A landscape analysis for responsible transparency and clinical data disclosure for interventional studies in Europe and beyond

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Table of Contents

1. Introduction to the report

This report focuses on clinical trial disclosure of interventional clinical trials in Europe and beyond. Clinical trial disclosure involves the disclosure of information related to patient health records, medical observations, treatment outcomes, and other relevant data.

The objective of this project was to conduct an analysis of the landscape around relevant voluntary and mandatory clinical trial disclosure venues to:

- Understand the perceived value for public health of the various mandatory and voluntary disclosure venues by relevant stakeholders;
- Develop an approach for the quantification of the use and value of mandatory and voluntary disclosure venues.

To accomplish these objectives, the project team undertook a review of both scientific/peer-reviewed and grey (non-academically published) literature. To understand the perceived value for public health of the various mandatory and voluntary disclosure venues by relevant stakeholders, semi-structured quantitative interviews and a survey were conducted. Input from all respondents contributed to the proposed indicators of impact on public health (see Section 3, Table 1).

A total of eight interviews were conducted with key stakeholders within the field of clinical data disclosure from different backgrounds, including academia, industry and non-governmental organizations. See appendix A for the interview guide.

For the survey, authors were invited who had a publication which included analysis from anonymized clinical data provided via a clinical research platform. The survey asked for experience and opinion on how the impact on public health by clinical data disclosure can be measured, see Appendix B for the survey questions. A total of nine authors responded to the survey.

Through this multi-faceted approach, the project aimed to contribute to the ongoing dialogue and policy-making processes around clinical trial disclosure. By providing a clearer picture of the current state of these practices and their perceived value, the project sought to inform future strategies that could enhance the impact of clinical trial disclosure activities.

The report consists of four sections: this introduction (Section 1), a brief review of clinical trial disclosure activities (Section 2), a discussion on quantification of the value of data trial disclosure activities (Section 3), and final conclusions (Section 4).

2. Clinical trial disclosure

The landscape of clinical research is rapidly evolving, prompting ever greater calls for disclosure of clinical trial data and their results. Biopharmaceutical companies have recognised the importance of transparency and collaboration, prompting a shift towards increased clinical trial disclosure. This shift is fueled by a confluence of ethical imperatives, regulatory expectations, and scientific necessities that emphasise the potential of clinical trial disclosure to accelerate medical breakthroughs, improve drug safety, and enhance patient outcomes.

Clinical trial disclosure platforms serve as critical hubs for the advancement of clinical trial disclosure among pharmaceutical companies but also the broader research community, including academia. There are multiple sites where clinical trial information can be accessed. Clinical trial disclosure platforms can have a national or regional focus (e.g. based on a regulatory area), or can have a global scope. A distinction can be made between mandatory and voluntary clinical trial disclosure venues.

2.1 Mandatory clinical trial disclosure venues

Mandatory clinical trial disclosure venues are those disclosure venues of which the use is required under certain conditions for certain organizations. Within the context of this document, mandatory clinical trial disclosure venues refer to those mandatory disclosure venues in the European Union, Canada and the United States for pharmaceutical companies, which were selected for this study.

Mandatory clinical trial disclosure venues have a regulatory or legislative basis and provide global access to information of clinical studies performed in their respective jurisdictions (and in some cases beyond their jurisdictions). By providing a transparent mechanism for clinical trial disclosure, these disclosure platform entities aim to play a pivotal role in enhancing research efficiency, increasing accountability and trust in research activities, fostering collaboration, and avoiding duplication of clinical trial activities. Information that is available on mandatory disclosure platforms can be freely accessed by anyone with an interest in the data. While there are benefits to clinical trial data disclosure, it is essential to address concerns related to patient privacy, data security, and ethical considerations. Balancing data disclosure with patient confidentiality is crucial to ensure the trust of patients and the responsible use of disclosed data, especially when freely accessible.

