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Navigating US participant data sharing requirements: implications for international clinical trials

Standfirst: Non-U.S. stakeholders should consider updating their standards to comply with new individual participant data sharing requirements for U.S. federal agency-funded trials.

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Key messages

–New US policies on federally funded trials mandate new requirements on sharing of individual participant data (IPD)

–Apart from trials conducted in both US and non-US sites, about 9% of all US federally funded trials are conducted with no US sites participation.

–It is expected that the implementation of these policies will not cause problems in many high-income countries –although this will depend on national regulations (e.g., data protection)

–IPD sharing and data storing in repositories for trials fully conducted outside the US could pose challenges in low- and middle-income countries.

Key words: individual participant data sharing; clinical trials; NIH-funded trials; US Agency-funded trials; update standards; investigators; research ethics committees; repositories

Practices and guidelines to promote the transparency of clinical trials such as the sharing of de-identified individual participant data (IPD) have been under discussion for years. However, evidence suggests that this practice is still the exception rather than the norm.¹⁻³

More recently, salient events have occurred in relation to IPD sharing. First, the US National Institutes of Health's (NIH) Policy for Data Management and Sharing ('DMS Policy'), aimed at promoting the sharing of scientific data generated from NIH-funded research, was enforced in January-2023.⁴ Second, the White House Office of Science and Technology Policy issued a memorandum ('OSTP-memo') in 2022 requesting that supporting data of all US federally funded research should be freely accessible immediately upon publication no later than 31-December-2025.⁵

The NIH policy for Data Management and Sharing and the White House Office of Science and Technology Policy requirements on IPD sharing

The DMS policy applies to all research submitted to the NIH on or after 15-January-2023 and funded or conducted in whole or in part by the NIH. DMS Policy stipulates that a) scientific data should be made available to third parties no later than the time of an associated publication or the end of performance period, whichever comes first, but considering any potential restrictions or limitations; and b) investigators must submit a DMS Plan with the trial protocol and other relevant documentation, which must be approved by the NIH.⁴ All data management and sharing practices should be consistent with the FAIR data principles, i.e., should be findable, accessible, interoperable, and reusable.⁶ Given that the NIH is the largest single clinical trial funder with a \$3 billion annual investment,⁷ the DMS Policy is an important step towards enhancing data transparency.

The OSRTP-memo requests that by no later than 31-December-2025, all Federal agencies, such as the Centers for Disease Control and Prevention, the Food and Drug Administration or the

Veterans Administration Office of Research and Development, will make available all trial supporting data immediately upon publication.⁵ Consistent with DMS Policy, scientific data includes all material of “sufficient quality to validate and replicate research findings”, and must follow FAIR data principles.⁵ Hence, not only NIH-funded trials, but all trials funded by any Federal agency must make IPD freely and publicly accessible “by default in agency-designated repositories without any embargo or delay after publication”.⁵

Impact of the NIH policy for Data Management and Sharing and the White House Office of Science and Technology Policy requirements on non-US sites

Adherence to DSM Policy requirements may be a challenge when trials are conducted outside the US. A search on ClinicalTrials.gov showed that out of the 10,720 US Federally funded trials started between 1-January-2018 and 31-December-2023, 918 (8.6%) did not involve US sites. The percentage of trials conducted completely outside the US varies depending on the interventions assessed to illustrate the scenario between 9.2% (drugs) and 5.1% (surgery) (Table-1) (Supplementary material-A).

In addition to these 918 trials carried out outside the US, many more trials include sites in both the US and other countries. In the above-mentioned period US federally funded trials were conducted in many countries in five continents, including Australia (48 trials), Brazil (n=43), Canada (n=180), China (n=24), Germany (n=19), India (n=40), Kenya (n=88), South Africa (n=102), and the UK (n=34). These trials included all types of intervention and were funded by any US Federal agency –albeit most were NIH-funded (Supplementary material-B)

NIH-funded trials conducted in whole or in part in countries outside the US need to take into consideration relevant national regulations on, for example, data protection, and how potential trial participants will be informed about data storage, management and sharing through the informed consent process which also undergoes approval by relevant local research ethics

committees (RECs). For example, data protection legislation varies considerably from one Sub-Saharan country to another.^{8,9} Furthermore, the meaning of anonymization and de-identification varies between jurisdictions. These topics can be highly complex in technical terms when national and supranational regulations are different from, and in some instances more rigorous than, those of the US (Box-1).

