCT has also received support from regulatory authorities. In recent years, regions such as Beijing have been continuously encouraging DCT pilot projects in various policies. On July 27, 2023, after nearly a year of solicitation of public opinions, CDE formally released the three documents: Technical Guidelines for the Design of Patient-Centered Drug Clinical Trials (for Trial Implementation), Technical Guidelines for the Implementation of Patient-Centered Drug Clinical Trials (for Trial Implementation), and Technical Guidelines for the Benefit-Risk Assessment of Patient-Centered Drug Clinical Trials (for Trial Implementation). Among them, the Technical Guidelines for Implementation have provided crucial guidance for DCT compliance in China. Compared with its previous draft for public comments, the formally adopted Technical Guidelines for Implementation have more explicitly reflected the regulatory authorities' embracing openness while maintaining cautious supervision regarding the practice of DCT. It emphasizes that new models such as DCT may be adopted subject to evaluation by the sponsors, investigators, and clinical trial sites, and that such new models and new methods should be pre-set in the protocols and shall comply with regulations such as the Good Clinical Practice ("**GCP**") and shall be approved by ethics committees. New models and new methods shall not be blindly pursued without exploring their rationality, necessity, and feasibility.

To facilitate the recognition and management of legal risks in the implementation of DCT, the following section will, based on the Technical Guidelines for Implementation and other regulations closely related to clinical trials, explore and discuss the compliance and regulatory issues for conducting DCT in China. The key points cover various aspects including responsibilities of sponsors and investigators, electronic informed consent, telemedicine, drug distribution, privacy and personal information protection, and handling of safety incidents.

[3] See *Pfizer Conducts First "Virtual" Clinical Trial Allowing Patients to Participate Regardless Of Geography*, https://www.pfizer.com/news/press-release/press-release-detail/pfizer_conducts_first_virtual_clinical_trial_allowing_patients_to_participate_regardless_of_geography.

Responsibilities of sponsors and investigators

As a specific form of clinical trial, DCT shall, first and foremost, comply with a series of basic laws and regulations governing clinical trials, such as the *Drug Administration Law*, *Measures for the Administration of Drug Registration*, and the *GCP*. The *Technical Guidelines for Implementation* also emphasize that the *GCP*, the guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ("**ICH**"), and other relevant guidelines shall be followed. It highlights that clinical trials shall strictly follow relevant laws, regulations, the *GCP*, and ethical requirements. Therefore, in the process of DCT, the sponsors, the investigators, and other key participants shall strictly abide by their respective responsibilities under the above-mentioned laws and regulations.

As the primary responsible party in clinical trials, the sponsors should conduct a comprehensive and thorough evaluation of the design and operation of the clinical trials and should establish a sound quality management system. As the ultimate responsible party for the quality and reliability of clinical trial data in drug registration, the sponsors should also pay attention to key issues such as the formulation of the protocols, the qualification and supervision of vendors, and the establishment of sound standard operating procedures ("**SOPs**"), to ensure the smooth conduct of the clinical trials and the successful progress of drug registration.

On the other hand, the investigators are responsible for the quality of the clinical trial and the rights and interests of the subjects. They should establish corresponding SOPs and quality management systems for the conduct of DCT and make contingency plans for potential challenges during the DCT process, such as handling safety incidents and addressing data transmission failures.

Electronic informed consent

Informed consent is an essential measure to safeguard the rights of the subjects and a prerequisite for their participation in clinical trials. In previous practice, sites and investigators usually would introduce and discuss the project face-to-face with the subjects and obtain handwritten informed consent from them. However, with the development of DCT, electronic informed consent may achieve broader application. The *Technical Guidelines for Implementation* explicitly state that electronic informed consent may be considered for clinical trials.

When implementing electronic informed consent, attention should be paid to the following matters. Firstly, regarding the effectiveness of electronic signatures, according to the *Electronic Signature Law*, electronic signatures are only recognized as legally effective and equivalent to handwritten signatures or seals when they meet certain criteria such as data exclusivity and controllability, and being capable of detecting changes in the electronic documents. To ensure the effectiveness of electronic informed consent, it is recommended to seek certification of the signature's validity from qualified electronic certification service providers. Secondly, the way of implementing electronic informed consent is crucial. By using multimedia resources, electronic informed consent has advantages in introducing the clinical trial information to the subjects in a way that is easier to accept. However, it may also raise the barrier for communicating with the subjects. Therefore, the T*echnical Guidelines for Implementation* emphasize that the investigators shall focus on real-time communication with the subjects and shall ensure the subjects'

full understanding of the content under remote conditions. They can also provide assistance or offer traditional methods to the subjects who are not familiar with or unable to use electronic informed consent. In addition, the implementation of electronic informed consent shall also comply with the *GCP*, the *Personal Information Protection Law* and other regulatory requirements while adapting to the characteristics of DCT. Therefore, special attention should be paid to fully informing the subjects about the instruction on the digital medical technologies and other new technical methods used in the clinical trial, the scope of data collection, the risks and benefits from the clinical trial, the access and scope of use of the subjects' data, and other relevant information.

