Clinical trial transparency in the Americas: the need to coordinate regulatory spheres

Numerous initiatives have contributed to health data transparency in the Americas, but further coordinated effort is needed to ensure the reliability of research for health, argue **Trudo Lemmens** and **Carlos Herrera Vacaflor**

In its 2009 Policy on Research for Health, the Pan American Health Organization/World Health Organization (PAHO/WHO) reiterated the key role of transparency in ensuring reliable research for health.[1] In the wake of several high profile controversies, transparency has been particularly promoted in the context of industry sponsored pharmaceutical trials aimed at producing data for drug regulatory approval.[2] In response to these controversies, various stakeholders have pushed for clinical trial registration and access to data submitted to drug regulatory agencies as key transparency tools, to enhance evidence informed decision making by clinicians, regulators, and society.[2]

Notwithstanding widespread support for transparency, its implementation faces significant challenges. Transparency of pharmaceutical data has been hampered by the qualification of such data as commercially confidential information and by inconsistencies in overlapping regulatory spheres. This article will first discuss key developments related to registering pharmaceutical clinical trials and sharing data submitted to drug regulatory agencies in the Americas. Then, reports from three countries will show how they have implemented key transparency measures and what challenges remain. Finally, the paper will suggest how research ethical review, present in all jurisdictions, could play a role in moving forward with data transparency.

The three selected countries, representing the four major language groups in the Americas, have strong pharmaceutical industries at different stages of development: mature market (Canada), emerging market (Brazil), and second tier emerging market (Argentina). Most Latin American countries are in the last category. Argentina and Brazil represent countries with a growing number of clinical trials.[3] The drug regulatory agencies of all three countries are recognised as regional reference authorities (box 1). Given the region's diversity in terms of industry development and regulatory review, these case studies are neither exhaustive nor fully representative. Rather, they shed light on various initiatives, outcomes, and challenges.

KEY MESSAGES

- National health regulatory agencies involved in health related research governance should harmonise and streamline both research ethics committee governance and transparency requirements in different regulatory regimes
- Drug regulatory agencies in Pan American Health Organization member states should follow the approach taken by the European Medicines Agency with respect to clinical data used for a regulatory decision—that the data do not constitute commercially confidential information and that the burden of proof is on drug companies to argue why specific data should be kept confidential
- Research ethics committees can play a coordinating role in the promotion of transparency standards to the extent that the governance structure of committees reflects their public interest nature

Developments in trial transparency in the Americas

Over the past decade, WHO, PAHO, national governments, funding agencies, scientific journals, and some pharmaceutical sponsors in the Americas have taken steps to promote transparency.[2] Clinical trial registration, the first initiative to get widespread support, is now required in many countries, despite clear gaps (box 2).[2] WHO recognises the registries of Brazil, Cuba, and Peru as primary registries in the PAHO region for its International Clinical Trials Registry Platform.[5] Concurrently, there has been a significant increase in trial registration in the Americas.[3 6]

Regarding pharmaceutical data sharing, no national regulatory authority from the Americas has yet followed the example of the European Medicines Agency (EMA), which first facilitated data access in 2010, followed in 2014 by a policy which embraced as a principle that all clinical trials data from phase 1, 2, and 3 studies submitted for drug regulatory approval will be made public.[7] The 2014 policy starts from the premise that clinical data are not commercial confidential information, shifting the burden to companies to show why secrecy of specific data components is needed. In the Americas, even the United States—with disclosure obligations in its Food and Drug Administration Amendments Act (FDAAA) of 2007—does not require registration of all clinical trials, nor does it prospectively publish all trial data.[8] National freedom of information acts in various countries provide some level of access to data held by governments, but in those regimes, drug regulators have wide discretionary powers over data access requests.

Brazil

Since 2010, Brazil has implemented relatively successful transparency and data access policies. The Brazilian Registry of Clinical Trials (ReBEC) aims to make information for all studies available in English, Portuguese, and Spanish.[9] Registration with ReBEC is mandatory for all clinical trials involving drugs not yet officially approved and involving Brazilian researchers or participants. Proof of registration with WHO's International Clinical Trials Registry Platform (ICTRP) or another registry recognised by the ICMJE is mandatory for national regulatory authority authorisation.[10] From 2010 to 2015, 3112 protocols were registered with ReBEC,[11] with an increase in the registration of both state funded and pharmaceutical industry funded trials.[12] For 2016 and 2017, the number of registered trials was 1162 and 1279, respectively. ReBEC gives access to clinical trial summaries in accordance with WHO's Trial Registration Data Set. Clinical trial reports are submitted to Brazil's National Health Surveillance Agency (ANVISA), but can only be accessed on request.