In February 2000, the Food and Drug Administration (FDA) Modernization Act (1997) prompted the creation of a national clinical trials registry (ClinicalTrials.gov).(1) Similar databases (such as the ISRCTN; 'International Standard Randomised Controlled Trial Number') have been established elsewhere. Since 2007, registration of a trial and submission of results is required for regulatory submissions as a result of the FDA Amendments Act (FDAAA).

Since 2005, all International Committee of Medical Journal Editors (ICMJE) member journals have required that clinical trials must be registered in publicly available trials registers before they are considered for publication.(2) ICMJE journals include British Medical Journal, JAMA (Journal of the American Medical Association), Nature Medicine, New England Journal of Medicine, PLOS Medicine, and the Lancet.(2) Additionally, as of 2018 manuscripts submitted to ICMJE journals that report the results of clinical trials must also contain a data sharing

statement and clinical trials that begin enrolling participants on or after January 1, 2019 must include a data sharing plan in the trial's registration.(3)

As of 2016, the European Medicines Agency (EMA) started publishing clinical data submitted by pharmaceutical companies to support their regulatory applications for human medicines under the centralised procedure under Policy 0070.(4) This activity was suspended in December 2018 as part of Business Continuity Plans related to Brexit but it is now intended to gradually resume clinical data publication from September 2023 onward.(5) The scope of the relaunch applies to new active substances from September 2023 and includes negative and withdrawn products. It should be noted that this policy does not replace the existing Policy 0043 'Policy on access to documents (related to medicinal products for human and veterinary use)' which came into effect in December 2010.

The European Union Drug Regulating Authorities Clinical Trials (EudraCT) is a database used for the registration and tracking of clinical trials conducted within the European Union (EU) member states submitted to the National Competent Authorities (NCAs) of the European Union (EU)/European Economic Area (EEA) from 1 May 2004 until 30 January 2023. As of 31 January 2023, all initial clinical trial applications in the EU/EEA area must be submitted through the Clinical Trials Information System (CTIS). CTIS, established by the European Medicines Agency (EMA), serves as a centralized database and communication hub for various stakeholders involved in clinical research, including sponsors, regulatory authorities, ethics committees, and researchers. CTIS facilitates the submission, evaluation, and supervision of clinical trial applications. Researchers and sponsors use CTIS to submit their trial applications, including detailed information about the study protocol, investigational product, and study sites. Regulatory authorities then use CTIS to review and assess these applications, ensuring compliance with regulatory standards and ethical principles.

The Canadian Public Release of Clinical Information (PRCI) allows Health Canada to publicly release clinical information from drug submissions and medical device applications after a final regulatory decision, enhancing transparency in the regulatory process for health products. This initiative is grounded in amendments to the Food and Drug Regulations and the Medical Devices Regulations, which came into force on February 28, 2019, specifying the conditions under which clinical information ceases to be confidential business information.

As of 2022, clinical trial disclosure is now a requirement for research funding awarded by the World Health Organization (WHO) and by the special Programme for Research and Training in Tropical Diseases (TDR).(6)

2.2 Voluntary Clinical Data Sharing venues

Clinical study sponsors across the globe have invested heavily in creating an ecosystem of tools, processes, and procedures to support the transparency of clinical research and sharing of data. An important milestone for research based pharmaceutical companies is the publication of the European Federation of Pharmaceutical Industries and Associations (EFPIA)/ Pharmaceutical Research and Manufacturers of America (PhRMA) Principles for Responsible Clinical Trial Data Sharing.(7) This set of principles reflects the biopharmaceutical industry's commitment to responsible, routine sharing of clinical trial data and other detailed clinical trial information in a manner consistent with the need to safeguard patient privacy, respect the integrity of national regulatory systems, and maintain incentives for investment in biomedical

research. These commitments were adopted in July 2013, as the EFPIA-PhRMA Principles for Responsible Clinical Trial Data Sharing (Principles), with implementation on January 1, 2014.(8)

As a result of this initiative, the volume of information available to researchers, patients, and members of the public has increased significantly. For this, companies have made use of various voluntary data sharing platforms, or have provided individual disclosure routes through their company. Voluntary data sharing platforms act as centralized repositories where researchers can access, request, and analyze anonymized patient-level data from completed clinical studies. These platforms provide a stable, long-term home for the data, improve the security and quality of archiving through active data curation, increase the discoverability of data through the application of metadata schemes, and facilitate the processes of request and transfer of data from generators to users, as well as tracking data utilization.(7,9)

After registration, anyone with an interest in the data can submit a data request. Each data request is reviewed according to contributor's publicly stated requirements. After access has been approved, the data can be downloaded within a given timeframe from a secure research environment. The data can be anonymized at a less conservative level because of the controls that are in place which means higher data utility for the deliverable.

