WHITE PAPER

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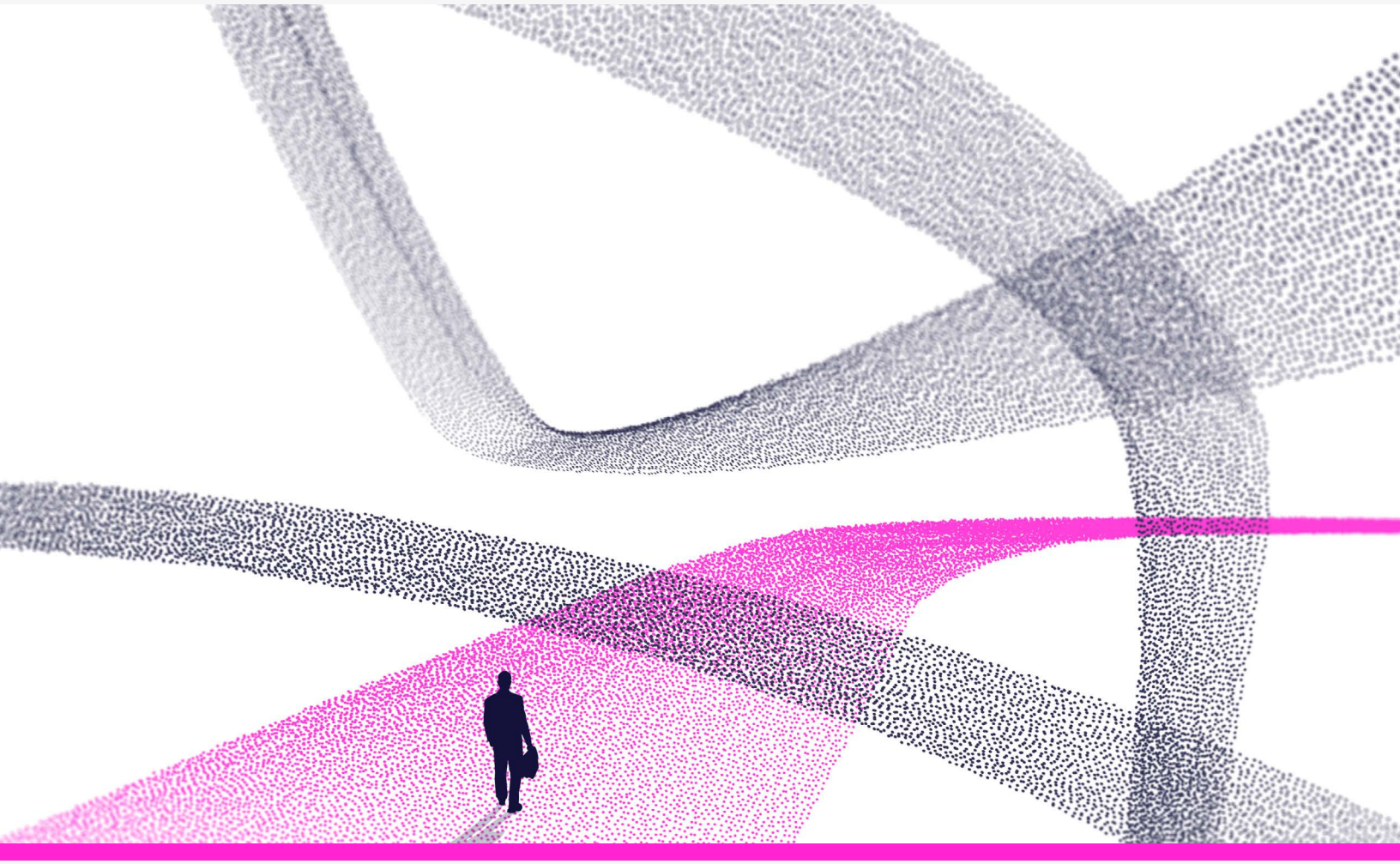
Harmonization of Global Data: Bridging the Gaps Among Local Registries



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The clinical trial disclosure space has evolved considerably over the more than two decades since the US introduced ClinicalTrials.gov in 2000. ClinicalTrials.gov, a system that started with a mere 1,255 registered trials within its first year[1], now has 473,067 registered trials.[2] International Committee of Medical Journal Editors (ICMJE) policy requires studies to be registered to be considered for publication. And clinical trial registries have been established in countries across the globe.