ANVISA coordinates data access under Brazil's access to information law. Anyone can request research data for use, re-use, or redistribution providing they cite authorship and data origin. ANVISA has created an open data repository, Plano de Dados Abertos, which meets quality standards under current regulations. Data access may be restricted based on protection of fundamental rights or the interest of society or the state.[13] A National Health Council regulation requires researchers involved in public or privately funded research to publish their results.

Box 1: National regulatory authorities (NRAs) in the Americas

NRAs recognised by PAHO as regional references of medicines and biological products

- Argentina: National Administration of Drugs, Food, and Medical Technology (ANMAT)
- Brazil: National Health Surveillance Agency (ANVISA)
- Canada: Health Canada (HC)
- Chile: Public Health Institute (ISP)
- Colombia: National Institute of Food and Drug Surveillance (INVIMA)
- Cuba: Center for State Control of Drug Quality (CEMED)
- Mexico: Federal Commission for Protection against Sanitary Risks of the United Mexican States (COFEPRIS)
- United States of America: Food and Drug Administration (FDA)

NRAs classified under PAHO's evaluated and pre-evaluated status

- Argentina: National Administration of Drugs, Food, and Medical Technology (ANMAT)
- Bahamas: Bahamas National Drug Agency (BNDA)
- Barbados: Barbados Drug Service (BDS)
- Bolivia: Medicines and Health Technology Unit (UNIMED)
- Brazil: National Sanitary Surveillance Agency—Ministry of Health (ANVISA)
- Canada: Health Canada (HC)
- Chile: Public Health Institute (ISP)
- Costa Rica: National Board of Health Research (CONIS), University RECs, Costa Rican Social Security Fund (CCSS)
- Cuba: Center for State Control of Drug Quality (CEMED)
- Dominican Republic: General Directorate of Medicines, Food, and Health Products (DIGEMAPS)
- Ecuador: National Institute for Hygiene and Tropical Medicine—Ministry of Health
- El Salvador: National Directorate of Medicines
- Guatemala: Department of Regulation and Control of Pharmaceutical and Related Products (MEDICAMENTOS)
- Guyana: Food and Drug Department (FDD)
- Haiti: Direction de la Pharmacie, du Médicament et de la Médicine Traditionnelle (DNM/MT)
- Honduras: Health Secretariat, General Directorate of Sanitary Regulations
- Jamaica: Standards and Regulation Division (DSR)
- Mexico: Federal Commission for Protection against Sanitary Risks of the United Mexican States (COFEPRIS)
- Panama: Directorate of Pharmacy and Drugs
- Paraguay: National Directorate of Health Surveillance
- Peru: General Board of Medicines, Supplies, and Drugs (DIGEMID)
- Suriname: National Regulatory Authority
- Trinidad and Tobago: National Regulatory Agency
- United States of America: Food and Drug Administration (FDA)
- Venezuela: Rafael Rangel National Institute of Hygiene (IHRR)

Note: All the above agencies operate as part of the national ministries of health. In the English speaking Caribbean, PAHO's Caribbean Public Health Agency (CARPHA) is involved in establishing uniform standards. There is also PAHO's Pan American Network for Drug Regulatory Harmonization (PANDRH).

Interruption of research and failure to publish must be explained to the Research Ethics Committee (REC) and the national REC agency, CONEP.[14]

Progress in promoting transparency appears threatened by ReBEC's budget restrictions and staff shortages.[15] At the regulatory level, data sharing may further be affected by ANVISA's confidentiality agreements with other regulatory agencies.

Argentina

Argentina has developed policies for mandatory clinical trial registration and access to research data. These initiatives have been timidly implemented, however, in part hindered by jurisdictional problems.

Argentina enacted the Good Clinical Practice Regime in Pharmacology Research (Disposition 6677/10-ANMAT), applicable to research aimed at obtaining data for regulatory approval and product registration. Local jurisdictions can also impose additional requirements. ANMAT guidelines mention the Declaration of Helsinki (DOH, 1964 and current versions) and the Council for International Organizations of Medical Sciences (CIOMS, 2002 version) as references for its application, incorporating DOH and the CIOMS 2002 version as part of Good Clinical Practices (GCP). Given that both sponsors and researchers must respect these international guidelines, reference to different guidelines and different versions in overlapping governance regimes—not unique to Argentina—may raise compatibility and consistency issues. More detailed, current ethical obligations regarding transparency of health related research prescribed in CIOMS 2016 version are not yet part of Argentina's GCP.