Two major data sharing platforms used by multiple companies are ClinicalStudyDataRequest (CSDR) and Vivli, and are a focus of this report.

CSDR was established to promote transparency and scientific advancement by enabling researchers to access and analyze clinical trial data. The platform collaborates with several pharmaceutical companies and sponsors who voluntarily contribute their clinical trial data. These data sources include studies conducted by pharmaceutical companies, academic institutions, and other research organizations.

The Vivli organization is another data sharing platform and consortium. Vivli provides a workflow request tool, support by an independent review board, and a technical environment to support the statistical analysis of the researchers.(7) Vivli links existing data-sharing platforms and communities, while hosting data from investigators who aspire to share data but lack the resources to do so.(10) An important added value of Vivli is its contribution to the creation of standards that enables the re-analysis of clinical trial data across different platforms and including all relevant players in the process.(11)

Other examples of data sharing platforms include the Yale University Open Data Access (YODA) Project and the Supporting Open Access to Researchers (SOAR) initiative. The YODA project was launched in 2011 with the intent of making research data available to the broader scientific community. In 2014, the YODA Project formed a partnership with Johnson & Johnson to facilitate sharing of clinical trial data for the company's pharmaceutical products (including data from legacy trials), as well as devices and diagnostics.(12) The SOAR platform is a collaboration among the Duke Clinical Research Institute (DCRI), academia, and industry that is intended to facilitate open and transparent sharing of clinical research data among investigators, data scientists, and statisticians to inform and accelerate science for the benefit of human health.

3. Quantification of value of data disclosure activities

Measuring the real value of data disclosure and its impact on public health is a complex task as it involves assessing various aspects and impacts. Indicators of the value of data disclosure platforms, either mandatory or voluntary, can be deployed at different stages of the data disclosure process.

This section explores fundamental concepts of performance/value measurements based on the Donabedian model. The Donabedian model originally provided a framework for examining health services and evaluating quality of health care. However, the principles behind the model can be applied in other settings as well. In the context of this report, the Donabedian framework is used as a basis for deploying indicators of the perceived value of data disclosure activities. (13)

Below a brief overview is provided of different types of structure, process and outcome indicators. For the purpose of this report, we focus on outcome measures.

3.1 Structure

Structure measures focus on the organization and resources that contribute to data disclosure, for example, a voluntary platform for data sharing. Structure indicators can be expressed in metrics and are relatively easy to measure. For instance, the number of affiliated companies included in platforms, the number of datasets available on the platform and the number of patients included in the available datasets. Data on many of these indicators is regularly collected by voluntary data sharing platforms in order to assess the data sharing platform, in contrast to mandatory disclosure venues which have ample information on structure measures publicly available.

3.2 Process

Process measures evaluate the actual delivery of services, and in this case assess the activities and operations undertaken to transform inputs (e.g. a dataset) into tangible outputs (e.g. a publication). Process indicators review the usage of platform and can here be expressed by metrics including measuring the number of registered users, active users, the volume of data shared, and metadata views.

Evaluation of data disclosure activities in terms of process measurements can also be performed by measuring the quality of the data disclosure platform and may include indicators of data quality, such as completeness (e.g. percentage of records with all required fields populated) or consistency (e.g. percentage of values following predefined rules and standards).

3.3 Outcome measures

Outcome measures contain all the effects of healthcare on patients or populations. In this report a distinction is made between output and outcome. Output measures focus on the tangible and immediate results of a process, such as number of datasets delivered. This also includes monitoring citations, (type of) publications, patents, and other research outcomes resulting from the shared data.

