Introduction to Taiwan's Guidelines for Implementing Decentralized Elements in Medicinal Product Clinical Trials

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The development of digital tools such as the internet, apps, and wearable devices have meant major breakthroughs for clinical trials. These advances have the potential to reduce the frequency of trial subject visits, accelerate research timelines, and lower the costs of drug development. The COVID-19 pandemic has further accelerated the use of digital tools, prompting many countries to adopt decentralized measures that enable trial subjects to participate in clinical trials regardless of their physical location. In step with the transition into the post-pandemic era, the Taiwan Food and Drug Administration (TFDA) issued the Guidelines for Implementing Decentralized Elements in Medicinal Product Clinical Trials in June, 2023[1]. The Guidelines are intended to cover a wide array of decentralized measures; they aim to increase trial subjects' willingness to participate in trials, reduce the need for in-person visits to clinical trial sites, enhance real-time data acquisition during trials, and enable clinic sponsors and contract research organizations to process data remotely.

I. Key Points of Taiwan's Guidelines for Implementing Decentralized Elements in Medicinal Product Clinical Trials

The Guidelines cover primarily the following matters: General considerations for implementing decentralized measures; trial subject recruitment and electronic informed consent; delivery and provision of investigational medicinal products; remote monitoring of trial subject safety; trial subject reporting of adverse events; remote data monitoring; and information systems and electronic data collection/processing/storage.

1. General Considerations for Implementing Decentralized Measures

(1) During clinical trial execution, a reduction in trial subject in-person visits may present challenges to medical observation. It is recommended that home visits for any given trial subject be conducted by the principal investigator, sub-investigator, or a single, consistent delegated study nurse.

(2) Sponsors must carefully evaluate all of the trial design's decentralization measures to ensure data integrity.

(3) Sponsors must conduct risk assessments for each individual trial, and must confirm the rationality of choosing decentralized measures. These decentralized measures must also be incorporated into the protocol.

(4) When electronically collecting data, sponsors must ensure information system reliability and data security. Artificial intelligence may be considered for use in decentralized clinical trials; sponsors must carefully evaluate such systems, especially when they touch on determinations for critical data or strategies.

(5) As the design of decentralized clinical trials is to ensure equal access to healthcare services, it must provide patients with a variety of ways to participate in clinical trials.

(6) When implementing any decentralized measures, it is essential to ensure that the principal investigator and sponsor adhere to the Regulations for Good Clinical Practice and bear their respective responsibilities for the trial.

(7) The use of decentralized measures must be stated in the regulatory application, and the Checklist of Decentralized Elements in Medicinal Product Clinical Trials must be included in the submission.

2. Subject Recruitment and Electronic Informed Consent

(1) Trial subject recruitment through social media or established databases may only be implemented after the Institutional Review Board reviews and approves of the recruitment methods and content.

(2) Must comply with the Principles for Recruiting Clinical Trial Subjects in medicinal product trials, the Personal Data Protection Act, and other regulations.

(3) Regarding clinical trial subject informed consent done through digital software or devices, if it complies with Article 4, Paragraph 2 of the Electronic Signatures Act, that is, if the content can be displayed in its entirety and continues to be accessible for subsequent reference, then so long as the trial subject agrees to do so, the signature may be done via a tablet or other electronic device. The storage of signed electronic Informed Consent Forms (eICF) must align with the aforementioned Principles and meet the competent authority's

access requirements.

3. Delivery and Provision of Investigational Medicinal Products

(1) The method of delivering and providing investigational medicinal products and whether trial subjects can use them on their own at home depends to a high degree on the investigational medicinal product's administration route and safety profile.

(2) When investigational medicinal products are delivered and provided through decentralized measures to trial subjects, this must be documented in the protocol. The process of delivering and providing said products must also be clearly stated in the informed consent form; only after being explained to a trial subject by the trial team, and after the trial subject's consent is obtained, may such decentralized measures be used.

