TRIALSCOPE INTELLIGENCE
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White Paper

The State of Global Clinical Trial Disclosure:

What Noncompliance Penalties Are in Place, and How They Are Enforced

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Contents

Introduction

By Darcy Grabenstein

The coronavirus pandemic put clinical trials in the spotlight — or hot seat, depending on one's perspective. Around the globe pressure came from multiple fronts: regulatory agencies, the public, patients, advocates, pharmaceutical industry watchdogs ,and investors all clamored for increased clinical transparency. The push for accountability has not abated for study sponsors to publish results in a timely manner. However, just as there are numerous regulatory agencies and guidelines (approximately 90 countries have requirements related to the disclosure of clinical trial data made publicly available on over 30 clinical trial registries), enforcement of clinical trial disclosure requirements varies greatly.

While study sponsors have come under fire for failure to disclose trial information, so too have regulatory agencies. The US National Institutes of Health (NIH) failed to ensure the timely reporting of results in roughly half of the clinical trials it funded in 2019 and 2020, according to a report released by the Department of Health and Human Services' Office of Inspector General. In some cases, the agency allowed noncompliant researchers to launch new trials.

A 2022 Health and Human Services inspector general's office audit of the NIH revealed that of 72 intramural and extramural trials, only 35 submitted results were on time, 12 were submitted late, and 25 never submitted. The report reads: "NIH did not have adequate procedures for ensuring that responsible parties submitted the results of clinical trials, took limited enforcement action when there was noncompliance, and continued to fund new research of responsible parties that had not submitted the results of their completed clinical trials."

Its recommendation included that the NIH "take enforcement actions against responsible parties that are late in submitting trial results or do not submit results."

The European Medicines Agency (EMA) refused to release major documents containing clinical data, including adverse effects, produced by pharmaceutical companies, according to a 2022 report. The report concluded: "The European Parliament and the European Commission, which are responsible for adherence to the institutional and regulatory principles of the EU, should also ensure that clinical study reports are published in their entirety, as required by the Clinical Trials Regulation [CTR]."

That said, lack of transparency at a regulatory agency does not diminish the sponsor's responsibility to comply with disclosure deadlines.

Industry Organizations

Many pharmaceutical industry groups have issued statements or developed policies regarding clinical trial disclosure. Following are several organizations that have taken a stance on transparency.

The **International Committee of Medical Journal Editors (ICMJE)** "requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication." In addition, the ICMJE recommends that journals publish the trial registration number at the end of the abstract.

The trade organization **International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)** provided this statement on disclosure: "The innovative pharmaceutical industry is committed to the transparency of clinical trials that are sponsored by our member companies. We therefore commit to a set of principles regarding the disclosure of information relating to clinical trials we sponsor and appeal to all sponsors of clinical trials to commit to keeping these registries accurate and up to date."

The **Pharmaceutical Research and Manufacturers of America (PhRMA)**, in response to a request for comment, released this statement: "PhRMA members are committed to enhancing public health and advancing the development of medicines by sponsoring and conducting clinical research that fully complies with all legal and regulatory requirements. Further, our Principles for Responsible Clinical Trial Data Sharing set forth PhRMA members' commitment to enhancing public health through responsible sharing of clinical trial data in a manner that safeguards the privacy of patients, respects the integrity of national regulatory systems, and maintains incentives for investment in biomedical research."

In May 2017, over 20 international regulatory agencies and related organizations signed a joint statement from the **World Health Organization (WHO)** on public disclosure of results from clinical trials. The signatories agreed to the following: "Within 12 months of becoming a signatory of this statement, we each pledge to develop and implement a policy with mandated timeframes [12 months from primary study completion] for prospective registration and public disclosure of the results of clinical trials that we fund, co-fund, sponsor or support. We each agree to monitor registration and endorse the development of systems to monitor results reporting on an ongoing basis. We agree to share challenges and progress in the monitoring of these policies. We agree that transparency is important and therefore the outputs from the monitoring process will be publicly available."

A 2022 paper co-authored by Till Bruckner, PhD, founder of TranspariMED, a nonprofit working to end evidence distortion in medicine, posed this question: Do European medical research funders require grantees to register and report clinical trials in line with **WHO** best practices? This cross-sectional study of the 21 largest nonmultilateral public and philanthropic funders in Europe found that funders implemented a mean of 36% of WHO best practices in clinical trial transparency.

A total of 14 funders (66.7%) mandated prospective trial registration and six funders (28.6%) required that trial results be made public on trial registries within 12 months of trial completion. Less than half of funders actively monitored whether trials were registered (9 funders [42.9%]) or whether results were made public (8 funders [38.1%]).

The Global Landscape

Let's take a look at a broad spectrum of global regulations, whether penalties exist for noncompliance and, if so, whether they are being enforced. Citeline reached out to all major regulatory agencies; those listed below provided requested updates.

NORTH AMERICA

The US

As in all areas the FDA regulates, the agency's goal is to achieve voluntary compliance with applicable legal requirements. The FDA's compliance activities related to the ClinicalTrials.gov requirements provide the opportunity for responsible parties to take voluntary corrective actions before the agency proceeds with a civil or criminal enforcement action. The agency uses a risk-based approach to compliance and enforcement to prioritize the greatest risks to public health and works with responsible parties to help them voluntarily comply.

The FDA is authorized to seek civil money penalties for violations of the ClinicalTrials.gov requirements. Responsible parties that fail to submit clinical trial results information for certain applicable clinical trials to the ClinicalTrials.gov databank could also be subject to an injunction and/or criminal prosecution. Penalties of $13,327 (maximum adjusted penalty) are in place for all violations adjudicated in a single proceeding and, if a violation is not corrected within 30 calendar days following notification of such violation, the law provides for an additional civil money penalty for each day the violation continues until it is corrected.