While output measures offer valuable insights into overall performance, they may not provide a complete picture of the ultimate impact of the data disclosure activities. Therefore, outcome

measures are also recognized, which encompass the broader and long-term effects and impacts of the activities (e.g. impact on medical breakthroughs).

Outcome measures reflect the policy and societal impact and therefore include the influence on policy development, public health interventions, or decision-making processes. Outcome measures monitor instances where shared data has had Primary research impact (e.g. publications, presentations at conferences, academic capacity building), influence on policy-making (e.g. presentations to policymakers, policy impact (changes to legislation), building new policy networks), health-care and health systems impact (e.g. more evidence-based practice, improved quality of care, Regulatory/HTA decision-making, cost-effectiveness of treatment), health-related & Societal impact (e.g. improved health-literacy, attitudes and behaviours, improved social equity & cohesion) and economic impact (e.g. attracting investments, contributing to IP development, research contracts, spin-outs).

Outcome measurements are in general difficult indicators to quantify due to their broad scope. It is important to note that measuring the value of disclosure deliverables may require a combination of qualitative and quantitative approaches, as well as considering long-term impacts. Each platform may have specific goals and indicators that align with its purpose and user base.

3.4 Categorizing and prioritizing indicators

Based on scientific and non-academically published literature and the stakeholders consultations (semi-structured interviews with key stakeholders and online survey among researchers), potential indicators measuring the impact on public health by clinical data disclosure were collected.

Table 1 provides a comprehensive overview of potential indicators for various aspects of disclosure and its impact on public health. For each of the indicators, an assessment was included of the expected data source, feasibility and value of the measure. Feasibility indicates the estimated probability in obtaining the information ranging from low (red) to medium (orange) to high (green). Value was defined as the extent to which the indicator expresses a direct link between the disclosure activity and impact on public health. A measure in which there is both a strong link with the disclosure activity, as well as with public health impact scores high on this measure (indicated in green). If the link is more indirect, or further 'downstream', the measure scores lower, indicated in orange (medium) and red (low). Taking into consideration both the feasibility of measurement and the value, table 1 shows that there is a set of measures (measures 5 – 8) which is of high value, although with low feasibility.

3.4.1 Measures published by data disclosure platforms

Based on publicly available sources we have assessed the information available in various voluntary and mandatory disclosure venues. Table 2 displays a select overview of the data observed on voluntary disclosure platforms, mandatory disclosure platforms and registries. As depicted in Table 2, voluntary disclosure platforms do report metrics. However, these are mainly *structure*- and *process*-based measures, hence not measuring actual impact on public health. Both mandatory disclosure platforms and the registries have made little to no information available on measures of the data disclosed.

Table 1: Overview of indicators measuring public health impact from disclosure based on stakeholder consultation and literature

#	Indicator	Indicator type	Objective	Interpretation	Data source	Feasibility[1]	Value[2]
1	The number of citations	Output	Primary Research impact	Total N citations following the use of a shared data set	Data platform/ researcher	🟢	🟠
2	Number and impact factor of publications	Output	Primary Research impact	Total N publications including impact factor following the use of a shared data set	Data platform/ researcher	🟢	🟠
3	Type of publications	Output	Primary Research impact	Total N of meta-reviews or opinion articles	Data platform/ researcher	🟠	🟠
4	Number of patents	Output	Health-care and health systems impact	N of publications based on a shared data set that are part of a patent request	Researcher	🟠	🟠
5	Number of instances where shared data has informed policy discussions	Outcome	Influence on policy-making	Number of instances where shared data has informed policy discussions	Researcher	🔴	🟢
6	Number of influenced regulatory decisions	Outcome	Influence on policy-making	Number of influenced regulatory decisions	Researcher/ Regulator	🔴	🟢
7	Number of changes in legislation	Outcome	Influence on policy-making	Number of changed legislations	Researcher/ Regulator	🔴	🟢
8	Number of publications that contributed to evidence-based practices/guidelines	Outcome	Health-care and health systems impact	Number of publications that contributed to evidence-based practices	Researcher	🔴	🟢
9	Number of citations in guidelines	Outcome	Health-care and health systems impact	Number of publications that are cited in (renewed) guidelines	Researcher	🟠	🟠
10	Disease burden across different demographics	Outcome	Health-related & Societal impact	Δ Disability adjusted life years (DALY's) in years	Data platform/ Researcher	🔴	🔴
11	Number of investments contributing to IP development	Outcome	Economic impact	Number of investments contributing to IP development	Researcher	🔴	🟠
12	Number of research contracts	Outcome	Economic impact	Number of research contracts following the work after approved clinical data request	Researcher	🔴	🟠