(3) Investigational products prescribed by the principal investigator/sub-investigator must be reviewed by a delegated pharmacist to confirm that the investigational products' specific items, dosage, duration, total quantity, and labeling align with the trial design. The pharmacist must also review each trial subject's medication history, to ensure there are no medication-related issues; only then, and only in a manner that ensures the investigational product's quality and the subject's privacy, may delegated and specifically-trained trial personnel provide the investigational product to the subject.

(4) Compliance with relevant regulations such as the Pharmaceutical Affairs Act, Pharmacists Act, Regulations on Good Practices for Drug Dispensation, and Regulations for Good Clinical Practice is required.

4. Remote Monitoring of Subject Safety

(1) Decentralized trial designs involve trial subjects performing relatively large numbers of trial-related procedures at home. The principal investigator must delegate trained, qualified personnel to perform tasks such as collecting blood samples, administering investigational products, conducting safety monitoring, doing adverse event tracking, etc.

(2) If trial subjects receive protocol-prescribed testing at nearby medical facilities or laboratories rather than at the original trial site, these locations must be authorized by the trial sponsor and must have relevant laboratory certification; only then may they collect or analyze samples. Such locations must provide detailed records to the principal investigator, to be archived in the trial master file.

(3) The trial protocol and schedule must clearly specify which visits must be conducted at the trial site; which can be conducted via phone calls, video calls, or home visits; which tests must be performed at nearby laboratories; and whether trial subjects have multiple or single options at each visit.

5. Subject Reporting of Adverse Events

(1) If the trial uses a digital platform to enhance adverse event reporting, trial subjects must be able to report adverse events through the digital platform, such as via a mobile phone app; that is, the principal investigator must be able to immediately access such adverse event information.

(2) The principal investigator must handle such reports using risk-based assessment methods. The principal investigator must validate the adverse event reporting platform's effectiveness, and must develop procedures to identify potential duplicate reports.

6. Remote Data Monitoring

(1) If a sponsor chooses to implement remote monitoring, it must perform a reasonability assessment to confirm the appropriateness of such monitoring and establish a remote monitoring plan.

(2) The monitoring plan must include monitoring strategies, monitoring personnel responsibilities, monitoring methods, rationale for such implementation, and critical data and processes that must be monitored. It must also generate comprehensive monitoring reports for audit purposes.

(3) The sponsor is responsible for ensuring the implementation of remote monitoring, and must conduct risk assessments regarding the implementation process' data protection and information confidentiality.

7. Information Systems and Electronic Data Collection, Processing, and Storage

(1) In accordance with the Regulations for Good Clinical Practice, data recorded in clinical trials must be trustworthy, reliable, and verifiable.

(2) It must be ensured that all organizations participating in the clinical trial have a full picture of the data flow. It is recommended that the trial protocol and trial-related documents include data flow diagrams and additional explanations.

(3) Define the types and scopes of subject personal data that will be collected, and ensure that every step in the process properly protects their data in accordance with the Personal Data Protection Act.

II. A Comparison with Decentralized Trial Regulations in Other Countries

Denmark became the first country in the world to release regulatory measures on decentralized trials, issuing the "Danish Medicines Agency's Guidance on the Implementation of Decentralized Elements in Clinical Trials with Medicinal Products" in September 2021[2]. In December 2022, the European Union as a whole released its "Recommendation Paper on Decentralized Elements in Clinical Trials"[3]. The United States issued the draft "Decentralized Clinical Trials for Drugs, Biological Products, and Devices" document in May 2023[4]. The comparison in Table 1 shows that Taiwan's guidelines a relatively similar in structure to those of Denmark and the EU; the US guidelines also cover medical device clinical trials.

