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Initiating clinical trials in China: What foreign medtech companies need to do

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This article discusses numerous recent changes in the regulation of clinical trials in China and proposes that Chinese clinical trials for medical device and in vitro diagnostic device (IVD) products are an increasingly viable option for non-Chinese companies of all sizes.

China's regulatory framework

Most life sciences products, including medical devices and IVDs, sold in China are supervised by the National Medical Products Administration (NMPA). The agency uses a risk-based classification system with three classes, in which Class III is the highest-risk and requires the most regulatory scrutiny. (NMPA was known as the China Food and Drug Administration until its name was changed in 2018.)

Premarket approvals for Class II and Class III medical devices and IVDs in China will, by default, require clinical trials in support of the application dossier,[1] unless the applicant can:

- Identify its product on the clinical trial exemption list,
- Provide sufficient information about a predicate device that is approved by NMPA, or
- Provide sufficient overseas clinical trial data.

The requirements are largely the same whether a company is a domestic or foreign applicant. If clinical trials are required, non-Chinese companies often see this as a "show-stopper" for their China market entry. But this need not be the case. With an ageing population, rising prosperity, and government encouragement even before the healthcare-focused accelerations from COVID-19, the China healthcare market is attractive for foreign medical device and IVD companies.

Healthcare teams at Chinese hospitals are increasingly knowledgeable about, and open to, supporting clinical trials. Some provinces – such as Hainan, an island province off the south coast of China – have even developed specific solutions to try to attract global players into their hospitals to run certain trials.

China-based clinical trials are therefore an increasingly viable option for foreign companies of all sizes, although that may not have always been the case.[2]

This article discusses numerous recent regulatory developments encouraging the China clinical trial trend and outlines what foreign medical device and IVD companies should consider before initiating a clinical trial in China. The article does not address clinical trial regulations relating to drugs, but readers should be aware of a revised Drug Registration Regulation that took effect

on 1 July 2020, which makes changes to the regulation of clinical trials of pharmaceutical products in China.[3]

Exempted and mandatory trials

Exempted

Although the default position for Class II and Class III medical devices and IVDs is that they will require a clinical trial, the NMPA regularly issues lists of products it considers exempted from clinical trial requirements. At the time of writing, there were more than 1,000 Class II and 200 Class III medical devices and IVD product categories exempted from clinical trials. For those listed products, a greatly simplified clinical evaluation report is sufficient to support a premarket approval application.

The NMPA most recently updated the list of products exempted from clinical trials in China in January 2021, with the addition of 85 medical devices and 7 IVDs. The clinical trial exemption lists are available on the NMPA website.[4]

Mandatory

The regulator also expressly requires certain high-risk product categories to undergo clinical trials. This requirement will generally be stipulated in product-specific standards and guidelines.

- Clinical trials will generally be required for:
- Devices in which there is a completely new design or new intended use;
- Nonactive implantable medical devices not approved on the domestic or overseas markets;
- Orthopedic and dental implants not been approved on the domestic or overseas markets, but where safety and effectiveness are not clear; or
- Products approved in the overseas markets, but not for China, and where evidence on safety and effectiveness is not sufficient.

Examples of high-risk devices include implantable cardiac pacemakers, implantable blood pumps, and certain orthopedic implants.

Overseas data

Since January 2018, qualified clinical data collected outside China is permitted to form the basis of a clinical evaluation report in place of conducting a China-based clinical trial.[5] This is even the case for devices the NMPA considers high risk, such as implantable pacemakers and heart pumps.

Data is qualified for the NMPA if it is ethical, legal, and scientific:[5,6]

- **Ethical principle.** This refers to the requirement that the collection of clinical data must have been approved by a local ethics committee, and the opinion of the relevant local ethics committee will need to be submitted to the NMPA as part of the registration dossier.
- **Legal principle.** This means the clinical trial must have been conducted in accordance with China good clinical practice (GCP) for medical devices,[7] which is substantially similar to globally recognized GCP standards (in particular, ISO 14155[8]), but with additional, China-specific requirements. China GCP became effective 1 June 2016. The protocol and planning of the trial will need to be submitted together with the registration application.
- **Scientific principle.** This refers to the requirement that the data are authentic, reliable, traceable, and nonselective. Complete clinical data will need to be submitted with the registration application.