The FDA is required by law to issue a Notice of Noncompliance to a responsible party whom the FDA has determined has failed to comply with this requirement. To date, the FDA has issued 92 Pre-Notice Letters and four Notices of Noncompliance to encourage compliance with the ClinicalTrials.gov requirements. The four recipients of Notices of Noncompliance submitted the required clinical trial information, a testament to the effectiveness of enforcement, and the agency did not pursue civil money penalties against them. The FDA has not yet pursued civil money penalties against any responsible parties.

However, the FDA has defined a limited approach to identify violations. A violation may be detected during a Bioresearch Monitoring (BIMO) inspection or based on an evaluation of complaints received by the agency. FDA enforcement to date is perceived as being extremely slow. Even though over 4,000 clinical trial results are missing in the US (24% of trials that require results under the Final Rule), the FDA is currently only sending out two notices per week. "Just put 10,000 letters in the mail," advises TranspariMED's Bruckner. "Sending out letters to people who break the law is not a difficult regulatory decision."

While the US may be one of the few countries taking baby steps to enforce clinical trial disclosure, some say more enforcement is needed.

US Academia Brings Up Its Grades, After 'Report Card' Goes Public

Navya Dasari is a woman on a mission. A student at New York University's School of Law, she is a member of the North American Coordinating Committee for Universities Allied for Essential Medicines (UAEM). The health justice organization focuses on access to medications and drug pricing.

She said the issue of clinical trial results reporting "struck me as something that shouldn't be controversial." In 2019, UAEM, in conjunction with TranspariMED, published first report on clinical trials conducted by US universities.

A key takeaway, Dasari noted, was the significant lack of transparency in academia, even more so than at pharmaceutical companies. After UAEM members discussed the results with administrators at various universities, Dasari said some of the worst offenders became 100% compliant.

UAEM conducted a follow-up report in 2021, which revealed that over half of the top 40 research universities were in violation of transparency regulations. In the wake of the report, Columbia University went from a 16.7% compliance rate in 2019 to 100% in 2021. And the number of institutions above an 80% compliance rate increased from 16 to 36.

Dasari said FDA Commissioner Robert Califf has highlighted the need for better compliance: "I think with him at the head of the FDA we're really excited to see greater enforcement."

Dasari isn't the only one who expressed her dissatisfaction in writing. In January 2023, Frank Pallone, ranking member of the House Energy & Commerce Committee, sent a six-page letter

Navya Dasari

to the Food and Drug Administration (FDA) and National Institutes of Health (NIH), criticizing the organizations for not doing enough to enforce pharmaceutical companies' disclosure compliance on ClinicalTrials.gov. "FDA and NIH both have a role in enforcement of ClinicalTrials.gov requirements," the letter reads.

Making a Case for Clinical Trial Transparency

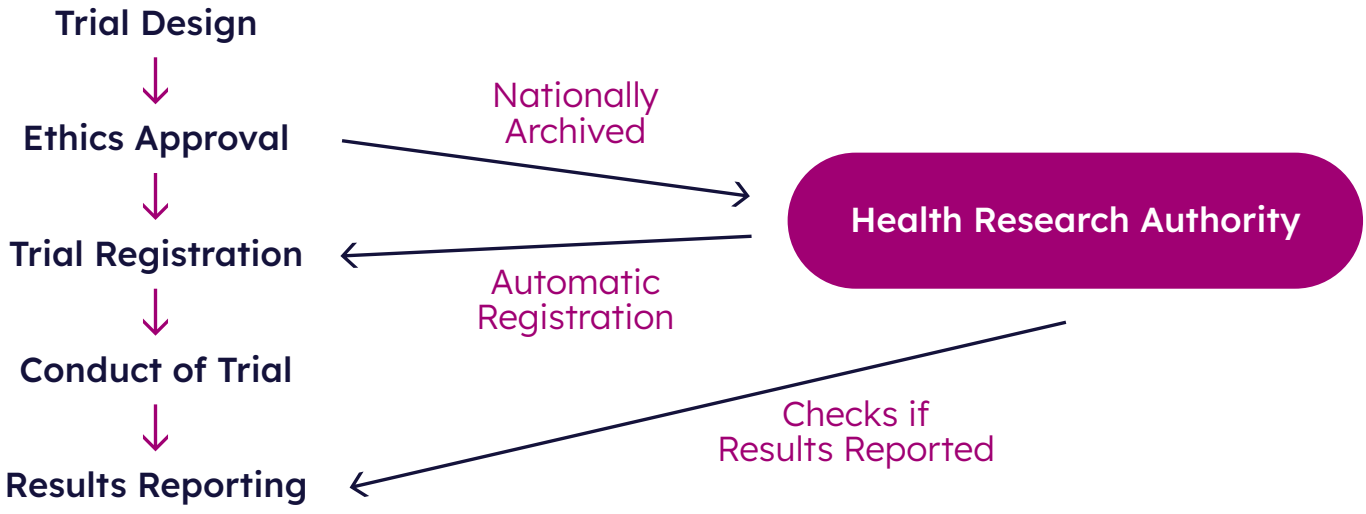
Bruckner, who founded the aforementioned TranspariMED in 2017, is a vocal advocate for clinical trial transparency. He is also a partner in Consilium Scientific, a nonprofit research and educational organization dedicated to informing and enacting health policy change in the UK and around the world. "Failure to register and fully report clinical trials harms patients, wastes taxpayers' money, and slows down the development of new treatments, vaccines and cures," Bruckner said.

He said one of his biggest accomplishments is getting a lot more groups to understand the problem and push for policy solutions. He has brought together over 30 groups in over a dozen countries. He brought Transparency International on board because it is "outside the narrow medical scene; that's sustainable." One of his biggest challenges is capacity/bandwidth to keep up with so many countries' regulations.

