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Essay

Clinical Trial Registration and Reporting in China and the United States: Legal and Regulatory Frameworks, Compliance and Enforcement

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Abstract: Background and Objectives: Clinical trials are a critical step in the development of new medicines and medical devices, testing the efficacy and safety of new treatment regimens. However, if the results of clinical trials are not made public, the evidence base on interventions is incomplete and possibly distorted, which lead to suboptimal treatment choices and negatively affect public health. This study analyses and contrasts the laws and regulations governing clinical trial registration and reporting in China and the United States. **Methods:** We used desk research to compile, assess and compare current laws, regulations, compliance patterns, and enforcement mechanisms and actions in China and the United States (U.S.). Policy documents were downloaded from Chinese and U.S. government websites. A spreadsheet analysis was utilized for direct comparison. **Results:** Both China and the U.S. have laws and regulations governing clinical trial registration and reporting. Chinese legislation covers a broader range of trials. In the U.S. trial results must be disclosed to both the national regulator and the public, while Chinese law mandates disclosure to the regulator alone. Cross-country comparisons of regulatory compliance by trial sponsors are impossible due to the opacity of the Chinese data platform. Neither country effectively ensures that all clinical trial results are made public as required by the Declaration of Helsinki and recommended by the WHO. **Interpretation:** While neither country is perfect, both may be able to learn from each other. There is a major gap in the literature regarding the extent of non-publication of clinical trial results by sponsors operating in China.

Keywords: clinical trial; transparency; legislation; regulation; policy analysis; China; United States; publication bias

1. Introduction

1.1. Clinical Trial Transparency

Clinical trial transparency is crucial because it prevents research waste and selective reporting of scientific research, thereby enhancing the robustness of the medical evidence base and building public trust in medicine [1]. Transparency also helps to identify gaps in health research agendas and the unnecessary duplication of trials, and improves access to clinical trial information for policymakers, researchers, healthcare workers, and patients [2,3]. Nonetheless, previous studies have consistently shown that a large number of clinical trial results are not made public [4–7]. In addition, there is mounting concern about the completeness, accuracy and veracity of trial outcomes published in medical journals [6,8]. These dynamics can lead to significant distortions in the medical evidence base, with potentially profound negative implications for patients and the healthcare system [9].

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Therefore, it is essential to improve the transparency of clinical trials and enhance public access to comprehensive clinical trial information [3,10,11].

Clinical trial transparency is a multifaceted concept, and its definition can vary depending on the perspective and goals of different organizations and stakeholders. A 2017 report by Cochrane, Transparency International and TranspariMED identified five pillars of clinical trial transparency: prospective trial registration; timely posting of summary results onto a trial registry; the publication of full trial reports (clinical study reports); publication of trial results in academic journals; and individual participant data sharing [2].

This study focuses on two of these transparency pillars: trial registration and summary results reporting on trial registries. Prospective trial registration is the initial step toward openness. It puts a trial onto the global map of medical research efforts thereby supporting recruitment of patients and helping to avoid the unnecessary duplication of studies. It also deters questionable research practices such as p-hacking and 'silent outcome switching' [12]. In 2004, the International Committee of Medical Journal Editors (ICMJE) mandated that all clinical trials must be registered with a recognized public clinical trial registry in order to be considered for publication [13]. Prospective clinical trial registration and the publication of trial results are ethical and scientific obligations under the Declaration of Helsinki [14,15]. The World Health Organisation's (WHO's) "Joint statement on public disclosure of results from clinical trials" built on those requirements by stipulating that registry entries should be kept up to date during a trial, and that the results of all clinical trials should be made public specifically on a trial registry within 12 months of study completion [16].

The WHO's International Clinical Trials Registry Platform (ICTRP), established in 2005, combines data from 18 trial registries to ensure the public availability of clinical research data. It improves the validity and usefulness of the data from scientific research by making it easier and quicker for healthcare decision-makers and researchers to find clinical trial information [17].