On the basis of being authentic, scientific, reliable, and traceable, overseas medical device clinical trial data submitted by the applicant should at least include an ethical opinion review and approval documents; complete clinical trial protocol; and complete clinical trial report, which includes an analysis of the complete clinical trial data and the conclusions.

A guideline regarding overseas clinical data for IVD reagents is also currently being drafted and solicitations for comments from industry have been sought.[9] Once effective, this guideline will provide additional guidance in respect of acceptance in premarket approval applications of IVD clinical data obtained outside of China.

Trial initiation and notifications

Since April 2019, preapproval to begin a clinical trial is no longer required for most devices. Instead, notice of

the trial is given to NMPA's Centre for Medical Device Evaluation (CMDE), and if no response has been received within 60 working days, the trial can begin.[10] This simplifies the previously required preapproval process. Instead of an approval notification, the NMPA's website will display the approval number; the applicant's name and address; and the name, model specification, structure, and composition of the medical device.

However, the CMDE will still require pre-approval for certain high-risk devices. These products are listed in the Catalog of Class III Medical Devices Requiring Clinical Trial Approval.[11]

In addition, sponsors should still register their clinical trials with an online registry, such as the Chinese Clinical Trial Registry, before the first participant is recruited. The registry was established in 2005 and was assigned the Ministry of Health of China to represent China at the World Organization of Health's (WHO's) International Clinical Trials Registry Platform in 2007.[12]

The minimum information to be registered is specified in the WHO Trial Registration Data Set, which is available on the WHO website.[12,13] The registry record will be the only publicly available document on a trial until results from the trial are published.

Hospital-based clinical trials

China clinical trials must generally be conducted at two or more NMPA-approved hospitals and meet NMPA registration requirements. Class III IVD trials will generally require a multicenter trial with at least three clinical sites.

The key guideline that sets out much of the requirements for the clinical trial process is China's Good Clinical Practice for Medical Devices.

Because top-tier hospitals in China are concentrated in the major cities, close consideration should be given to site selection to ensure duration and efficiency of the trial are optimized.

There is a tiered hospital system in China, with Level III A+ at the highest tier and Level I C at the lowest. The levels are determined by the Chinese government according to treatment ability, staff training, and research capability. Level III hospitals are generally selected for clinical trials and, for high-risk medical devices, the hospital should be at the highest level, Level IIIA.

A number of regulations have been issued in recent years, adding to the list of hospitals approved as clinical trial centers.[14,15] The list of hospitals is available on the NMPA website and includes the name, address, contact details, and level or tier of the hospital within China's tiered hospital system.[16]