Argentina created its National Registry for Health Research (RENIS) to increase clinical trial and other health research registration.[16] Health research funded by the Ministry of Health or conducted under National Administration for Drugs, Food, and Medical Technology (ANMAT) regulations must be registered in order to receive authorisation. The implementation of registration requirements of other clinical trials taking place in the provinces depends on the local health authorities. RENIS also contains information on research ethics boards, sponsors, researchers, and contract research organisations. For 2016 and 2017, RENIS contains 145 and 180 registered research projects,[17] respectively, while 191 and 125 clinical trials were entered into ANMAT's database for clinical pharmacology studies[18] for the same period. ANMAT's guidelines contain rules about patient confidentiality and reporting data (such as clinical trial reports) to ANMAT, but not to the public.

Different statutes impact on access to research data. Laws governing access to information require government, state, and decentralised agencies to provide access to any data under their control.[19] A 'Habeas Data Law' also regulates data access.[20] There are further privacy obligations regarding

Box 2: Status of PAHO member states

States with formal, mandatory clinical trial registration requirements*
- Brazil
- Colombia
- El Salvador
- Guatemala
- Panama
- Peru
- Uruguay
- USA

States with national registries†
- Argentina
- Brazil
- Cuba
- Mexico
- Peru
- USA

*Compiled on the basis of WHO survey of national pharmaceutical profiles in the Americas, with verification of country information submitted with its current policies on national regulatory agency websites.[4] The site contains only countries that have mandatory registration in their drug regulatory structure. Some countries (such as Canada) have partial registration requirements through funding agency guidelines that are also part of good clinical practices.

†The registries of Argentina, Mexico, and the US are not recognised as WHO primary registries.[3]

personal data. If data are de-identified, however, access cannot be restricted if such access is for scientific purposes or is in the public interest. De-identified data can also be shared and transferred internationally without consent.[21] The law characterises safety and efficacy data submitted to ANMAT as trade secrets or commercial data.[22] This may create challenges for implementing data sharing with independent researchers and the public.

Argentina is among the countries with the highest clinical trial registration rate by population,[3] making RENIS a valuable effort. Even though the registry displays clinical trial summary data, RENIS neither fulfils the WHO dataset standard, nor does it provide access to data in PAHO languages (English, Portuguese, and French) other than Spanish.[23] This may impede the visibility of local research for attracting international trials.[9] Furthermore, access to research data is regulated under multiple legal frameworks. This creates confusion regarding researchers and civil society organisations' rights to access data.

Canada

Canada does not have its own comprehensive trial registry. Health Canada's Clinical Trials Database provides information on clinical trials but primarily aims to stimulate research enrollment.[24] Trial registration and public reporting of results are mandatory in federally funded institutions through the federal funding agencies' research ethics standard, the Tri Council Policy Statement (TCPS2),[25] and specific funding agency requirements.[26] However, Health Canada's Health Products and Food Branch, the federal drug regulator, does not explicitly require registration of clinical drug and medical device trials. Health Canada's Good Clinical Practice Guidelines[27] refer to the principles of the Declaration of Helsinki (DOH) as part of the history of good clinical practices, and Health Canada's own REC follows the TCPS2. Both DOH and TCPS2 require trial registration and results reporting. Such indirect references are not legally enforceable, even though they could perhaps still be seen as part of good clinical practice. Official reports have long emphasised the need to improve transparency in the regulatory record for clinical trials.[28] Trials tend to be registered on the US FDA registry and prior registration is also required by most, if not all, Canadian medical journals.

Access to information legislation can be used to request data access, but Health Canada has insisted in the past that applicants show how their information needs outweigh the potential commercial harm to the data submitting company—thus hindering data transparency. A 2014 amendment to the Food and Drug Act creates a legal basis for disclosure of data from clinical trials without consent from the sponsor once a drug receives approval, and could be used for further regulations about trial registration.[29] Yet, the law refers to clinical trials data as commercially confidential information—seemingly undermining the concept of data as a public good. Health Canada currently also requires a signed confidentiality agreement before providing access to data, thus delaying access and subsequent sharing of data.[30] A draft regulation[31] reveals, however, a potential shift in the regulatory approach about data transparency. Seemingly inspired by the EMA's approach, the draft regulation states that "clinical summaries, reports, and supporting data of clinical trials" submitted in the drug evaluation process will not be considered commercial confidential information following a final regulatory decision. This would shift the burden of proof to pharmaceutical sponsors to show why the regulator must keep specific data confidential. The regulation remains silent about the requirement for researchers to sign a confidentiality agreement, a practice that may continue to hinder access and sharing of data. The draft regulation also does not tackle the matter of trial registration, which would need another new regulation.

Implementation challenges and regional strategies

A key challenge to a coherent data transparency strategy, particularly regarding access to clinical trials data on pharmaceuticals, is the fact that distinct but overlapping regulatory regimes determine whether, and to what extent, data sharing may occur. Most countries have specific ethics guidelines for publicly funded research. Inspired by international guidelines, like the frequently referenced Declaration of Helsinki[32] and the Council for International Organizations of Medical Sciences,[33] they increasingly include transparency obligations such as registration and summary results reporting.