1.2. The Status of Clinical Trial Transparency in China

China is gradually strengthening clinical trial regulations. In recent years, China's National Medical Products Administration (NMPA) has issued and updated a series of policies and guidelines, such as the 2020 Drug Registration Regulation [18] and the 2020 Regulations for the Administration of Drug Clinical Trial Regulation and Information Disclosure [19], which set out registration and information disclosure requirements for clinical trials.

Currently, clinical trial registration and summary results reporting on registries in China are achieved through two platforms: the Chinese Clinical Trial Registry (ChiCTR) and the Drug Clinical Trial Registration and Information Disclosure Platform (ChinaDrugTrials.org.cn) [20].

As China conducts one of the highest numbers of clinical trials globally and is now a major exporter of medical products, China's clinical trial transparency policies and practices have global implications [23]. A 2019 study found that ChiCTR ranked third among all ICTRP-linked registries in terms of the number of registered trials, with over 24,000 studies registered [21]. As of May 2022, China had exported nearly two billion doses of COVID-19 vaccines, accounting for 32.2% of the world's share of exports and ranking second among all producing economies, ranking behind the European Union but ahead of the U.S. [22].

Some researchers have argued that clinical trial registration and reporting disclosure in China is still underdeveloped, with only rudimentary clinical trial registration information provided [24,25]. Moreover, compared to the European Union and the U.S., only a small number of tabular summary results have been posted onto ChiCTR and ChinaDrugTrials.org.cn [24]. A survey conducted by the Chinese government in 2016 found that over 80% of new drug registrations in China were "spurious" [26,27]. Some pharmaceutical companies had hidden or deleted records of adverse events and manipulated data to align with their expected outcomes, highlighting the potential value added of increasing transparency [28].

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1.3. Purpose of This Study

The existing English language literature has not systematically compiled or analyzed clinical trial transparency laws and regulations in China or compared these with frameworks in other jurisdictions. This study fills this important gap by exploring the strengths and weaknesses of China's framework with reference to corresponding laws, regulations, and regulatory practices in the U.S.

First, we present an overview and content analysis of China's national clinical trial registration and reporting laws and regulations. Second, we compare and contrast Chinese laws and regulations with those of the U.S. We conclude that disclosure requirements in China are weaker than those in the U.S.

2. Methodology

2.1. Data Sources

We comprehensively searched existing laws, regulations, and guidelines on clinical trial transparency in China and the U.S. in Chinese and English language to retrieve relevant policy documents. These documents were sourced from official websites including that of the Chinese National Medical Products Administration (NMPA, https://www.nmpa.gov.cn/), and the US Food and Drug Administration (FDA, https://www.fda.gov/), and the U.S. ClinicalTrials.gov registry (https://clinicaltrials.gov/).

Additionally, we conducted a narrative review of the relevant academic literature in both Chinese and English language. Chinese language publications were sourced through the China National Knowledge Infrastructure (CNKI). English language publications were located via searches of Google Scholar and PubMed. We used keywords including clinical trial, transparency, registries, drug registration, and results reporting.

2.2. Data Extraction and Analysis

To gain a comprehensive understanding of China's laws and regulations on clinical trial registration and results reporting, our primary data source was the official website of the NMPA. After an initial keyword search, we browsed through the documents on the NMPA in reverse chronological order. We excluded laws and regulations that had been abolished or had expired. We also excluded documents exclusively applicable to cosmetic and/or medical device trials as those are beyond the scope of this study. Our data sources for U.S. laws and regulations were the FDA website and Clinicaltrials.gov.

To systematically compare and analyze the regulatory frameworks in China and the US, we drew on the existing academic and grey literature on clinical trial transparency to create a list of elements salient to trial registration and reporting. We captured the following key elements: responsible agencies; key laws and regulations; study types and trial phases; formats of results disclosure; permissible delays; maximum fines; compliance monitoring and enforcement; and data platforms. We then populated an Excel spreadsheet with relevant data on China and the U.S. for side-by-side comparison. This structured approach enabled a comprehensive assessment of the similarities and differences in the two countries' regulatory landscapes.