Table 1: Summary of Decentralized Clinical Trial Guidelines in Taiwan, Denmark, the European Union as a whole, and the United States

	Taiwan	Denmark	European Union as a whole	United States
What do the guidelines apply to?	Medicinal products	Medicinal products	Medicinal products	Medicinal products and medical devices

Trial subject recruitment and electronic informed consent	Covers informed consent process; informed consent interview; digital information sheet; trial subject consent form signing; etc.	Covers informed consent process; informed consent interview; trial subject consent form signing; etc.	Covers informed consent process; informed consent interview; digital information sheet; trial subject consent form signing; etc.	Covers informed consent process; informed consent interview; etc.
Delivery and provision of investigational medicinal products	Delegated, specifically-trained trial personnel deliver and provide investigational medicinal products.	The investigator or delegated personnel deliver and provide investigational medicinal products.	The investigator, delegated personnel, or a third-party, Good Distribution Practice-compliant logistics provider deliver and provide investigational medicinal products.	The principal investigator, delegated personnel, or a distributor deliver and provide investigational products.
Remote monitoring of trial subject safety	Trial subjects may do return visits at trial sites, via phone calls, via video calls, or via home visits, and may undergo testing at nearby laboratories.	Trial subjects may do return visits at trial sites, via phone calls, via video calls, or via home visits, and may undergo testing at nearby laboratories.	Trial subjects may do return visits at trial sites, via phone calls, via video calls, or via home visits.	Trial subjects may do return visits at trial sites, via phone calls, via video calls, or via home visits, and may undergo testing at nearby laboratories.
Trial subject reporting of adverse events	Trial subjects may self-report adverse events through a digital platform.	Trial subjects may self-report adverse events through a digital platform.	Trial subjects may self-report adverse events through a digital platform.	Trial subjects may self-report adverse events through a digital platform.
Remote data monitoring	The sponsor may conduct remote data monitoring.	The sponsor may conduct remote data monitoring.	The sponsor may conduct remote data monitoring (not permitted in some countries).	The sponsor may conduct remote data monitoring.
Information systems and electronic data collection, processing, and storage	The recorded data must be credible, reliable, and verifiable.	Requires an information system that is validated, secure, and user-friendly.	The recorded data must be credible, reliable, and verifiable.	Must ensure data reliability, security, privacy, and confidentiality.

III. Conclusion

The implementation of decentralized clinical trials must be approached with careful assessment of risks and rationality, with trial subject safety, rights, and well-being as top priorities. Since Taiwan's Guidelines for Implementing Decentralized Elements in Medicinal Product Clinical Trials were just announced in June of this year, the status of decentralized clinical trial implementation is still pending industry feedback to confirm feasibility. The overall goal is to enhance and optimize the clinical trial environment in Taiwan.

[1] 衛生福利部食品藥物管理署，〈藥品臨床試驗執行分散式措施指引〉，2023/6/12，https://www.fda.gov.tw/TC/siteListContent.aspx?sid=9354&id=43548（最後瀏覽日：2023/11/2）。
[2] [DMA] DANISH MEDICINES AGENCY, The Danish Medicines Agency's guidance on the Implementation of decentralised elements in clinical trials with medicinal products (2021), https://laegemiddelstyrelsen.dk/en/news/2021/guidance-on-the-implementation-of-decentralised-elements-in-clinical-trials-with-medicinal-products-is-now-available/ (last visited Nov. 2, 2023).
[3] [HMA] HEADS OF MEDICINES AGENCIES, [EC] EUROPEAN COMMISSION & [EMA] EUROPEAN MEDICINES AGENCY, Recommendation paper on decentralised elements in clinical trials (2022), https://health.ec.europa.eu/latest-updates/recommendation-paper-decentralised-elements-clinical-trials-2022-12-14_en (last visited Nov. 2, 2023).
[4] [US FDA] US FOOD AND DRUG ADMINISTRATION, Decentralized Clinical Trials for Drugs, Biological Products, and Devices (draft, 2023), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/decentralized-clinical-trials-drugs-biological-products-and-devices (last visited Nov. 2, 2023).

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