Telemedicine activity

Clinical drug trials are built upon diagnosis and treatment activities, which are also carried out between the research site, the investigators and the subjects (who are also medical institutions, doctors and patients). During the implementation of DCT, investigators may conduct research through a combination of telemedicine and in-person visits. Consequently, these telemedicine activities shall also comply with regulations related to diagnosis and treatment, such as the *Administrative Measures for Internet-based Diagnosis and Treatment (for Trial Implementation)*, the *Administrative Measures for Internet Hospitals (for Trial Implementation)*, and the *Supervision Rules for Internet-based Diagnosis and Treatment (for Trial Implementation)*.

The key points of regulation for telemedicine activity include site qualifications, applicable scope of internet-based diagnosis and treatment, and quality control of diagnosis and treatment activities, among other aspects. For instance, in the process of conducting telemedicine activities for clinical trials, it is essential that the diagnosis and treatment activity are always provided directly by the doctors themselves, without delegation to artificial intelligence technology or clinical research coordinators ("**CRC**"). In recent years, the practice of CRC performing some responsibilities on behalf of doctors has led to increased risks in certain clinical trial projects, drawing attention from the industry and regulatory authorities. During the implementation of DCT, it is crucial to emphasize the doctors' responsibility and ensure the compliance of CRC involvement in the research. Additionally, the administration of online prescriptions must be stringent, prescriptions shall only be issued by the doctors and become effective after approval by pharmacists. Under no circumstances should any prescription drug be provided before the prescription is issued.

Drug delivery

With the development of DCT, the delivery of drugs for clinical trials will undergo more flexible changes. The *Technical Guidelines for Implementation* stipulate that, considering factors like drug safety and subjects' medication adherence, certain drugs can be directly delivered to the patient (Direct to Patient, DTP) in combination with some home visits (if necessary). To ensure the safety of subjects and the quality of the trial, the following key points should be considered:

- **Determine delivery methods based on specific characteristics of drugs.** When considering whether to adopt DTP, factors such as drug safety characteristics, storage conditions, routes of administration, and geographical locations of subjects should be carefully evaluated to control risks

during drug delivery and usage. For example, drugs that require intravenous infusion or interventions by physicians are generally not recommended for DTP. On the other hand, drugs that are administered orally or self-administered, with a longer shelf life and can be stored at room temperature may be suitable for DTP.

- **Strengthen sites and investigators' responsibilities for drug administration.** According to *GCP*, investigators and clinical trial sites are always responsible for drug administration during the clinical trial. Changes in the clinical trial models should not lead to relaxed administration requirements for sites and investigators. Instead, they should reinforce drug administration practices by engaging qualified third-party drug distributors, providing subject training, conducting necessary home visits, devising appropriate plans for safety events, closely monitoring safety events, actively following up on drug usage by subjects, and strictly regulating the return of unused investigational drugs.

- **Strengthen the whole process of drug safety control.** Comply with or refer to the provisions of the *Good Supply Practice* ("**GSP**"), the *Good Manufacturing Practice Appendix for Investigational Drugs*, *GCP* and other regulations related to investigational drugs and reference drugs for clinical trials. Ensure drug safety throughout the entire process of drug delivery and storage, including delivering the drugs to the subjects and storing them in the subjects' homes. Additionally, ensure that participants return any leftover drugs from the trials in a proper manner.

- **Conduct subject training.** In DCT, the significance of subjects is emphasized, and providing them with training is a crucial aspect of ensuring drug safety and maintaining the quality of clinical trials. Investigators should offer comprehensive training to subjects, covering various aspects such as drug usage methods, drug storage requirements, and countermeasures for safety events. Additionally, when providing drug guidance to subjects, investigators shall also adhere to the requirements stipulated in the trial protocol, such as implementing blinding studies.

Privacy and personal information protection

In recent years, privacy and personal information protection have emerged as significant concerns for regulatory authorities, which the industry shall pay significant attention to throughout the process of conducting DCT. This becomes particularly crucial in DCT when incorporating innovative technologies, methods, and models for collecting, storing, and processing subjects' personal information. The T*echnical Guidelines for Implementation* stress the significance of following privacy and personal information protection requirements throughout the entire process of DCT, which includes subject recruitment, trial data collection, drug delivery, data monitoring, and subject injury compensation. This shall be achieved through the compliant obtaining of informed consent, management of raw data, preservation data and data retrospectivity, data de-identification processing, administration of data access permission, and other approaches.