It is unknown how the DSM policy is currently affecting investigators who want to conduct trials outside the U.S. On the one hand, it is impossible to know how many non-US investigators refuse to apply for NIH funding because they are unable or unwilling to comply with the requirements of the DSM policy. On the other hand, the number of DSM plans rejected (and the reasons) for this are known only to the NIH. However, we can get an idea of what kind of trials might be affected with recent examples of completed NIH-funded trials conducted outside the US. We can focus our attention in two critical requirements of the DSM policy: the commitment to share IPD at the time of publication of trial results, and the use of appropriate repositories.

Free and immediate access to IPD from non-US sites

ACTT²³ and ACTT-2²⁴ are good examples of trials where participants, investigators, and RECs were fully aware that IPD could be immediately shared. These trials on COVID-19 hospitalized patients were conducted in nine countries of three continents, including the UK, and 4 EU member states (Denmark, Germany, Greece, and Spain) where EU's GDPR was in force. So, immediate IPD sharing seems to have no main issues in many countries.

Conversely, concerning NIH-funded trials conducted in 2021-2022 in low- and middle-income countries (LMICs), there are examples of trials where the commitment of IPD sharing is mentioned, but with an embargo period of 9 to 36 months following publication (NCT04971967, China, HIV/contact tracing; NCT05005130, Zambia, HIV-noncommunicable diseases), and others without no commitment to share IPD (NCT04733157, Zimbabwe,

postpartum hemorrhage; NCT04354168, Lesotho, preconception care). These scenarios will not be possible from 2023 for NIH-funded trials (and from 2026 for all US federally funded trials).

Appropriate repositories for trial data outside the US

Non-US sponsors and trialists should be aware of the repositories identified as suitable by US Federal agencies to host and preserve de-identified IPD. Recent research that assessed 5,700 repositories on their adherence to the FAIR criteria determined that while findability was met by 100%, accessibility, interoperability and reusability were achieved by only 22%, 47%, and 61%, respectively.²⁵ US Federal granting agencies will require the use of repositories that have been approved and adhere to FAIR principles. One possible strategy is for all Federal agencies to collectively establish a network of repositories accepted as validated sources of IPD. To transform and promote transparency at a global scale, any non-US repository fulfilling a minimum set of requirements should be eligible to join this network.

Resource limitations may make it difficult to establish repositories that meet the requirements of US federal agencies in many LMICs. Many institutions of Sub-Saharan countries lacked formally established processes for storing data beyond the duration of the research.²⁶ These countries seem to be doomed to accept that they will lose control of the IPD of these trials. For example, in the above-mentioned trial conducted in Zambia, with an agreed commitment for IPD sharing, “all study data will be owned by the Zambia Ministry of Health”. However, in the same trial conducted following the policies discussed here, all IPD will need to be immediately made freely available and publicly accessible from the repository –that presumably will likely be in the US. The question is whether all concerned countries will accept this situation? If governments of countries with no appropriate repositories reject this approach, will it mean that these trials will not be conducted in these countries. This problem of the lack of control of nation’s research data by LMICs researchers has been already flagged concerning other

requirements recently issued by NIH.²⁷ In China, the Data Security Law requires that all scientific data generated be submitted to government-sanctioned data centers, be kept in China and that permission is required to export it.²⁸ Furthermore, according to WHO many researchers in LMICs feel that policies mandating immediate data sharing –as the ones discussed here– could put them at a disadvantage.²⁹

Should non-US clinical investigators and RECs take action?

