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Acceptance of overseas clinical trial data of medical devices for pre-market registration: general principles and considerations of the National Medical Products Administration

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A clinical trial is a systematic investigation or study in or on one or more human subjects, undertaken to assess the safety, clinical performance, and/or effectiveness of a medical device.[1] In this paper, "overseas clinical trial data" refers to data generated from a clinical trial(s) conducted in a foreign country or jurisdiction and proposed to be used as clinical evidence for a pre-market registration application in China.

Many pre-market or post-market clinical trials of medical devices, including *in vitro* diagnostics (IVD), are conducted outside of China and generate credible data. Overseas clinical trials data can be accepted and used in clinical evaluation for pre-market registration in China, if they meet relevant requirements.[2]

The overseas clinical trial must follow the International Code of Medical Ethics laid out in the World Medical Association *Declaration of Helsinki*, as well as the recognized standards or other ethical rules, laws, and regulations of the countries where the clinical trial is conducted. The sponsor also needs to guarantee that the trial is ethical and scientific and the rights, safety, and well-being of study subjects are protected.

To ensure high-quality data, an overseas clinical trial should be conducted in a country that implements a quality management system for clinical trials. Generally, trials should follow local regulations or meet recognized standards, which may differ in certain aspects from the Good Clinical Practice (GCP) for Medical Devices in China. As long as these differences do not affect the authenticity, reliability, and traceability of the results, and the subjects' rights and interests are protected, the trial may be considered to meet the requirements of the GCP.

Overseas clinical trial data should be authentic, scientific, reliable, and traceable. The full data should be provided without screening.

The sponsor needs to ensure that: (a) the purpose of the clinical trial is appropriate, (b) the intended data are obtained through a scientific and reasonable trial design and process, (c) the conclusion is clear, (d) and the rights and interests of the subjects and other relevant persons have been protected from undue risks.

All three principles are necessary conditions for the acceptance of overseas clinical trial data. The National Medical Products Administration (NMPA) will not accept the data if any of the principles are not followed.

Medical devices differ in mechanisms of action in or on the human body, type, and duration of contact with the human body, and expected clinical effects. Therefore, a medical device may have different risks and clinical performances across populations. The NMPA will accept data from human subjects that can be extrapolated to Chinese users. Factors that may influence clinical trial data among diverse subjects include:

Intrinsic factors including human genetic polymorphism or demographic characteristics, such as race, age, and gender. Extrinsic factors: including the social or natural environment and, more likely, cultural, and behavioral factors such as dietary habits, environmental exposures, smoking,

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drinking, disease incidence, rare or regional comorbidity, obesity, social and economic conditions, religious beliefs, educational background, and medical compliance.

Intrinsic and extrinsic factors usually act together and may affect the safety and effectiveness of a device when used in human subjects.

Two examples of when factors related to differences between subjects should be considered are presented below. Example 1: A pulse oximeter device is used for non-invasive pulse oxygen saturation and pulse rate measurements. The working mechanism is based on time-dependent changes in optical tissue properties caused by pulsatile flow. Since the operating principle involves the interaction between optical signals and tissues, issues related to melanin deposition should be considered. Specifically, the overseas subjects and Chinese target group may have differences in skin color. Thus a bridging clinical study may be needed. Example 2: An *in vitro* diagnostic reagent kit for gene detection of a genetic disease. Suppose the target genes selected from the overseas human subjects differ from those of the Chinese target group. In that case, it is necessary to conduct a bridging clinical study of influencing factors (eg, mutation sites, mutation frequency of genes of the genetic disease) in the Chinese target group.

The medical practices in which a clinical trial is set are influenced by factors such as clinical environments, medical facilities, investigators' abilities (ie, learning curve), and diagnosis and treatment concepts or codes. Differences in clinical conditions may impact whether the data are extrapolatable to the Chinese target population. For example, due to different diagnostic and treatment concepts or criteria, clinical practice in other countries may not be relevant to clinical management guidelines in China. Some devices may perform differently in overseas clinical trials under the standard operating procedures of Chinese hospitals. In addition, differences in facility equipment and investigators' abilities or experience may also influence trial outcomes, especially for medical devices requiring a skilled operation.