3. Policy Analysis

3.1. The Legal Framework on Drug Trial Registration and Reporting in China

The national medicines regulator NMPA regulates drug development clinical trials that are aimed at gaining subsequent market approval in China. The Center for Drug Evaluation (CDE), an NMPA-affiliated institution, is responsible for the technical review and approval of applications for such drug trials. It also manages market authorization, assessing the safety, efficacy, and quality of new drugs based on data provided by the applicant.

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The 2020 Drug Registration Regulation (DRR) is a key regulatory document developed by the NMPA [18]. It plays an essential role in regulating drug registration practices, guiding drug research and development, and promoting the development of the pharmaceutical industry. In addition, the 2020 Regulations for the Administration of Drug Clinical Trial Regulation and Information Disclosure were developed by the CDE in accordance with the DRR to implement the Drug Administration Law of the People's Republic of China. These documents regulate the registration and information disclosure of all drug trials [19]. Vaccines are regulated as medicines under these laws.

As mentioned above, there are currently two clinical trial registration platforms in China: the Drug Clinical Trial Registration and Information Disclosure Platform (ChinaDrugTrials.org.cn) and the Chinese Clinical Trial Registry (ChiCTR). ChinaDrugTrials.org.cn is essentially a regulatory platform governed by national law. ChiCTR is a conventional trial registry not codified in national law. Only ChiCTR forms part of the WHO's global ICTRP network of 18 primary registries. The two registries are not interlinked, meaning that registrations and data are not and cannot be transferred directly from one to the other.

3.2. The ChinaDrugTrials.org.cn Platform

ChinaDrugTrials.org.cn is managed by the CDE. The NMPA requires the registration of all drug clinical trials conducted in China, covering chemicals, biologics, and traditional Chinese medicines [18]. For drug clinical trials conducted outside of China, if the results are intended for drug registration applications in China, they must also be registered on ChinaDrugTrials.org.cn. However, this platform does not accept registrations for drug clinical trials conducted abroad that are not intended for the Chinese market. ChinaDrugTrials.org.cn requires all trials to be registered in Chinese language, and the entire user interface and data are exclusively in Chinese. It has a search function enabling users to search for individual trials (http://www.chinadrugtrials.org.cn/clinicaltrials.searchlist.dhtml).

According to the DRR, the entity responsible for seeking approval to conduct a drug clinical trial, known as the "sponsor", must register the drug clinical trial protocol and other information on ChinaDrugTrials.org.cn before commencing the trial. The DRR specifies the required content for registration. The sponsor bears responsibility for the accuracy and authenticity of the information. Ethics Committee (EC) approval is a prerequisite for initiating a study and a copy of the EC approval letter must also be submitted during the registration, although this is not publicly disclosed. The CDE manually checks the completeness and accuracy of registration data to ensure compliance with NMPA requirements before making the registration public [19]. The publicly available registration data fields and content broadly correspond to those commonly found in WHO primary registries.

During the trial, the sponsor is obliged to keep the information up-to-date and provide updates within 20 days of any new developments. If a trial is voluntarily suspended or terminated for safety reasons, the applicant must update the trial status information within 10 working days. In cases of an ordered suspension or termination, the CDE should promptly update the trial status. If a trial concludes prematurely with fewer participants than initially planned, the sponsor is required to report this and provide reasons within 10 working days. Additionally, if the trial has collected any results prior to termination, these should be uploaded within 12 months from the trial's termination date.

According to the DRR and the 2020 regulations for the Administration of Drug Clinical Trial Regulation and Information Disclosure, the applicant must post a clinical trial's results onto ChinaDrugTrials.org.cn within 12 months of the trial's completion date. Results data should at a minimum contain the content of the clinical study report synopsis as stipulated in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline "E3: Structure and Content of Clinical Study Report" [29]. The CDE then manually checks the completeness and accuracy of the results data [19].

