Regulatory Matters

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Editorial

On June 21, 2023, EMWA's Clarity and Openness in Reporting: E3 (CORE) Reference Project team presented a webinar which featured an overview of the current clinical trial disclosure landscape in Asia. The comprehensive overview table, along with a brief description, are also presented in the Regulatory Public Disclosure section in this issue of *Medical Writing* on p. 91.

Over the past two decades, we have seen rapid evolution of drug regulations in China, including the re-organisation of their drug regulatory authority from the State Drug Administration (SDA) which was inaugurated in 1998, to China Food and Drug Administration (CFDA) in 2013, to the current National Medical Products Administration (NMPA) since 2018. Then, China joined the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)in 2020. Significant changes in drug regulations are being introduced constantly to accelerate drug review and approval while staying in alignment with international guidelines.

In this article, I provide further background on the existing clinical trial registries, the development of the current national registry, and regulations pertaining to drug registration in China. This complementary background information provides extended reading on the concise content for China in the overview table mentioned above. I hope you find it useful and enjoy reading it!

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Current clinical trial disclosure landscape in China

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Existing clinical trial registries in China

In China, before the launch of the current national clinical trial registry in 2013, i.e., ChinaDrugTrials.org.cn (http://www.chinadrugtrials.org.cn/index.html), two common trial registries already existed and have been in use until the present day. In addition, two new registries for traditional medicines were established after 2013. These registries and their brief descriptions are presented in Table 1.

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Development of the new National Clinical Trial Registry

- **November 2012** – The Centre for Drug Evaluation (CDE) in China launched a trial run of the new Clinical Trial Registration and Information Disclosure Platform for Drugs via the CDE website.
- **September 2013** – The then China Food and Drug Administration (CFDA) released Notification No. 28 on the Clinical Trial Information Platform for Drugs,[1] requiring all clinical trials conducted in China (including bioequivalence, pharmacokinetic, Phase 1 to 4) to be registered and trial information be disclosed on the abovementioned platform on the CDE website. Pre-registration to obtain the trial's unique identifier must be completed within 1 month after obtaining an approval of the trial. The rest of the registration must be completed before the first subject enrolment. Trial registration is to be seen as a pre-requisite for the subsequent communication and consultation with the regulatory authority during the clinical trial.
- **October 2013** – The CDE released further information following Notification No.28, announcing the effort of completing a new clinical trial disclosure platform.
- **November 2013** – An independent registration platform called ChinaDrugTrials.org.cn was first launched. The trial run of the original platform on the CDE website was terminated.
- **December 2015** – The then-CFDA released Notification No. 257 on the Management of Bioequivalence Trials of Chemical Drugs,[2] which indicated the integration of the Registry for Generic Drugs and Bioequivalence Clinical Trials into the ChinaDrugTrials.org.cn platform.
- **2020** – In conjunction with the enforcement of the Drug Administration Law in 2019 and the Drug Registration Regulation in 2020, the original ChinaDrugTrials.org.cn platform was upgraded and officially merged with the Registry for Generic Drugs and Bioequivalence Clinical Trials.

Drug Registration Regulation in China

The Drug Registration Regulation[3] was enforced in July 2020. According to the regulations:

- **Article 28** – Sponsors should submit a safety update report every year during the clinical investigation of the drug. [...] Any suspected unexpected adverse reaction and other underlying important safety issues must be reported to the CDE promptly as required. The trial protocol, subject informed consent, or the investigator's brochure should be updated as necessary based on the severity of the safety risks. A trial may be suspended or terminated if deemed appropriate.
- **Article 33** – Sponsors should register the clinical trial protocol and other trial information on the registration and information disclosure platform before starting a trial. During the trial, sponsors should continue to update the registration information and to include the trial results following the completion of the trial. The sponsors are

responsible for the authenticity of the trial information.