There are currently at least 79 countries with clinical trial disclosure requirements, including 31 countries that follow European Union (EU) requirements. And there are currently 40 countries with at least one clinical trial registry (see Table 1) as well as regional registries including CTIS (the EMA Clinical Trial Information System), PACTR (the pan-African Clinical Trial Registry), and ISRCTN (a global registry based in the UK).

Table 1: Countries with Clinical Trial Registries

Argentina	Indonesia	Malaysia	Philippines	Sri Lanka
Australia	Iran	Mexico	Portugal	Switzerland
Brazil	Israel	Nepal	Russia	Taiwan
China	Italy	Netherlands	Saudi Arabia	Tanzania
Cuba	Japan	Nigeria	Singapore	Thailand*
Germany	Jordan	Pakistan	South Africa	Turkey
Hong Kong	Kenya	Panama	South Korea	United States
India	Lebanon	Peru	Spain	Zimbabwe

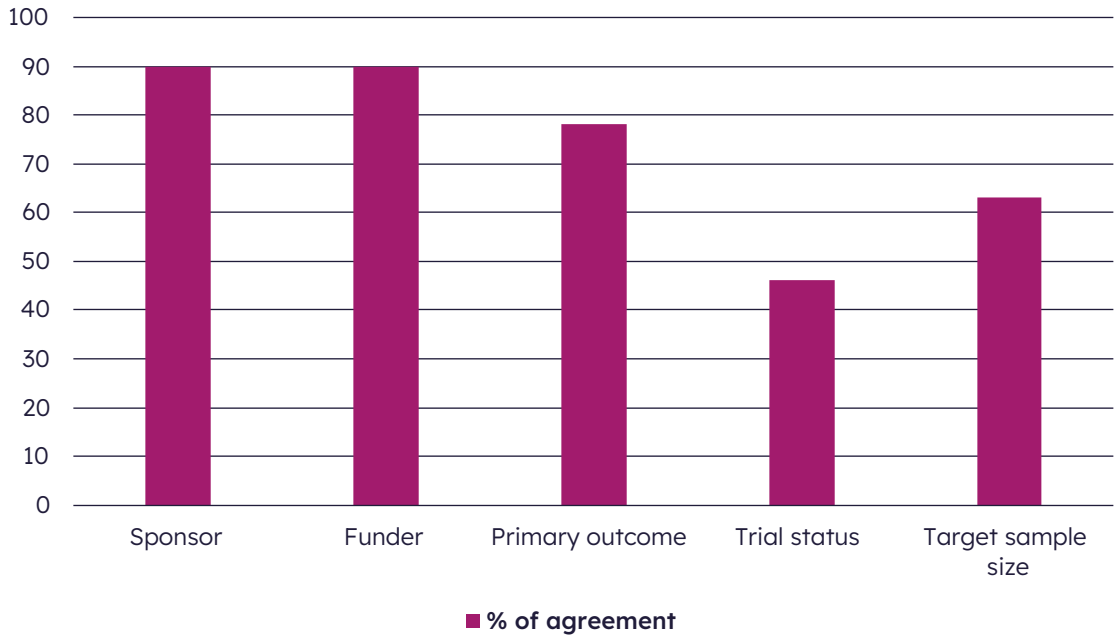
*As of Nov. 13, 2023, the Thai Clinical Trials Registry will no longer accept new trial registrations.