The degree to which sponsors comply with the legal requirement to upload trial results is unclear. ChinaDrugTrials.org.cn does not allow comprehensive dataset downloads and contains no

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search field enabling users to filter trials by results availability status. The registry states that trial results are for regulatory reference only and will not be made public. Entries for individual trials contain a data field where a "summary of clinical trial results" can be displayed, but those fields are typically blank or else contain data unrelated to trial outcomes (examples: CTR20160828, CTR20160797, CTR20160795). In sum, even if sponsor compliance was high and Chinese regulators had comprehensive access to results, ChinaDrugTrials.org.cn is not effective in terms of public disclosure.

The DRR outlines penalties for non-compliance [18]. Companies failing to prospectively register a clinical trial or upload trial results information in a timely manner may be given a compliance deadline by the regulatory authority. Non-compliance within the stipulated timeframe can lead to a one-off fine imposed by NMPA, ranging from RMB 10,000 (around $1,400) to RMB 30,000 (around $4,200). However, there is currently no information in the public domain about whether such penalties have been imposed in practice.

3.3. The ChiCTR trial Registry

The second platform in China is the public ChiCTR trial registry (https://www.chictr.org.cn/index.html). Legally, it operates as a non-profit academic institution established by the West China Hospital of Sichuan University in 2005. Registration with ChiCTR is voluntary and encompasses various types of clinical trials, including drugs, medical devices, preventive or therapeutic interventions, plus observational studies.

ChiCTR joined the WHO's ICTRP network in 2007. The WHO states that ChiCTR's registration procedures and contents comply with ICTRP and ICMJE standards [32]. This means that trials registered with ChiCTR meet Declaration of Helsinki registration requirements and can publish results in medical journals as per ICMJE policy. ChiCTR accepts registrations for clinical trials conducted in any country and makes all ICTRP data elements public. Furthermore, ChiCTR requires trials to be registered on its platform in both Chinese and English language.

According to ChiCTR's terms of use, the summary results of all clinical trials must be uploaded onto the registry one year after trial completion [33]. The registry does not state how soon after submission the results are shown in the public record. This requirement is not backed by national law.

In response to recommendations of the ICMJE on the sharing of clinical trial data [34] and an ICTRP statement [35], ChiCTR has since 2016 also mandated the submission of an individual participant data (IPD) sharing plan. This plan must include a description of the data repository and its management, as well as the incorporation of IPD sharing information in the informed consent form. IPD must be shareable, with public disclosure required no later than 6 months after the study results are published [36]. The IPD from submitted studies can be viewed through the clinical trial management platform ResMan (medresman.org.cn). ResMan has a public-facing section that lists all submitted trials, allowing the public to search for the corresponding record and review any submitted data on ChiCTR. This requirement too is not legally binding.

3.4. Comparing the Two Chinese Trial Platforms

Table 1 below outlines some important differences between ChinaDrugTrials.org.cn and ChiCTR.

Table 1. Comparing and contrasting ChinaDrugTrial.org.cn and ChiCTR.

	ChinaDrugTrials.org.cn	**ChiCTR**
Authorities and administrators	National Medical Products Administration (NMPA)	Non-profit academic institution
ICTRP primary registry	No	Yes

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Types of studies	Interventional trials only	Interventional and observational
Foreign trials accepted	Only if the results to be used in a Chinese market application	Yes
Language(s)	Chinese	Chinese and English
Registration fees	Range from RMB 192,000 to RMB 502,000 ($26,500 to $69,400)	Free
Mandatory registration	Yes	No
Registration publicly visible	Yes	Yes
Mandatory results reporting	Yes, within 1 year of completion (mandated by national law)	Yes, 1 year after completion (no legal requirement, but registry terms of use require results submission)
Results format	Clinical study report synopsis	Tabular summary results
Results publicly visible	No	Yes