- **Article 116** – Sponsors who violate Article 28 and Article 33, or any of the following events will be warned and ordered to take corrective action; failure of corrective action within the given time window may result in a penalty of 10,000 to 30,000 Chinese Yuan. The events that require corrective actions include:
  1. Failure to register the clinical trial on a registration and information disclosure platform;
  2. Failure of timely submission of safety reports;
  3. Failure to provide trial results after the completion of the trial.

In response to the new regulation, the CDE issued a draft guidance on the Management of Clinical Trial Registration and Information

Table 1. Clinical trial registries in China

Clinical trial registry description
Chinese Clinical Trial Registry (ChiCTR) • https://www.chictr.org.cn/ • Established in 2005 • Accepts registration of clinical trials in China and globally • Operated in Mandarin and English • Primary registry of the WHO International Clinical Trials Registry Platform (ICTRP) since 2007 • Served as the primary registry for clinical trials in China before the launch of ChinaDrugTrials.org.cn. Thereafter, the role of the ChiCTR became unclear in relation to the regulation.
Centre for Clinical Research and Biostatistics – Clinical Trials Registry (CCRBCTR) • https://www2.ccrb.cuhk.edu.hk/ • Partner registry of ChiCTR since 2009 • Accepts registration of clinical trials globally • Operated in English only (only the study title is bilingual in Mandarin and English) • Compliant with WHO ICTRP trial registration requirements
Acupuncture-Moxibustion Clinical Trial Registry (AMCTR) • Partner registry of the WHO ICTRP[4] • Established in 2014 and became a partner registry of ChiCTR since 2016 • Accepts registration of clinical trials using acupuncture-moxibustion as interventions • Compliant with WHO ICTRP trial registration requirements
International Traditional Medicine Clinical Trial Registry (ITMCTR) • Primary registry of the WHO ICTRP since March 2023[5] • Operated in Mandarin and English • Accepts registration of clinical trials conducted in China or globally since 2019 • For trials in the field of traditional medicine, including but not limited to Chinese medicine, acupuncture, tuina massage, herbal medicine, ayurveda, homeopathy, and complementary and alternative medicine

Disclosure,[6] which came into effect on July 1, 2020. The draft guidance specifies the following important registration and disclosure policies:

- **Article 6** – All clinical trials that obtain approval from the National Medical Products Association (NMPA) and are conducted in China, including bioequivalence and Phase 4 or post-marketing surveillance studies, are required to be registered on the registration and information disclosure platform.
- **Article 14** – [...] Trial registration should be completed before subject enrolment.
- **Article 15** – [...] Following trial completion, the trial results should be posted on the platform within 12 months of trial completion; for trials supporting a New Drug Application (NDA), sponsors are recommended to post the trials' results before NDA submission, whichever occurs first. The trial results should at least consist of the content of the clinical study report synopsis as described in the ICH E3 guideline.

As a note, results of clinical trials completed before July 1, 2020, without an NDA submission, should still be posted on the platform within 12 months of trial completion or before the NDA submission. Nevertheless, if an NDA is already submitted, trial results posting is at the discretion of the sponsors.[7]

Afterthought

From a quick glance at the completed trials dated between 2020 and 2022 in the ChinaDrugTrials.org.cn registry, not all registered trials have included the trial results. Imposing a penalty for failure to provide trial results as stated in the regulation is only the first step. Effective and consistent oversight in trial registration and result posting must not be overlooked in the effort towards improving transparency of clinical trial information.

There potentially are issues of redundancy, inadequate maintenance, and missing information as we have seen with many other major clinical trial registries worldwide.

As of June 25, 2023, more than 70,000 clinical trials were registered on the older ChiCTR whilst just shy of 21,000 clinical trials are found on ChinaDrugTrials.org.cn. How many clinical trials are registered on both platforms and maintained equally, how many are registered on only one and not the other? There potentially are issues of redundancy, inadequate maintenance, and missing information[8] as we have seen with many other major clinical trial registries worldwide. It is suggested that data exchange between ChiCTR and ChinaDrugTrials.org.cn and mutual recognition of the two platforms should be considered to improve transparency and sharing of clinical trial information.[9]

Disclosures and conflicts of interest

The author declares no conflicts of interest.

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