Bruckner said the UK is the only country that has addressed the transparency problem since 1980. He cited the UK's national clinical trial strategy as "the gold standard," cutting unnecessary bureaucracy and paperwork. "Countries should really look to the UK for a way to solve this problem in a way that doesn't aggravate sponsors, the industry, in a way that's efficient.... Look to the UK model." (See more on UK regulations below.)

Till Bruckner

Figure 1: Potential Solution: UK Model



Canada

In 2019, the Canadian government created a new online portal to access clinical study reports. However, according to a 2022 article in Citeline's In Vivo, the Canadian regulator never passed regulations to build on a 2014 law stating there is a duty to publicize clinical trial information. New draft guidelines on registration of trials and public disclosure of results were released in February 2023 and are out for public consultation until April 24.

LATIN AMERICA

Argentina

According to the book *Clinical Trials in Latin America: Where Ethics and Business Clash* (2014), in 85% of the protocols approved by external private research ethics committees (RECs), the Institutional Council for the Review of Research Studies (CIREI) found a total of 92 infractions of **The National Administration of Drugs, Foods and Medical Devices of Argentina's** (ANMAT's) standards and regulations. For example, 42% of the protocols did not state that results of the trial would be made public and 24% did not assume any obligation to participants following the conclusion of the study. Another study, focused on clinical trial registration, suggested that to increase compliance and promote clinical trial registration, national health authorities, sponsors, and local investigators could implement a grassroots educational campaign to improve clinical trial regulation.

Mexico

Most industry-sponsored studies in Mexico aim to comply with FDA regulations, while national regulations are less strict compared to international standards. The agency responsible for regulation in Mexico is the **Federal Commission for the Protection against Sanitary Risks (COFEPRIS)**. In terms of registration, once an applicant has received an authorization letter from COFEPRIS, registration is mandatory and must be completed within five business days. Many trials are tracked on ClinicalTrials.gov, where Mexico currently has over 4,000 registered trials, many of which have yet to report results.

According to the *Clinical Trials in Latin America* book, "No specific provisions exist to assure study participants that they will benefit from the results of the clinical trial."

THE UK

The timeframe for publishing summary results is within one year (six months for pediatric trials) of the end of trial, according to **UK's Medicines and Healthcare products Regulatory Agency (MHRA)**. Where applicable, it advises sponsors to publish summary results within this timeframe in the public register(s) where the trial is registered.

The UK government will introduce a legal requirement to make public the results of all clinical trials within 12 months of trial completion. Any company or university breaking the law will be refused permission to start new trials, the UK drug regulator announced on March 21.

Sponsors do not need to submit the summary report to the MHRA, but must confirm via email once the result-related information has been uploaded to the public register. If a clinical trial is not on a public register or the results will not be published in the register (for example, an adult Phase I study), summary results should be submitted via MHRA Submissions. Sponsors should also submit a final report to the Research Ethics Committee within the same timeframe

for reporting the summary of results. Sponsors of trials conducted in UK already registered in the EU Register are able to submit results to EudraCT.

A spokesperson for the UK's Health Research Authority said: "Transparency about what research is going on, and what its findings are, is important for patients, service users and the public. It builds trust and accountability, acknowledges their contribution and encourages participation in research. Being transparent also avoids duplication of effort and enables findings to be used to develop new and better treatments for patients and service users.

"Our Make it Public campaign demonstrates our commitment to support and encourage the research sector to be transparent and open."

THE EUROPEAN UNION (EU)

From July 2014 to Jan. 31, 2023, it was possible to register a trial on EudraCT under the EU Clinical Trials Directive. While results were required under the directive, there was no enforcement mechanism and no penalties could be imposed. Since Jan. 31, 2022, trials posted on the Clinical Trials Information System (CTIS) under the EU Clinical Trials Regulation (mandatory for new trials since Jan. 31, 2023), European Economic Area (EEA) member states have the regulatory framework to impose penalties, as described below.

The regulation enables significant improvements concerning the public availability of information on clinical trials conducted in the EU/EEA, including summary of results, via the public CTIS website. Article 37(4) of the regulation provides a clear legal obligation to post clinical trial results, together with a plain language summary of the results, within one year from the end of the clinical trial. It allows member states to impose penalties applicable to infringements of the Regulation (Article 94), and to take all measures necessary to ensure that they are implemented. In January 2023, Pink Sheet reported that the EMA is working on restarting this landmark policy on publishing clinical trial data, with the first phase expected to start this year.

The EMA notes that it is important to make the distinction between the disclosure rules which have been applying in the context of the EudraCT website (and its public interface, the Clinical Trials Register), and those which apply now since the implementation of the Clinical Trial Regulation and the launch of the CTIS, which became mandatory for submissions as of Jan. 31, 2023.

In a prepared response, the EMA said: "[T]ogether with the European Commission and the member states, [the EMA is] aware that there is still work to be done to improve the situation and have taken a number of actions to further improve the reporting rate of summary of results in the Clinical Trial Register. Since September 2018, EMA has been regularly identifying trials with missing due results. EMA, together with the European Commission and the member states, have been working on a number of actions to further improve the reporting rate in the EU Clinical Trials Register. EMA has substantially improved the EudraCT website and its instructions in order to make results reporting easier for academia and for commercial sponsors."

The EMA concluded with this statement: "Transparency is an essential component of clinical research, and clinical trial information and results need to be publicly available."