In countries like Canada, commercially funded pharmaceutical clinical trials undertaken in federally funded institutions must abide by these guidelines. Food and drug regulations, including good clinical practice requirements, often refer to international ethics guidelines.[32] Nonetheless, industry sponsors insist—and regulatory regimes often accept—that clinical trials data constitute commercially confidential information. This creates barriers to data sharing, although access to information regimes often allow researchers to request access to regulatory data following product approval. In such cases, however, regulatory agencies tend to exercise discretionary power and are often under pressure to respect industry's insistence on secrecy.

RECs could play a role by insisting on data access as a key ethical requirement and by ensuring that transparency commitments are added to the consent forms of research subjects. Ensuring individual consent for data sharing may also help tackle potential concerns about privacy of personal health information contained in clinical trials data. In all countries, pharmaceutical clinical trials must receive REC approval before recruiting human subjects. There is widespread recognition, including in international good clinical practice standards, of RECs having key obligations to protect research subjects' rights, safety, and wellbeing. If—as national and international ethics guidelines recognise—transparency is a key component of ethical research, RECs should require researchers and sponsors to make specific transparency commitments as a condition for ethics approval. Additionally, considering the growing recognition of RECs post-approval role, arguably they should actively verify and, to the fullest extent possible, enforce transparency standards.[34]

We recognise the difficulties in achieving this. Even in Europe, where transparency faces fewer regulatory barriers, RECs lack adequate procedures to verify results publication or minimise selective reporting.[35] In the Americas, different countries' substantive rules on research transparency are also reflected in different REC governance regimes. Some countries have a coherent, centralised administrative structure with

uniform rules for RECs that may facilitate the enforcement of transparency standards. For example, in Brazil, all institutional RECs are responsible for reviewing trials conducted at their site. However, CONEP reviews the RECs' decisions and may request changes. It also authorises, registers, and monitors institutional RECs. Although Brazil's structure creates public accountability and coherent REC review, CONEP remains underfunded.[9]

RECs for industry sponsored trials in other jurisdictions follow a more market oriented structure. In countries like Canada (in some major provinces), the US, and Argentina (except the Province and City of Buenos Aires),[36] most industry sponsored trials are reviewed by commercial RECs. These are in a direct client-provider relationship with industry sponsors and compete for their business.[37] They are stakeholders in the knowledge production industry that supports pharmaceutical and medical device industries and operates under the same commercial market norms—including commercial confidentiality norms.[38] Market oriented REC governance for industry sponsored research appears ill suited for enforcing and promoting trial registration and data sharing. Jurisdictional matters may create additional barriers to attempts to promote a publicly accountable REC structure. This is the case, for example, in Argentina and Canada. In each Argentinean province, institutional and commercial RECs are coordinated by central RECs. Resolution 1002/2016 created the National Advisory Committee on Research Ethics, which collaborates with provincial RECs and promotes coordination. Its mandate includes registering RECs operating at national institutions or decentralised agencies of the Ministry of Health; yet it does not cover private RECs. A recent Argentinean case study on industry sponsored trials documents the failure of the government and a commercial REC to enforce basic transparency rules.[39] In Canada, there is also no federal regulation or federal monitoring of RECs.[40] The most populated provinces with the highest pharmaceutical clinical trials activities, Ontario and Quebec, largely rely on private commercial RECs to review pharmaceutical clinical trials. Only one province, Newfoundland and Labrador, enacted legislation that explicitly mandates a central Health Research Ethics Authority to organise the review of all research in the province by one central REC.[41]

Conclusion

Countries in the Americas have taken important steps in implementing transparency standards. Some have achieved significant progress in implementing mandatory clinical trial registration and a level of transparency. Nonetheless, some leading countries still fail even to impose registration with a publicly accessible registry. While data sharing initiatives have been undertaken in several countries, the transparency of pharmaceutical clinical trials data has been hindered by its characterisation as commercially confidential information. Nevertheless, most jurisdictions recognise the strong ethical basis for data transparency, often with explicit reference to international research ethics guidelines. This is also reflected in human rights and public goods approaches to data sharing.[38] If countries in the region were to streamline the different overlapping regulatory fields that govern clinical trials data, and follow the EMA's lead in creating a presumption that data should be publicly accessible, they would take an important step towards the implementation of comprehensive data transparency.

To implement coherent transparency of health data in the Americas, countries need to juggle different applicable rules, guidelines, and governance tools successfully. This means different regulatory agencies and funding agencies coordinating applicable transparency rules at each national level. The further development of publicly accountable REC systems, directly accountable to the state, must be part of promoting meaningful transparency.

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