Source: TrialScope Intelligence, December 2023

With these growing registries comes the challenge of submitting multinational clinical trial data. Each registry has its own data standards and requirements, and there is often a lack of overlap between the information each registry requires in their submissions. That can lead to inconsistencies in the data among registries.

In one systematic review of 197 randomized clinical trials registered in more than one trial registry, sponsor and funder had the highest level of agreement among registries. However, agreement level declined as the investigators worked their way down the list of data points (see Figure 1).[3]

Figure 1: Level of Clinical Trial Registry Data Agreement Across Multiple Registries



Source: JAMA Network Open[3]

Regulators zeroing in on disclosure compliance

In the past, there has been little enforcement of disclosure rules. But in recent years, regulators in many regions have begun to enforce the rules around clinical trials disclosure — particularly disclosure of results.

Since 2021, the US Food and Drug Administration (FDA) has issued several public notices of noncompliance to sponsors that have failed to comply with certain requirements for registering and submitting results information to ClinicalTrials.gov.[4] The FDA's maximum penalties for these violations are $14,262 per violation that isn't corrected within 30 days of notice plus $14,262 per day of violation after that 30-day period.[5] All sponsors receiving public notices addressed the issues raised, saving them from these penalties.[4] Still, this shows the FDA is taking a more active role in ensuring sponsors are keeping up with disclosure rules.

In Europe, enforcement of disclosure rules is left up to the individual member states.[6] Fourteen out of the 30 European Economic Area (EEA) member states have stated they will impose fines ranging in the thousands of euros for those who do not comply with disclosure regulations. Belgium has one of the steepest penalties, with fines of up to €500,000 and up to three years in prison for noncompliance.[7]

Though the EU and European Medicines Agency (EMA) haven't published any lists of sponsors in noncompliance with their rules, they have indicated in the past that sponsors often don't post results to EudraCT. For example, the EMA noted that as of April 2019, the EudraCT database included a total of 57,687 clinical trials, of which 47% were completed.[8] Out of these completed trials, sponsors had complied with the publication requirements for 68%, but results were still lacking for 32%.[8]

Currently, the EMA's Clinical Trial Information System (CTIS), which went fully live in January 2022, has 2,395 registered trials[2], with some of those trials being transitioned from EudraCT to CTIS. This total falls short of the estimated 8,000 clinical trial applications[9] taking place in the EU each year.

The bottom line: Some sponsors may be falling behind on disclosure in the EU, which could have them running afoul of EU member states' disclosure regulations and leave them open to penalties.

Disclosure content challenges

For trials conducted in multiple countries, the sponsor typically must deal with each country's registry individually. Each registry requires data at slightly different points in time during the study and requires slightly different data sets. Trying to meet these requirements while harmonizing data across these registries can put a heavy burden on the sponsor.

When conducting trials in multiple regions, sponsors often use local affiliates for support in each country. Each respective local affiliate team may be fully compliant with local disclosure requirements. However, its disclosed data may not align with the data publicly available in other countries. Because there currently are no global disclosure data standards that support submitting the same data to multiple registries, this can make harmonization of data even more complex.

Sometimes local affiliates or CROs responsible for disclosing data outside the US and EU may not coordinate those disclosures with the main sponsor, leading to inconsistencies in disclosed content. Also, there is no good way to track needed translations and whether they are being done in a timely and consistent manner.

Different registries often require data in specific formats or structures, challenging uniform submission. For example, one registry might allow a free-text entry to describe the inclusion/exclusion criteria, while other registries may have drop-down menus or radio buttons with preset text. These differences make alignment difficult, if not impossible.

This also can present a challenge when handling complex study designs. In some cases, it can be difficult to accurately represent complex study designs and protocols in a way that aligns with registry requirements. One registry may have extensive and detailed data fields, while another may be more limited in scope. Depending on the study, there is also the issue of ensuring all required information is provided in each registry.

There is often a need to frequently update and amend trial data as the trial progresses, which can be cumbersome and time consuming when multiple registries are involved. It can be challenging to ensure that the relevant trial registries are updated with consistent data to reflect the updates and amendments.