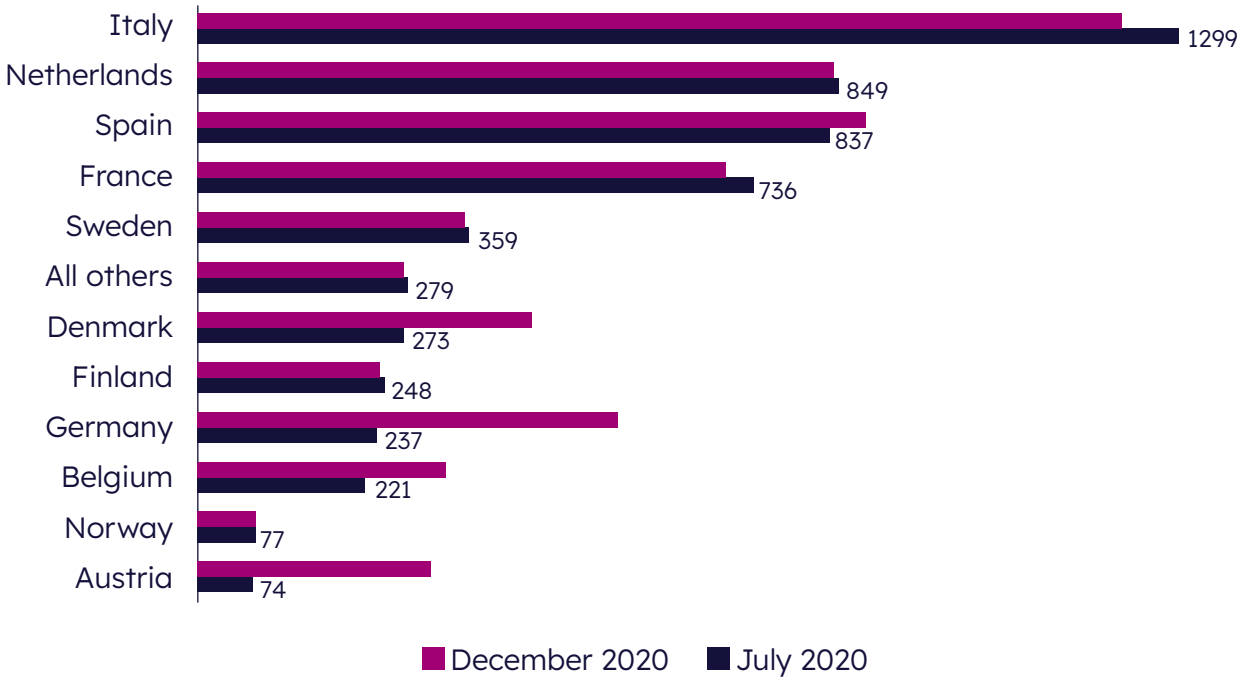
Following the June 2019 issuing of a joint letter reminding all sponsors of clinical trials conducted in the European Union of their obligation to make summaries of results of concluded trials publicly available, national competent authorities (NCAs) and the EMA have sent reminders to noncompliant sponsors, to

increase compliance with the transparency rules and their follow-up on reporting obligations. According to the EMA, due to these reminders, the percentage of posted results substantially increased. However, for some trials the reminders were not successful: Many sponsors could not be reached. A list of trials for which sponsors could not be reached, or for which sponsors did not follow up on the request of results posting, is published on https://www.clinicaltrialsregister.eu/.

The posting and publication of summary results in the EU Clinical Trials Register is further set out in a European Commission guideline. The publishing of results has been required since July 2014. However, there is no legal basis for EMA to impose penalties on sponsors who are not fulfilling the legal requirements to provide results in EudraCT. According to section 4.7 (noncompliance, factual inaccuracy) on posting and publication of result-related information on clinical trials, it is the responsibility of the member states to verify that, for clinical trials authorized by them, the result-related information is posted to the agency and therefore to decide on further actions.

A study published in January 2023, "Towards full clinical trial registration and results publication: longitudinal meta-research study in Northwestern and Central **Switzerland**," found that approximately 10% of clinical trials remained unregistered despite the legal obligations. "More support for investigators and stricter enforcement by regulators are needed to improve the transparency of investigator-sponsored trials in particular."

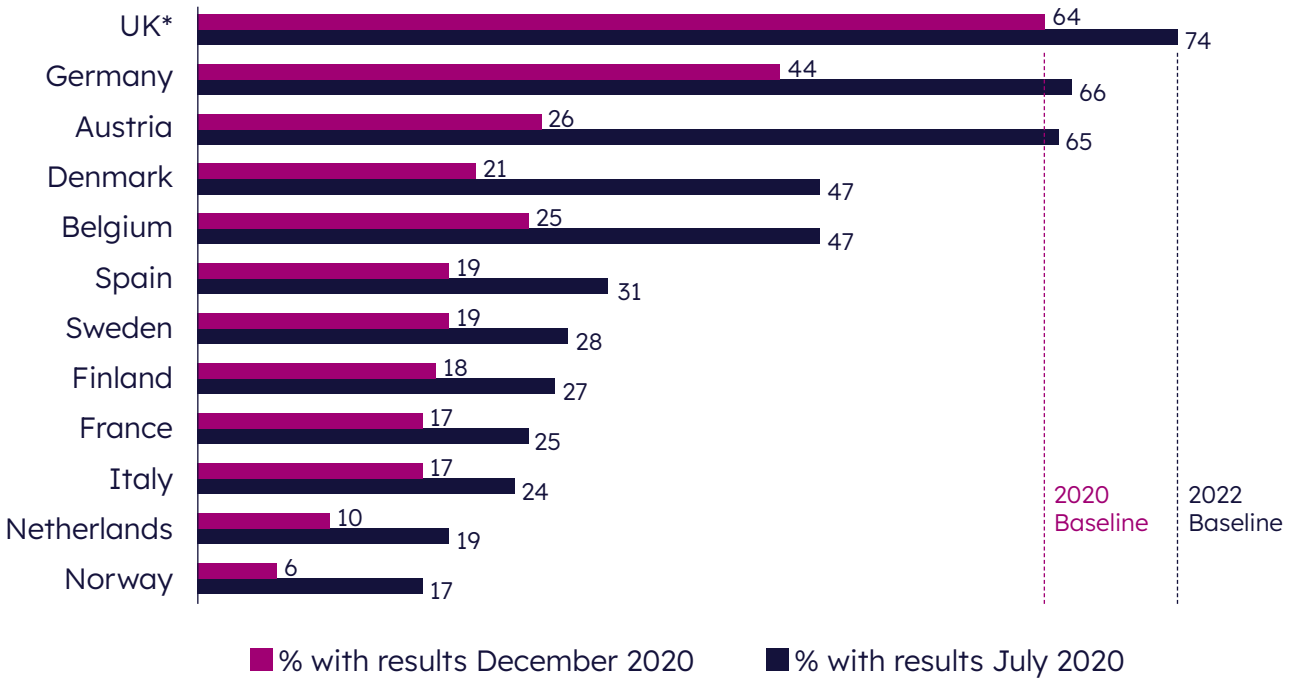
Figure 2: Number of Missing Trial Results
Single-country trials approved up to 2016 only, estimate