[1]Feasibility indicates the estimated probability in obtaining the information ranging from low (red) to medium (orange) to high (green).
[2]Value is the estimated extent to which the indicator expresses a direct link between the data disclosure activity and impact on public health ranging from low (red) to medium (orange) to high (green).

Table 2: Selected overview of information available at clinical trial disclosure venues

#	Indicator	Voluntary (Vivli**(14)**[a], CSDR**(15)**[b], YODA**(16)**[c])	Regulator documents (EMA policy 0070**(17)**, PRCI**(18)**)	Registries (Clinicaltrials.gov**(19)**, EudraCT**(20)**)
	Primary research impact:			
	The number of citations, Number and impact factor of publications, Type of publications	Generally, information provided on publications. Limited longitudinal analysis/citation analysis	No information provided	No information provided
	Health-care and health systems impact			
	Number of patents, Number of publications that contributed to evidence-based practices/guidelines, Number of citations in guidelines	Some (qualitative) information published in news items / interviews with researchers by individual voluntary venues.	No information provided	No information provided
	Influence on policy-making			
	Number of instances where shared data has informed policy discussions, Number of influenced regulatory decisions, Number of changes in legislation	Some (qualitative) information published in news items / interviews with researchers by individual voluntary venues.	No information provided	No information provided
	Health-related & Societal impact			
	Disease burden across different demographics	Some (qualitative) information published in news items / interviews with researchers by individual voluntary venues.	No information provided	No information provided
	Economic impact			
	Number of investments contributing to IP development, Number of research contracts	Some (qualitative) information published in news items / interviews with researchers by individual voluntary venues.	No information provided	No information provided

[a]Status on 31OCT2023; [b]Status on 01MAY2023; [c]Status on 01OCT2023
CSDR, Clinical Study Data Request; EudraCT, European Union Drug Regulating Authorities Clinical Trials Database; PRCI, Canadian Public Release of Clinical Information PRCI; YODA, Yale University Open Data Access

4. Conclusions & Recommendations

In this report, the perceived public health value of various mandatory and voluntary disclosure venues was studied. To address this issue, a mixed methods approach was used by assessing literature, and conducting semi-structured quantitative interviews and surveys with stakeholders from academia, industry, and NGOs, as well as authors who had published using anonymized clinical data from disclosure venues.

Our investigation highlights a significant focus in current literature and stakeholder feedback on the initial stages and processes of data sharing (e.g. number of requests, requests granted). However, there is a gap in understanding the broader public health impacts of these activities.

This focus can also be observed in the mandatory and voluntary venues that were included in this study. We found that various voluntary disclosure venues do report some metrics in a systematic manner, and these provide indications of added value. However, these measures are mostly output-related hence not fully representative for the impact on public health. This provides an opportunity to build on the existing activities for a more comprehensive measurement of added value for public health.

For the mandatory disclosure venues, and based on publicly available sources, we found no systematic reporting of indicators that measure the potential impact on public health of their mandatory disclosure requirements.

Collective efforts are necessary to prospectively collect data which will allow for the measurement of the proposed indicators. Stakeholders should work towards an agreed set of indicators that measure the value of disclosure efforts. As part of this process, a small cohort of data requests could be followed up prospectively, which will offer deeper and more nuanced understanding of optimal ways to implement measurement activities. These steps are crucial to capture the full potential of clinical trial data transparency within the biopharmaceutical industry for the advancement of public health.

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