In the NIH-funded trials conducted in both US and non-US sites, it is expected that IPD will be preserved much like in trials that are exclusively conducted in the US. The situation is less clear when the NIH is only one of several funders and in trials exclusively funded by NIH but conducted outside the US. It is reasonable to expect that NIH should fund trials conducted in foreign countries willing to store all IPD in established non-US repositories. These repositories would have to be regularly assessed for compliance with DSM Policy. The NIH could potentially publish the list of approved non-US repositories validated for long-term preservation and access to IPD. This would allow sponsors to identify suitable and valid non-US repositories at the time of designing the trials.

Ideally, training may be required for clinical investigators and RECs to successfully address the requirements set forth in the DSM Policy or OSTP-memo on IPD sharing. Investigators will need to learn and be trained in the principles, governance structures, skills, and operational infrastructure of IPD sharing. Preferably, clinical investigators should need to be familiar with the regulations, informatics, data science, and ethical, legal, and social issues around IPD sharing.³⁰ It is advisable that organizations involved in the conduct of trials such as hospitals, clinical trials networks, professional societies/associations, start considering the need of having trial data-sharing experts, already adopted in disciplines like statistics, data protection, and/or biobanking.

Non-US-based RECs should understand their role and responsibilities in ensuring the implementation of such policies. Although a US Federal granting agency would typically review DSM plans submitted with funding proposals to ensure that applicable policy requirements are met, relevant non-US RECs will also need to ensure national regulations are met. Non-US RECs should consider having access to experts in data management, security, and information technology.³¹ This may be challenging in many LMICs settings and would likely require transnational sharing of expertise –through organizations like AVAREF (Africa Vaccine Regulatory Forum) which has as one of its missions to reach consensus on issues relevant to RECs.³² Examples of such sharing include the support provided by the George Institute of Global Health³³ to operationalize the ASCOT trial (COVID-19) in India and Nepal³⁴ and the TRIUMPH study (hypertension) in Sri-Lanka.³⁵

Addressing challenges and moving forward

The lack of regulatory IPD sharing requirement outside the US could hinder the set-up of trials in some countries. It is important to begin implementing activities and processes at the country level to minimize the potential pitfalls of how and where to host and preserve anonymized IPD. Organizations such as the EQUATOR network³⁶ should consider supporting the development of consensual DSM plans encompassing the US requirements but also accounting for the global research ecosystem, recognizing the importance of data generators. In this regard, organizations such as the European and Developing Countries Clinical Trials Partnership (EDCTP)³⁷ or the Oxford University Clinical Research Unit (OUCRU)³⁸ could play a critical role in capacity-building. Thus, EDCTP has established four regional networks of excellence (Congo, Mozambique, Senegal, and Uganda), and OUCRU has a clinical trials unit in Viet Nam (also present in Indonesia and Nepal) aiming, among other things, to infrastructure development, training and mentoring and resource sharing harmonization.^{37,38} In addition, there is important

value in researchers in LMICs re-using IPD. The potential of re-using IPD from other trials might compensate any loss of competitiveness associated with IPD sharing of their own trials.

Conclusion

With the move towards open science gaining momentum^{39,40} implementation of the IPD sharing requirements of the DSM Policy and the OSTP-memo will become the gold standard against which regulations in other jurisdictions should be compared.

The IPD sharing requirements will impact trial transparency beyond US federally funded trials. Funders around the world should ask themselves why they should not require clinical trial sponsors to comply with the DSM Policy and OSTP-memo requirements. Industry-sponsored trials with US Federal agency collaboration will disappear if the sponsoring companies want to have control over IPD sharing.

One of the reasons claimed by the ICMJE seven years ago not to mandate IPD sharing –that the requisite mechanisms were not in place⁴¹– must be revisited. Following *PLOS* journals,⁴² *The BMJ* recently announced that from May-2024 authors of published trials must post relevant trial data in a publicly accessible repository.⁴³ Hopefully many other journals and funders will soon follow. It is reasonable to believe that these US policies will help shaping the future of clinical trials at a global scale.

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Box-1.- NIH policy for Data Management and Sharing and data protection regulations in the EU, India, and South Africa

A.- The European Union.