Source: TranspariMED

National medicines regulators in Europe have failed to ensure the publication of at least 5,488 clinical trial results, the report states. On a more positive note, the star performer was **Austria**, which increased its reporting rate from 26% to 65% within less than two years. **Germany** and **Austria** also achieved high reporting rates, and **Denmark** and **Belgium** made substantial progress.

Figure 3: Percentage of Trials with Results
Single-country trials approved up to 2015 only



Source: TranspariMED

A September 2022 report, the first of its kind, published by TranspariMED, Consilium Scientific and other and other European health groups, found gaps in clinical trial disclosure regulations across Europe.

Key findings of the report include:

- Regulators in at least five countries — **Austria, Belgium and Denmark** — are actively prompting trial sponsors to make the results of their past drug trials public.
- Regulators in four countries — **France, Italy, Spain and Sweden** — appear to be taking little or no action on missing drug trial results. In January 2023, Italy released its Register of Observational Studies (RSO); registration is mandatory for new requests submitted for Ethics Committee review, and results are due within 12 months of study completion. Legal basis for the RSO is Article 6 of the Ministerial Decree of Nov. 30, 2021.

- None of the countries covered have laws requiring the publication of clinical trial results that do not involve investigative drugs or medical devices. Legislation for Austria, Germany and Sweden is unclear whether regulations apply specifically to results reporting.

EU member states that impose fines for failing to report the results of a drug trial*:

Country	Fines
Austria	€25,000 - €50,000
Belgium	€550 - €250,000
Denmark	To be determined
Finland	To be determined
Germany	€25,000 maximum
Netherlands	€33,500
Sweden	To be determined

*Updated to reflect current fines.

A month later, TranspariMED published another report on compliance in the EU. The report showed that the majority of unreported drug trial results in Europe were concentrated within just four countries: **Italy, the Netherlands, Spain and France**.

TranspariMED's Bruckner commented: "We are seeing a clear willingness by many national regulators within the European Union to impose sanctions if clinical trial sponsors fail to comply with legal CTIS results reporting requirements. I think many regulators' patience has run out."

Belgium

Belgium was the first EU country to disclose specific details about its penalties. As of February 2022, the **Federal Agency for Medicines and Health Products (FAMHP)** has the authority to impose fines of €550 to €250,000 and a prison sentence of up to two years for failure to report results. Repeat offenders can face maximum penalties of a €500,000 fine and a three-year prison sentence. What's more, a judge can ban repeat offenders from participating in clinical trials for three to 10 years. It's important to note that this law applies only to trials for drugs, not medical devices, and only covers drug trials registered on the new EU-CTIS trial registry since January 2022.

An August 2021 notice from the Federal Agency for Medicines and Health Products calling for sponsors to publish clinical trial results begins: "The FAMHP reminds all sponsors they are obligated to publish the results of their clinical trials in the European Clinical Trials Database (EudraCT) within one year after the end of trial date (or six months for a paediatric trial). Publication on external sources or the transmission of reports to national competent authorities is not sufficient. The guideline applies retrospectively. Results should be posted in the EudraCT database as soon as possible…." In terms of enforcement, the letter only states: "The FAMHP will contact all sponsors of clinical trials that have been conducted and completed in Belgium for which no results have been uploaded in EudraCT."

If a violation is found, a determination will be made by a GCP inspector of the FAMHP, who may then prepare a pharmacovigilance (PV) document of determinations. This PV document, together with the inspection report, will be transmitted to the violator and the FAMHP official-lawyer (being the head of the Division of Legislation and Disputes). The official-lawyer can then, in consultation with the inspection, propose an amicable settlement to the offender for a minimum €4,000, the minimum amount of the fine multiplied by the applicable surcharges.

The Czech Republic

The requirements for clinical trials of medical products and everything related to them are specified in the national legislation which, although not currently aligned to EU regulations, refers to the 2003 EU directive (Act on Pharmaceuticals; Decrees). The Czech Republic's first national law, Pharmaceutical Act, No. 79/1997, was amended several times. In short, a study sponsor must submit a final report into the EudraCT database (CTIS).

The Act on Pharmaceuticals also lists misdemeanors and sanctions for noncompliance. Sanctions could be imposed by the Legal Department of **SÚKL**, the State Institute for Drug Control. For enforcement, officials rely on GCP inspections. However, GCP inspections typically only focus on the conduct of the trial; it is unclear whether this would include clinical trial disclosure.

Denmark

In October 2020, the **Danish Medicines Agency** (DKMA) announced it was taking tougher action to ensure the publication of clinical trial results. It cited a 2019 survey showing that only 23.6% of the non-commercial sponsors in Denmark fulfilled their obligation to publish the results from clinical trials of medicines.