There is also the matter of reconciling data discrepancies between internal records and what is reported in registries, especially when multiple departments contribute data. Since data reside in multiple places, such as forms or attachments, it can be difficult to see an overview of all data and what has been disclosed where. And with updates required in

Risks of Noncompliance with Disclosure Regulations

Legal Penalties: Noncompliance can result in significant legal penalties, including fines and legal actions.

Reputational Damage: Failure to comply can harm the organization's reputation, impacting public trust and relationships.

Ethical Implications: Noncompliance can be seen as a breach of ethical standards in clinical research.

multiple places, there can be changes in data or failure to update between forms.

Failing to address these complexities can result in a lack of data harmonization across registries. This is important because some transparency advocates are starting to look at consistency of content disclosed across registries. That means regulators will likely start taking that into account, if they have not already.

Risks of poorly harmonized content

Having poorly harmonized content across registries is risky. For instance, inconsistent content can inadvertently expose intellectual property, jeopardizing patent protection. Poorly managed disclosures have resulted in the rejection of drug patents in at least two countries.[10,11]

Inconsistencies in content among registries can lead to questions about the trial data's integrity and reliability. Discrepancies in data can also attract additional regulatory scrutiny and investigations.

Inconsistent disclosure can decrease public trust in the sponsor and its research process. If the content for one trial differs from registry to registry, it can cause the public to doubt the truthfulness of all the sponsor's disclosures.

Discrepancies can hinder the effective redaction or anonymization of sensitive information, risking unintended disclosure. Inconsistencies can also complicate the interpretation and comparison of trial results, as well as increase operational costs and efforts.

Best practices to address these challenges

Many of the best practices for addressing risks of poor content harmonization across regions are similar to the best practices for addressing any disclosure challenges. Sponsors must look to their internal processes to see where gaps exist and do their best to close them.

One way to do that is by developing an overall disclosure and transparency policy to help align standard operating procedures (SOPs) across the organization and understand what should be disclosed and managed. It is also important for the policy and SOPs to be updated regularly to keep pace with the ever-changing global disclosure and transparency landscape.

It is also important for sponsors to clarify disclosure and transparency requirements with all stakeholders, including study teams, local partners, affiliates, and contract research organizations (CROs). This way, everyone is aligned as to what the SOPs are, and data are kept consistent across the board.

Sponsors should conduct audits of clinical trial disclosures to ensure compliance with all regional requirements and consistency of data content. As part of these audits, they should prepare detailed documentation in the event of regulatory inspection or request for information (RFI) from the regional agency in question.

A central team should track what trial sponsors and their local affiliates are disclosing, as well as when and where information is being disclosed. This will allow sponsors to have a general oversight of the trial across all regions in which it is conducted.

When building this central team, sponsors need to find and retain enough qualified experts with experience to operationalize disclosure regulatory requirements. The team should actively monitor local regulations for amendments and track inspections to see how they are being enforced.

Sponsors should actively engage with disclosure communities, industry associations, health authorities, and registries and advocate for reasonable disclosure practices with health authorities and ethics committees. As part of that effort, they should encourage these

stakeholders to take a hard look at global disclosure to identify the reporting requirement discrepancies from one country to the next so that they can begin to create alignment.

As disclosure demands increase, sponsors can implement process automation and technology solutions to minimize compliance risks, reduce duplicate work, and enable global visibility. One way to do this is by subscribing to a disclosure-focused intelligence tool and/or engaging specialized vendors to handle disclosure and transparency practices with confidence.

In conclusion

There is no question sponsors have made great strides in their global disclosure efforts. But more needs to be done to remain in step with this continually evolving field. One area where gaps remain is in data harmonization across multiple global regions. By establishing uniform SOPs, creating a central transparency and disclosure team, and utilizing technology solutions to manage data across stakeholders in all regions, sponsors can bridge those gaps and ensure global data consistency.