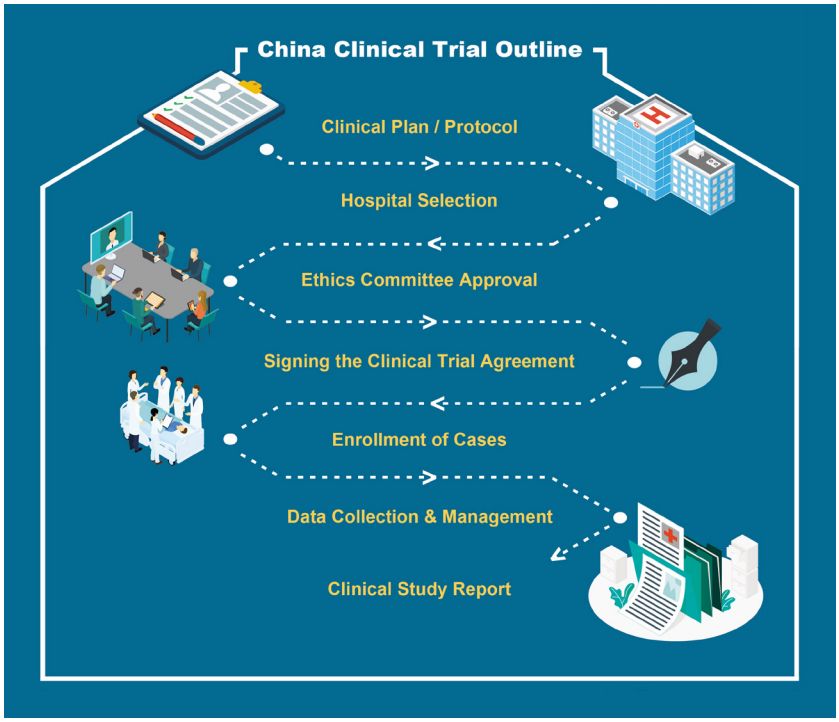
Key steps in the clinical trial process

The key guideline that sets out much of the requirements for the clinical trial process is China's Good Clinical Practice for Medical Devices (China GCP).[7] It largely follows international GCP, although there are some local differences, such as requirements relating to consideration of ethnic differences of the local Chinese population.[7]

Another Chinese-specific consideration is a requirement for any clinical trials involving genetic information to be registered with the Human Genetic Resources Administration of China, which should be factored into any relevant trial timelines for IVD or medical devices involving genetic data.[17]

An outline of the key steps is set out in the accompanying figure. The clinical protocol or plan should be drafted in parallel to initial preparation and planning of materials and equipment. Some specific considerations about the protocol are discussed further below. Once the hospitals are selected and the plan finalized, ethics committee approval is required before trial initiation.

Figure. Outline of key steps in clinical trials in China



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During the patient enrolment process, milestones of 10%, 30%, 60%, and 90% visit thresholds are common. Treatment, analysis, and data review are the critical stage of the process, but data follow-up and analysis, reporting, and site close-out are the scientific validation to the investigation. A reasonable timeframe from the author's experience is 2 years although this can vary considerably depending on the product and the circumstances.

Drafting clinical trial protocols

The protocol design should strictly follow NMPA's Medical Device Clinical Trial Design Guideline issued in January 2018.[18] In addition:

- The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement is referenced on the China clinical trial registry registration website and provides a checklist with recommended items to be addressed in a clinical trial protocol and related documents.[19,20]
- Devices that are brand new – that is, not yet approved in China or elsewhere in the world – must present supportive evidence from a small-scale feasibility study. Before completing the protocol for subsequent trials, a statistical analysis of the small-scale trial should be used to determine the sample size of those trials (Article 27, Decree No. 25).[7]
- Ten specific types of documents must be provided to the ethics committee before a clinical trial can begin, including the researcher's manual, proof of the experience of the researchers, and the forms used to recruit participants, among others (Article 17, Decree No. 25).[7]
- The ethics committee should have at least five members with a diverse constituency, including representation from both genders, and medical and nonmedical members.
- Any changes to the trial protocol should be submitted

to the ethics committee for ratification (Article 11, Decree No. 25).[7]

Additional information

The NMPA website has an English-language website with limited content, although the amount is expanding. In particular, China's Good Clinical Practice for Medical Devices (Decree No. 25) is available on the website in English and is a helpful free resource giving guidance on the key requirements.[7] There are also a variety of clinical research organizations and regulatory consultants active in the space with English language expertise.

Conclusion

China-based clinical trials are an increasingly viable option not only for large global medical device and IVD companies but also for medium and small-sized companies. Numerous regulatory developments relating to China clinical trials should clarify and encourage local China trials as requirements converge on international standards.

Abbreviations

CMDE, [NMPA's] Centre for Medical Device Evaluation; **GCP**, good clinical practice; **IVD**, in vitro diagnostic device; **NMPA**, National Medical Products Administration.

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