Sponsors are responsible for sending clinical trial results to EudraCT. Sponsors who fail to publish the results in alignment with CTIS requirements are liable to a fine or imprisonment of up to four months. Interpretation of Chapter 6 of the Act on Clinical Trials indicates that the DKMA will check for Article 37 of Regulation 536/2014 (to submit results to CTIS rather than EudraCT in this context). The DKMA will send a reminder to noncompliant sponsors and then take further steps if the results are not reported. The agency cannot itself issue a fine or sentence sponsors to imprisonment; it must go through the public prosecutor.

Estonia

The **Estonian Medicines Agency** is the regulatory body governing clinical trials in Estonia. All trials in Estonia are run according to the Medicinal Products Act. Chapter 5 of the act regulates clinical trials in humans, stating: "The sponsor must submit an Estonian summary of the results of a clinical trial of a medicinal product aimed at an ordinary user to the database specified in Article 81 of Regulation (EU) No 536/2014 of the European Parliament and of the Council in accordance with Article 37(4) of the same Regulation."

Estonia goes into great detail regarding various types of noncompliance. The sanction for noncompliance with the requirements of a clinical trial of a medicinal product, including provisions governing the submission of data or the safety of a trial subject, is a fine of up to 300 fine units. According to the European Commission, one fine unit equals €4, for a total fine up to €1,200. The sanction for the same act committed by a legal person is a fine of up to €32,000.

Finland

In Finland, no penalties have been established in legislation for noncompliance of clinical trial results reporting, neither under the Clinical Trial Directive 2001/20/EC or Clinical Trials Regulation No 536/2014.

Sweden

According to Article 67b of Sweden's Federal Act on Medicinal Products and Medical Devices, the Federal Council may, taking into account internationally recognized regulations, require publication of clinical trial results.

Chapter 14 section 3, referring to EU pediatric regulation and EU directives, and chapter 16 section 1 of the Medicinal Products Act (2015:315) (läkemedelslagen) provide the legal foundation for the **Swedish Medical Products Agency (MPA)** to issue injunctions and prohibitions necessary for compliance with the EU-CTR in relation to clinical trials. Although the legislation does not specify clinical trial results, decisions on injunctions or prohibitions may be accompanied by a fine, the amount determined per the Act on fines (viteslagen).

ASIA-PACIFIC

China

The Chinese Clinical Trial Registry (ChiCTR) is a WHO International Clinical Trials Registry Platform (ICTRP) primary registry. As per its guidelines, after the completion of a trial, the statistical results should be uploaded to ResMan, a public management platform for clinical trials, and the results should be published one year later.

Additionally, as per the Provisions for Drug Registration (SAMR Order No. 28) (managed by **Drug Evaluation Center of China**, NMPA), trial registration is required. The provisions were promulgated by the State Administration for Market Regulation (SAMR) and officially implemented July 1, 2020:

"The sponsor shall register the drug clinical trial protocol and other information on the drug clinical trial registration and information disclosure platform before carrying out the drug clinical trial. During the drug clinical trial, the sponsor should continuously update the registration information, and register the drug clinical trial results and other information after the drug clinical trial is completed. The registration information is publicized on the platform, and the sponsor is responsible for the authenticity of the drug clinical trial registration information."

Sponsors found in violation of the following shall be ordered to make corrections within a specified time limit. Failure to do so shall result in a fine of not less than 10,000 yuan but not more than 30,000 yuan:

1. Failure to register on the chictr.org.cn platform as required before conducting drug clinical trials;
2. Failure to submit a safety update report during research and development as required;
3. Information such as clinical trial results are not registered after the drug clinical trials are completed.

Hong Kong

Under Regulation 36B of the Pharmacy and Poisons Regulations (Cap. 138A), a Certificate for Clinical trial/medicinal test (the certificate) is required for the purpose of conducting a clinical trial on human beings. The certificate application must include a copy of the protocol. Anyone violating this regulation is liable to a fine. The regulation only applies to pharmaceutical products. The regulation does not address disclosure of results.

India

A 2018 study, "Trial publication after registration in Clinical Trials Registry of India (CTRI): A cross-sectional analysis of randomized controlled trials," is revealing about the lack of transparency in clinical trials in India. The study was conducted by the Campbell Collaboration, an international social science research network, and three other entities. It looked at trials from June 2009 to June 2015.

The study found that none of the trial details were fully complete as per WHO criteria. Out of 2,938 trials, publication details of 78 (2.6%) were mentioned in the Clinical Trials Registry - India (CTRI). From publication details of 676 trials, the average time to publication was 21.13 months. Sources of monetary support and government funding were found to be significant towards influencing publication status.

Prospective registration on CTRI is mandatory per the "New Drugs and Clinical Trials Rules," although results posting is not mentioned. Wording from the **Central Drugs Standard Control Organisation (CDSCO)** indicates that "Failure to comply with any provision of the Act may result in one or more of following actions: i) written warning issued; ii) rejection of the results of the clinical trial; iii) suspension or cancellation of permissions; iv) barring of the investigator or sponsor from future clinical research, for such period as considered appropriate by the DCGI [Drugs Controller General of India]."

Japan

The Japan Registry of Clinical Trials (jRCT) is a WHO ICTRP primary registry, funded by Ministry of Health, Labour and Welfare, while the Japan Medical Association, Center for Clinical Trials (JMACCT), Japan Pharmaceutical Information Center (JAPIC), and University Hospital Medical Information Network (UMIN) are the partner registries. According to PFSB/ELD Notification No. 0831-9, a trial should be registered before the first subject is enrolled, and the results should be registered within one year after the completion of the clinical trial, unless it conflicts with the laws and regulations of other countries or if it interferes with publication in peer-reviewed medical journals.

Korea

In Korea, pharmaceutical and biotech companies listed on the Korea Securities Dealers Association (KOSDAQ) index can be penalized if they do not properly disclose major information on clinical trials. They will be first designated publicly as dishonest disclosure companies and could be penalized such as paying fines. Such firms have the opportunity to discuss their positions during the process.