An overseas clinical trial may meet the requirements of the country where it was conducted but not fully meet the relevant pre-market technical review requirements of the NMPA. This does not mean that the clinical trial design or process was inappropriate. It may be due to different purposes, such as an overseas clinical trial not being designed to generate data for pre-market applications. In some circumstances, the extent of clinical data required for pre-market applications may also be related to variations in medical device regulatory frameworks. Normally, the NMPA requires clinical evidence of the performance and/or effectiveness of the device, as well as its safety.

Differences in technical requirements may exist individually or in combination when generating clinical trial data for medical devices. These differences may have impacts on clinical trial outcomes. The NMPA will consider these influences along with the medical device's characteristics and the clinical trial's purpose. For most devices, it may not be difficult to determine that such differences do not have a clinically significant impact on the clinical trial data, based on development status, experiences in clinical application, and current knowledge of related diseases and therapeutic interventions. In these situations, proving the impact of each difference is not necessary. Otherwise, an explanation of methods for reducing or eliminating the influence caused by those differences, such as subgroup analyses of existing clinical trial data, or a supplementary clinical trial in the Chinese population, may be required.

Overseas clinical trial data can be used in clinical evaluation documents for all medical devices, including an IVD's pre-market application to the NMPA. The data can be submitted as part of the clinical evaluation document, including the clinical trial protocol, ethical review documents, and the clinical trial report.

Overseas trial data that meet the requirements for pre-market registration in China will be accepted. Sometimes, despite overseas trial data meeting the principles and requirements mentioned above, a supplementary clinical trial may still be required by the NMPA to address safety and effectiveness questions. The supplementary trial may be conducted overseas or in China. If, after systematic evaluation, the supplementary and previous trial data meet the relevant technical requirements for registration in China, the data will be accepted.

Overseas clinical data may be generated from marketed comparable devices. These data could also be used to support the safety and/or effectiveness of the device under application. The comparable devices should have similar intended use, technical and biological characteristics. In this context, "similar" refers to the extent to which potential differences in these characteristics result in no clinically significant differences in the effectiveness and safety of the device. The NMPA may accept data from appropriate comparable devices that meet these requirements.

If the clinical trial data were generated from a multi-regional clinical trial with Chinese institutions, an explanation of the distribution of the cases is required for further evaluation.

It is recommended that the sponsor/applicant have prior communication with the medical device evaluation authorities to reach a consensus on the sufficiency of the overseas clinical trial data for the medical device under application.

Many different jurisdiction's medical device regulatory authorities, such as the Food and Drug Administration, European Parliament and EU Council, and Pharmaceuticals and Medical Devices Agency, have issued guidelines related to the acceptance of overseas clinical trial data.[3-6] These guidelines do not conflict with the one issued by the NMPA. The International Medical Device Regulators Forum also harmonized the requirements for the acceptance of overseas clinical trial data. The overseas clinical trial data can be used as a contributing data source for conducting a clinical evaluation.

Acceptance of overseas clinical trial data of medical devices is an effective method for utilizing existing data adequately. It plays a crucial role in avoiding or reducing repetitive clinical trials, and contributes to accelerating the product launch of, and patient access to, medical devices.

Conflicts of interest

None.

References

1. IMDRF MDCE WG/ N55FINAL: 2019 Clinical Evidence–Key Definitions and Concepts. [EB/OL]. The GLOBAL HARMONIZATION Task Force; 2019. Available from: http://www.imdrf.org/documents/documents.asp. [Accessed October 2019]
2. Opinions on Deepening the Review and Approval System Reform and Encouraging the Drug and Medical Device Innovation. The State council the people's republic of China. Available from: http://www.gov.cn/zhengce/2017-10/08/content_5230105.htm. [Accessed October 8, 2017]
3. Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions. Office of Medical Products and Tobacco, Center for Devices and Radiological Health; 2018. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-clinical-data-support-medical-device-applications-and-submissions-frequently-asked. [Accessed February 21, 2018]
4. EU Regulations on Clinical Trials on Medicinal Products for Human Use (EU No 536/2014). European Parliament and EU Council; 2014. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf. [Accessed on April 16, 2014]
5. Clinical Trial Guidance for Efficient and Accurate Approval and Development of Medical Devices. Association for the Advancement of Medical Instrumentation Japan: PMDA; 2017. Available from: http://www.pmda.go.jp/files/000221182.pdf. [Accessed March 2017]
6. Handling of Clinical Study Data on Medical Devices Which Was Carried out in Foreign Countries. Japan: PMDA; 2006. Available from: https://www.pmda.go.jp/files/000153073.pdf [Accessed March 31, 2006]

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