The de-identified IPD sharing between the EU and the US applicable to all NIH- funded as per the DMS Policy, requires compliance with several regulations including those applicable in the US, the EU GDPR¹⁰ and those applicable to the European Member state transferring the data to the US. Since July 16, 2020, and the judgment Schrems II¹¹ ruled by the Court of Justice of the European Union invalidating the first Privacy Shield adequacy decision,¹² there has been no treaty between the EU and the US allowing data transfers without negotiating standard agreement terms applicable to data controllers and processors, and carrying out a Data Transfer Impact Assessment, in accordance with GDPR (article 46). Since July 10, 2023,¹³ a new European Commission adequacy decision recognizes that the US ensures a sufficient level of protection of personal data through the Executive Order of President Biden of October 7, 2022.¹⁴ However, the Court of Justice of the European Union's "adequacy decision" ruled that is only valid for data transfers to US entities on the list of certified entities.¹⁵ European and American organizations need to pay attention to further developments. Currently, in addition to the UK(ICO),¹⁶ countries such as Argentina, Israel, New Zealand, Switzerland, and Uruguay ensure adequate level of protection with regards to GDPR requirements (EU Commission).¹⁷ Japan and South Korea could be reasonably added to this list(CNIL).¹⁸

B.- India

The Digital Personal Data Protection Act (DPDPA) was enacted in August 2023, and follows broadly similar principles to those set out in the GDPR. Yet, there are some differences. So, DPDPA does not differentiate between personal data and sensitive personal data (e.g., health data). The DPDPA regulates the processing of digital personal data (collected in digital form or not, but subsequently digitized). Sharing of personal data voluntarily shared by the individual for a specific purpose is permitted. Individuals, at the time of consenting the collection of personal data must be informed of details of transfers to any third country or international organizations. The DPDPA allows cross-border data transfers to other countries except to those specifically identified by the Indian government (list to be published in due course) to which data transfers will be restricted.^{19,20}

C.- South Africa

The Protection of Personal Information Act 2020 (POPIA) came into force in 2021. The sharing of individual participant data requires that the data-receiving country has in place adequate measures of data protection, similar to those of South Africa. As with other type of health data, IPD can be processed only if trial participants have consented to a specific purpose. Yet, consent is not required if data processing is for,

among other reasons, research purposes serving for a public interest, or it appears to be impossible or would require a disproportionate effort to ask for consent and there are sufficient guarantees that the processing will not adversely affect participants' privacy to a disproportionately extent.^{21,22}

GDPR: EU General Data Protection Regulation; IPD: individual participant data; NIH: US National Institutes of Health.

Table-1.- US Federal agency-funded clinical trials assessing all types of interventions, started between 1-January-2018 and 31-December-2023. Search on ClinicalTrials.gov as of 4-January-2024

Funder ^{a,b}	All interventions	Regulated interventions			Non-regulated interventions		
		Drug	Biologic	Device	Surgery	Diet	Behavioral
All trials	147910	70738	10121	26144	15395	9419	23175
A.-NIH- and Other US Federal agency-funded trials	10720	4598	1238	1494	570	659	4511
B.-NIH- and Other US Federal agency-funded trials conducted in the US	9802	4177	1140	1405	541	608	4132
C.-NIH-funded trials conducted in the US	7846	3549	1006	1045	445	488	3321
Number of trials conducted with no US-sites, n=A-B (%)	918 (8.6)	421 (9.2)	98 (7.9)	89 (6.0)	29 (5.1)	51 (7.7)	379 (8.4)

Some trials are assessing more than one of the interventions included in the table.

- (a) ClinicalTrials.gov considers a funder the organization that provides funding or support for a clinical study. This support may include activities related to funding, design, implementation, data analysis, or reporting. Organizations listed as sponsors and collaborators for a study are considered the funders of the study.
- (b) ClinicalTrials.gov considers the following funders: U.S. National Institutes of Health (NIH); Other U.S. Federal agencies; Industry (for example: pharmaceutical and device companies); All others (including individuals, universities, and community-based organizations)