Kospi-listed firms, however, do not appear to have separate disclosure guidelines for biopharma companies.

Singapore

As with many countries, the regulatory obligations for sponsors are vague. The government does, however, state that it establishes and maintains arrangements to ensure compliance with the principles of GCP. ICH guidelines regarding final reports read: "Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the [Institutional Review Board] IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required."

Very specific penalties are defined for lack of notification of trial status to the authorities. A person contravening Regulation 12 is considered guilty of an offense and is liable on conviction to a fine not exceeding $5,000 or to imprisonment for a term not exceeding two years or to both. However, this does not appear to extend to the public registry.

CENTRAL AMERICA

Central America has a common regulation called "Reglamento Técnico Centroamericano - RTCA" (Central American Technical Regulation). These rules vary depending on the type of product.

Costa Rica

In Costa Rica, the governmental bodies setting regulations are the "Ley General de Salud" (General Law of Health), and the "Ley Orgánica del Ministerio de Salud" (Organic Law of the Ministry of Health). While the regulation does

not appear to directly address the responsibility for disclosure, it does outline research participants' right to information, including:

- Access to the results of their analyses, when they have not undergone anonymization processes, if the study design allows it
- To be informed about the progress, the unexpected adverse events and overall results of the research
- All verbal and written information is provided in an understandable lexicon and in the language of the participants.

Costa Rica maintains a national register of trials conducted in the country, but it is not considered a registry from a disclosure standpoint.

Guatemala

Here, disclosure regulations fall under the General Directorate of Regulation, Surveillance and Control of Health through the **Department of Regulation and Control of Pharmaceutical and Related Products**. The office provided the following statement regarding Article 15 of the Law on Access to Public Information: "Use and dissemination of information. The interested parties will have criminal and civil responsibility for the use, management or dissemination of public information to which they have access, in accordance with this law and other applicable laws."

Clinical trial regulations suggest that a summary of results must be available to citizens through the agency website, but no specific regulatory language supports this.

SOUTH AMERICA

Colombia

The **National Institute for Food and Drug Surveillance** (INVIMA, Colombia's regulatory agency) manages different regulatory processes related to clinical trials. From the evaluation of the initial protocol proposal to the assessment of protocol amendments, follow-up of administrative changes, surveillance and control of the execution of trials at the approved sites, etc., all of these procedures have different timelines.

According to an INVIMA statement, "it is every stakeholder's responsibility to ensure strict compliance." The monitoring compliance of clinical trials is guided by international standards, such as ICH, Colombian legal rules or regulations: Resolution 2378 of 2008, Resolution 8430 of 1993, and internal guidelines, among others.

No specific language pertains to disclosure other than a broad statement defining that results should be relayed to the scientific community.

OCEANIA

Australia

The Australian clinical trial requirements are longstanding, with the ICH GCP Guidelines for Good Clinical Research Practice (GCRP) in Australia first adopted in 1991. Clinical trials are regulated at a number of levels under Commonwealth and state and territory legislation in Australia. The **Therapeutic Goods Administration's (TGA's)** role in clinical trials is to regulate access to "unapproved" therapeutic goods (medicines, medical devices and biologicals) for use in clinical trials through the Clinical Trial Notification (CTN) and Clinical Trial Approval (CTA) schemes.

Under the CTN scheme, trial proposals are submitted directly to the reviewing Human Research Ethics Committee/s (HRECs), which assume the primary responsibility for ethical and scientific review and approval. The CTA scheme involves TGA evaluation of scientific data for higher-risk trials in addition to the

ethical review and approval by the responsible HREC(s).

The legislation underpinning the CTN and the CTA schemes requires that clinical trials involving the use of "unapproved" therapeutic goods be conducted in accordance with the GCP guidelines, the National Statement on Ethical Conduct in Human Research (National Statement), and the protocol approved by the applicable HREC. Trial sponsors are also required to comply with other relevant requirements of Commonwealth and/or state and territory legislation. The Australian clinical trial handbook provides further information on conducting clinical trials in Australia using unapproved therapeutic goods.

In regard to compliance management, the TGA's approach is outlined in the Compliance management | Therapeutic Goods Administration (TGA) and Compliance actions and outcomes | Therapeutic Goods Administration (TGA).

Figure 4: Tools Used to Address Noncompliance

Source: Australian Therapeutic Goods Administration (TGA)

When a clinical trial is conducted in breach of the conditions of the CTA scheme, the TGA has power to revoke approval of the trial. The TGA also has power, in specific circumstances, to direct that a clinical trial under the CTN scheme not be conducted or be stopped. Continuation of a clinical trial after approval has been revoked or in breach of the conditions of the CTN scheme may amount to a criminal offense or a civil contravention under section

19B or 19D of the Therapeutic Goods Act 1989. Section 21A of the act specifies the grounds for prosecuting offenses related to not complying with conditions of registration or listing.

In relation to noncompliance identified in the GCP Inspection Program, the TGA adopted a pragmatic approach with its Corrective and Preventative Action Plan (CAPA). This allows the sites to amend their processes, procedures and systems, facilitating development of compliance strategy aligned with relevant legislation and guidelines.

- First, the TGA provides education and advice to the responsible entity.
- Next, a warning letter may be issued, identifying the noncompliance, what corrective action is needed, what other action the TGA may take if the noncompliance is not remedied within the specified timeframe, and education on how to remain compliant in the future.
- Civil penalties, if imposed, are 5,000 penalty units for an individual, or 50,000 penalty units for a corporation. A penalty unit is currently $275 for offenses committed on or after Jan. 1, 2023.
- Criminal penalties, if warranted, can include 5–7 years' imprisonment and fines of up to 4,000 penalty units.