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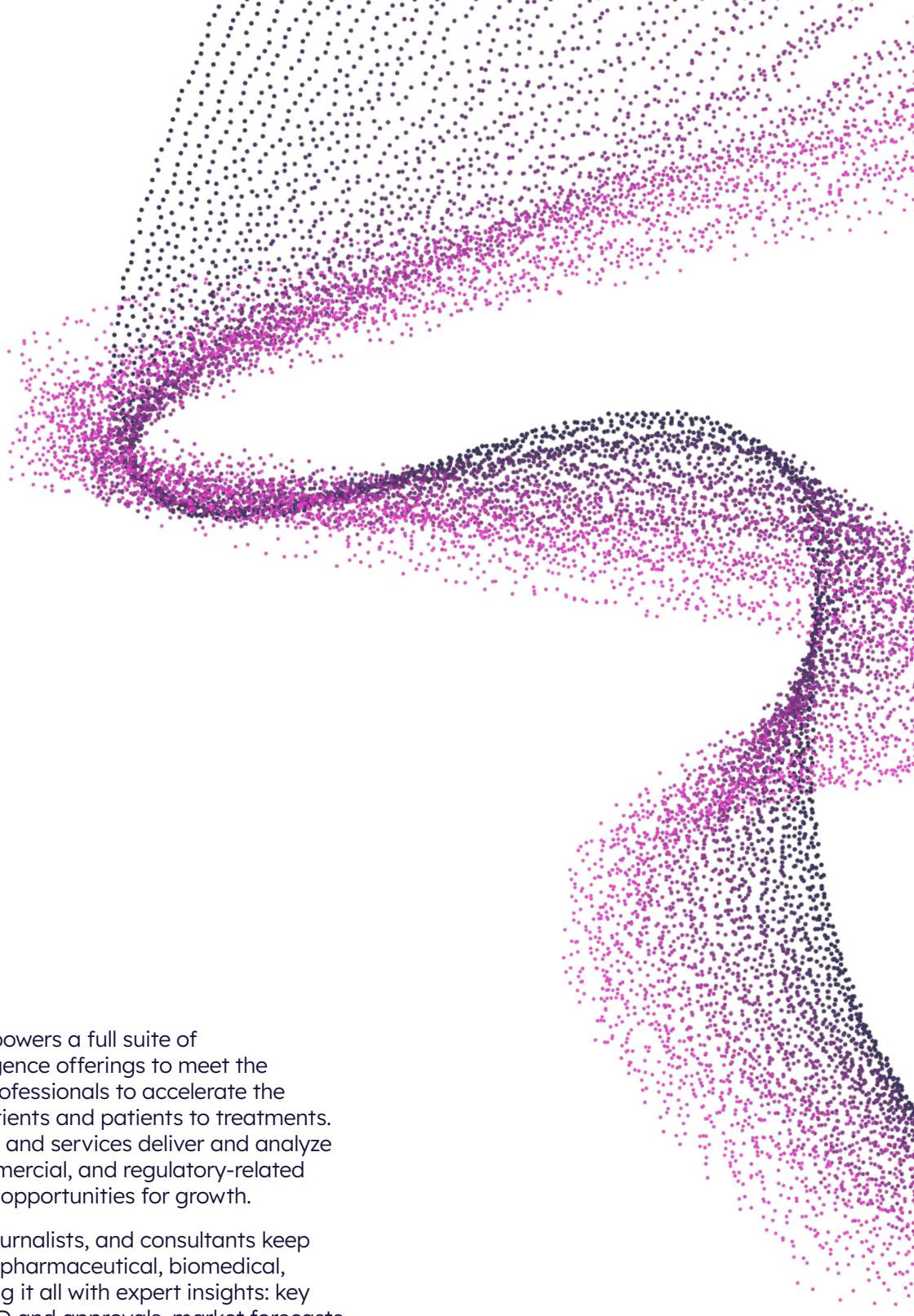

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