For example, the implementation of DCT may involve the use of innovative artificial intelligence technologies and devices for information collection, potentially involving various participants such as digital device suppliers. Therefore, when obtaining informed consent from subjects, investigators must thoroughly inform them about the privacy and personal information risks related to the use of digital

technologies. This includes providing subjects with comprehensive information about the scope and methods of using the trial data and other personal information, whether the data will be shared or reused, and the corresponding measures for confidentiality. Additionally, investigators should pay special attention to regulatory requirements regarding data exports, sensitive personal information, and important data.

Safety data monitoring and reporting

To ensure subject safety in DCT, timely monitoring and reporting of safety data are essential. The *Technical Guidelines for Implementation* recommend prioritizing the use of digital technology platforms to monitor and report subjects' safety data in real time. This can be achieved through methods such as subjects' smartphone apps, remote visit platforms, or wearable devices to collect subjects' safety data and directly transmit it to investigators.

To prevent delays in data viewing and processing during remote monitoring, the guidelines emphasize the need for a robust mechanism to handle safety data. Investigators should consider factors such as the characteristics of the investigational drug and team resources to set appropriate frequencies for viewing and processing safety data. Furthermore, investigators should inform subjects beforehand about specific circumstances in which they may contact investigators directly through phone calls or other means in case of safety events. The data monitoring platform should also have a well-developed mechanism for promptly processing severe adverse events.

Communication and training

The *Technical Guidelines for Implementation* also outline certain specific requirements for communication and training among research participants. Since DCT involves the adoption of various innovative technologies and models, practices in this area are continuously evolving and being explored. Compared to more mature traditional on-site clinical trials, effective communication among research participants becomes even more crucial in addressing challenges during DCT implementation.

Firstly, sponsors, investigators, and other parties should strengthen communication with trial subjects, especially when employing remote methods like remote visits, timely and effective communication will greatly help in understanding their needs, building a trusting relationship, and facilitating the implementation of DCT. Secondly, communication between sponsors, investigators, and contract research organizations ("**CROs**") should also be enhanced to promptly stay updated on the trials' progress, make necessary adjustments in a timely manner, and ensure the smooth implementation of DCT. Additionally, research teams should communicate with regulatory authorities in a timely manner, especially when using new technologies and models. Sponsors should provide detailed explanations regarding the necessity, scientific rationale, and feasibility of incorporating certain new elements into the DCT in the clinical trial protocol. This should include basic information about the new elements, the purpose and scenarios of their use, evaluation and validation data, comparison trial data with traditional methods, risk assessment and mitigation measures, and other relevant details.

In addition, training for investigators and subjects is also essential for the successful implementation of

DCT. Sponsors and investigators should provide comprehensive training to research staff on the methods of use, precautions, potential risks, and countermeasures for the various new technologies. This ensures that the trial is conducted properly and safely. Moreover, providing trial subjects with sufficient training will help them better understand the various new technologies and methods in DCT. It will also raise their awareness of potential risks and precautionary measures, enhance their adherence, and safeguard their rights and safety.

Conclusion

With the development of telemedicine and digital technology, the industry is actively exploring DCT, gaining increasing recognition and support from regulatory authorities. DCT is expected to provide trial subjects with improved research experiences, promote greater representativeness and diversity of clinical trial data, elevate the quality of clinical trials, and provide new avenues and impetus for innovative drug development. Despite the promising potential of DCT, it still encounters several challenges that need to be addressed before it can become a dependable alternative to traditional on-site clinical trials. Areas requiring further experience and verification include participant responsibility, effective control of safety risks, proper administration of investigational drugs, and privacy and information protection.

The issuance of the *Technical Guidelines for Implementation* and other relevant documents indicate that regulatory authorities have attached great importance to the adoption and innovation of the "patient-centered" approach in drug development. It also demonstrates the regulatory authorities' proactive exploration of DCT supervision. The industry should pay attention to the *Technical Guidelines for Implementation* and other applicable regulatory requirements to effectively identify and control legal risks throughout the DCT process. We eagerly look forward to collaborative efforts between regulatory authorities and the industry to drive the successful implementation and advancement of DCT in China.

Important Announcement

This Legal Commentary has been prepared for clients and professional associates of Han Kun Law Offices. Whilst every effort has been made to ensure accuracy, no responsibility can be accepted for errors and omissions, however caused. The information contained in this publication should not be relied on as legal advice and should not be regarded as a substitute for detailed advice in individual cases.

If you have any questions regarding this publication, please contact:

Aaron GU

Tel: +86 21 6080 0505
Email: aaron.gu@hankunlaw.com