It should be noted that the above guidance refers to clinical trial authorizations and conduct, not to trial registration in a publicly accessible register. However, the National Statement on Ethical Conduct in Human Research (and Australian Code for the Responsible Conduct of Research) encourage sponsors to register on a publicly accessible register and publicly disseminate results.

New Zealand

Medsafe is New Zealand's **Medicines and Medical Devices Safety Authority**, operating under the Ministry of Health. Under the Medicines Act of 1981, sponsors should submit routine progress reports to Medsafe online, with the first report sent not more than six months after the trial's approval date. Subsequent reports should be submitted at six-month intervals throughout the duration of the trial. At the global end of the trial, a synopsis of the final report should be sent to Medsafe when available. While the penalties for specific violations were unclear, the law states: "Every person who commits an offense against these regulations is liable on conviction to a fine not exceeding $500."

As per Australia, there is no legal mandate for clinical trial registration/results disclosure. However, the National Ethics Standards state that sponsors must register their clinical trials in a WHO-approved clinical trial registry prior to study start and must provide results in the public database of the registry.

In Conclusion

Nick Ide, formerly with ClinicalTrials.gov, shared his predictions for the future of clinical trial disclosure in the US:

- There will be more public scrutiny of content.
- The FDA might focus not just on whether studies were submitted, but the quality of the data.
- Standardization and better structure for outcome measures.
- Reaching agreement on key elements of eligibility criteria and how to specify them.

Interpretation of penalties as defined in legislation is difficult. In many cases, it is unclear whether regulations strictly apply to disclosure activities (registration in a publicly accessible registry and results dissemination) or more specifically to the direct interaction with authorities and clinical trial authorization requirements, which are often distinct processes.

While there has been movement toward greater enforcement of clinical trial reporting regulations across the globe, it is obvious that more needs to be done. Management of clinical trial disclosure is a complicated endeavor, and regulatory agencies should take steps to make compliance as easy as possible — and to enforce strict penalties for noncompliance. Doing so will protect clinical trial participants and, ultimately, the patients who rely on these life-saving treatments.

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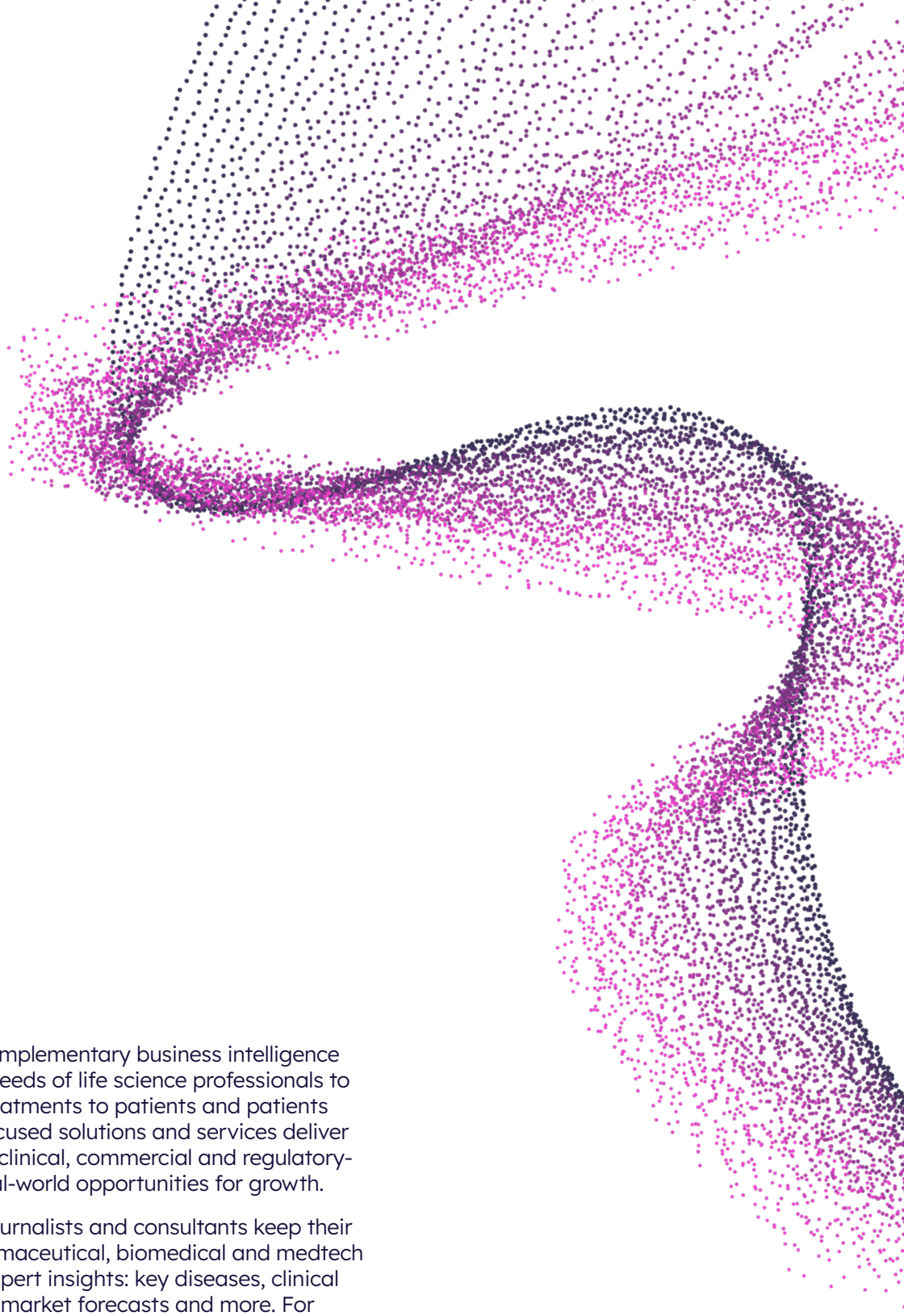

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