3.5. Clinical Trial Transparency Laws and Regulations in the United States

The FDA is the regulatory agency that oversees clinical research on medical products in the U.S. Several laws and regulations were introduced with the overarching goal of enhancing the transparency of clinical trials, promoting openness in medical research and advancing public health. In 1997, Congress initiated the establishment of the ClinicalTrials.gov registry in order to improve transparency in medical research [37]. However, drug manufacturers continued to selectively publish results [38]. Therefore, Congress revisited the issue in the form of the 2007 Food and Drug Administration Amendments Act (FDAAA). The Act significantly expanded the scope of trials required to be registered, encompassing clinical trials of drugs, biologics, and devices for all indications, with the exception of Phase I trials and small device trials [39]. The 2017 Final Rule (42 CFR Part 11) clarified the provisions of FDAAA regarding the regulatory requirements and procedures for submitting registration and results information for specific trials to ClinicalTrials.gov [40].

Under these regulations, the "responsible party" (either the sponsor or a person designated by the sponsor) is obliged to register trials meeting the legal definition of Applicable Clinical Trial (ACT) in the ClinicalTrials.gov database. This registration must occur within 21 calendar days of the first participant enrolling in the trial. EC approval must be obtained before the sponsor can initiate and register a clinical trial.

When any one of the following changes, the responsible party is required to update the relevant data elements on ClinicalTrials.gov within 30 days: Primary Completion Date, Recruitment Status, or Overall Recruitment Status. Protocol revisions and other updates to the record are to be made at least once every 12 months. Even in cases where there have been no modifications to the record, it is advised that the Record Verification Date for unfinished studies be updated at least every six months.

The 2017 Final Rule mandates the submission of tabular summary results clinical trials. These are highly structured concise tables providing an overview of the key features of a clinical trial [2]. The responsible party must upload the tabular summary results after the date of marketing authorization or product approval, and no later than 12 months after its primary completion date. The primary completion date is defined as the last data collection date for the primary outcome measure in a clinical study when the final participant is assessed or given an intervention [41]. Under

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the Final Rule, a responsible party can request permission to postpone the submission of the results if it intends to seek FDA approval for an unlicensed, uncleared, or unapproved product.

Under FDAAA, sponsors who fail to comply with registration and reporting requirements are subject to a civil penalty. The FDA conducts inspections under the Bioresearch Monitoring Program (BIMO) to determine any violations relating to ClinicalTrials.gov [42]. In theory, in the case of violations, the FDA sends a Pre-Notice of Noncompliance to the responsible party, followed by a Notice of Noncompliance. If the responsible party does not come into compliance within 30 days, the FDA can issue a fine of up to $13,237 per day until compliance is achieved, and can even initiate criminal sanctions [40,43].

In practice, the FDA's enforcement efforts have been limited and unfocused [44]. As of July 2023, the FDA had only issued less than 200 Pre-Notices of Noncompliance and 5 Notices of Noncompliance, and had not imposed any fines [45,46]. The Pre-Notices of Noncompliance are not publicly visible. According to the FDAAA TrialsTracker, more than 4,000 trial results remain undisclosed under the law, in theory accumulating more than $46 billion in fines as of September 2023 [47]. Less than one percent of trials currently in violation of reporting requirements have triggered FDA enforcement actions [48,49].

3.6. Comparison of Regulatory Frameworks in China and the United States

China and the U.S. are the two largest pharmaceutical product markets and exert significant impact on the global pharmaceutical industry [38]. Both jurisdictions have established regulations mandating the registration and disclosure of clinical trial information. Nevertheless, there are notable distinctions between China and the U.S., as Table 2 below shows.

Table 2. Overview of laws and regulations in China and the United States.

	China	**United States**
Authority	National Medical Products Administration - Centre for Drug Evaluation	U.S. Food and Drug Administration
Key laws & regulations	Drug Registration Regulation (2020)	FDAAA Section 801 (2007) and the Final Rule (2017)
Study type	Interventional trials; bioequivalence & bioavailability studies	Interventional trials subject to FDAAA
Trial phases	Phase I, II, III, IV	Phase II, III, IV
Format of results disclosure	Clinical study report synopsis on ChinaDrugTrials.org.cn (not publicly visible)	Tabular summary results on ClinicalTrials.gov (publicly visible)
Delays permissible	No	Yes, but only with FDA approval
Maximum fine ($)	One-off fine of up to $4,200	Up to $13,237 per day until the violation is corrected
Compliance monitoring and enforcement	Unknown	Very weak

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Data platform	ChinaDrugTrials.org.cn	ClinicalTrials.gov

Transparency rules in the U.S. apply to a narrower range of drug trials. In the US, the FDAAA and its Final Rule apply only to ACTs (a legal category that excludes many drug trials) in Phases II through IV. In China, comparable legislation covers all drug trials, including Phase I trials, bioequivalence studies, and bioavailability studies. In addition, sponsors have to update information on trials more frequently in China than in the U.S.

In the U.S., by law tabular summary results must be publicly disclosed on ClinicalTrials.gov. This provides access to trial outcomes not only to the FDA, but also patients, clinicians, and the scientific community. In contrast, ChinaDrugTrials.org.cn de facto only makes trial outcomes available to the national regulator. While the public does have access to trial results posted onto the nonprofit ChiCTR registry, there is no legal requirement for sponsors to disclose outcomes on that registry. China's approach of operating two separate non-interoperable platforms for clinical trial data thus fails to ensure consistent public disclosure of results. It also appears inefficient.

In general, US clinical trial policies are more complex and stringent than China's, possibly due to the longer history of clinical trial regulation in the US and its more sophisticated legal system. Official U.S. documents contain a lot of detail on compliance processes, which are absent in China [44]. Also, potential sanctions are far stronger in the U.S.

In practice, however, both countries' national drug regulators wield substantial discretion in enforcing transparency rules. FDA enforcement actions are very rare, are insufficient to ensure compliance, and are only partially publicly visible. There is no public information on whether Chinese sponsors comply with the law, or on how the Chinese regulator monitors and enforces compliance in practice. This opacity makes direct comparisons of compliance levels and enforcement efforts between the two countries impossible.

4. Conclusion

Recent reports of malfeasance by Chinese drugmakers and apparently lax regulatory oversight by the Chinese authorities have drawn the ire of U.S. Congress [50,51]. In addition, concerns about the safety and efficacy of Chinese COVID-19 vaccines have been raised in many countries [51,52]. The opacity of the inner workings of the Chinese regulator and the lack of public access to trial results submitted on ChinaDrugTrials.org.cn are unlikely to assuage these concerns.

The U.S. has also struggled with concerns about the safety and efficacy of its own COVID-19 vaccines. The failure of the FDA to effectively enforce long-standing transparency rules in the face of widespread and well-documented non-compliance by sponsors may have been a contributing factor.

Our study shows that neither country effectively ensures that all clinical trial results are made public as required by the Declaration of Helsinki and recommended by the WHO. The U.S. framework is significantly more transparent in that summary results uploaded to ClinicalTrials.gov become publicly visible, while results uploaded to ChinaDrugTrials.org.cn remain hidden from public view. At the same time, Chinese disclosure laws cover a far broader range of drug studies. While the U.S. seems to have a lead in terms of transparency, neither country is perfect, and both may be able to learn from each other.

Comparing the actual extent of non-publication across both jurisdictions was beyond the scope of our study. This is a major gap in the literature that we hope other researchers will address in future. More broadly, we encourage fellow regulatory scientists to take a global perspective and routinely include China, India, Japan, Iran and other non-Western hubs of medical innovation in future comparative legal and regulatory analyses.

Conflicts of Interest: The authors have no competing interests to declare. JW works for Citeline (www.citeline.com), a for-profit company that provides a range of services including regulatory intelligence and clinical trial disclosure to industry.

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