Pharma Intelligence
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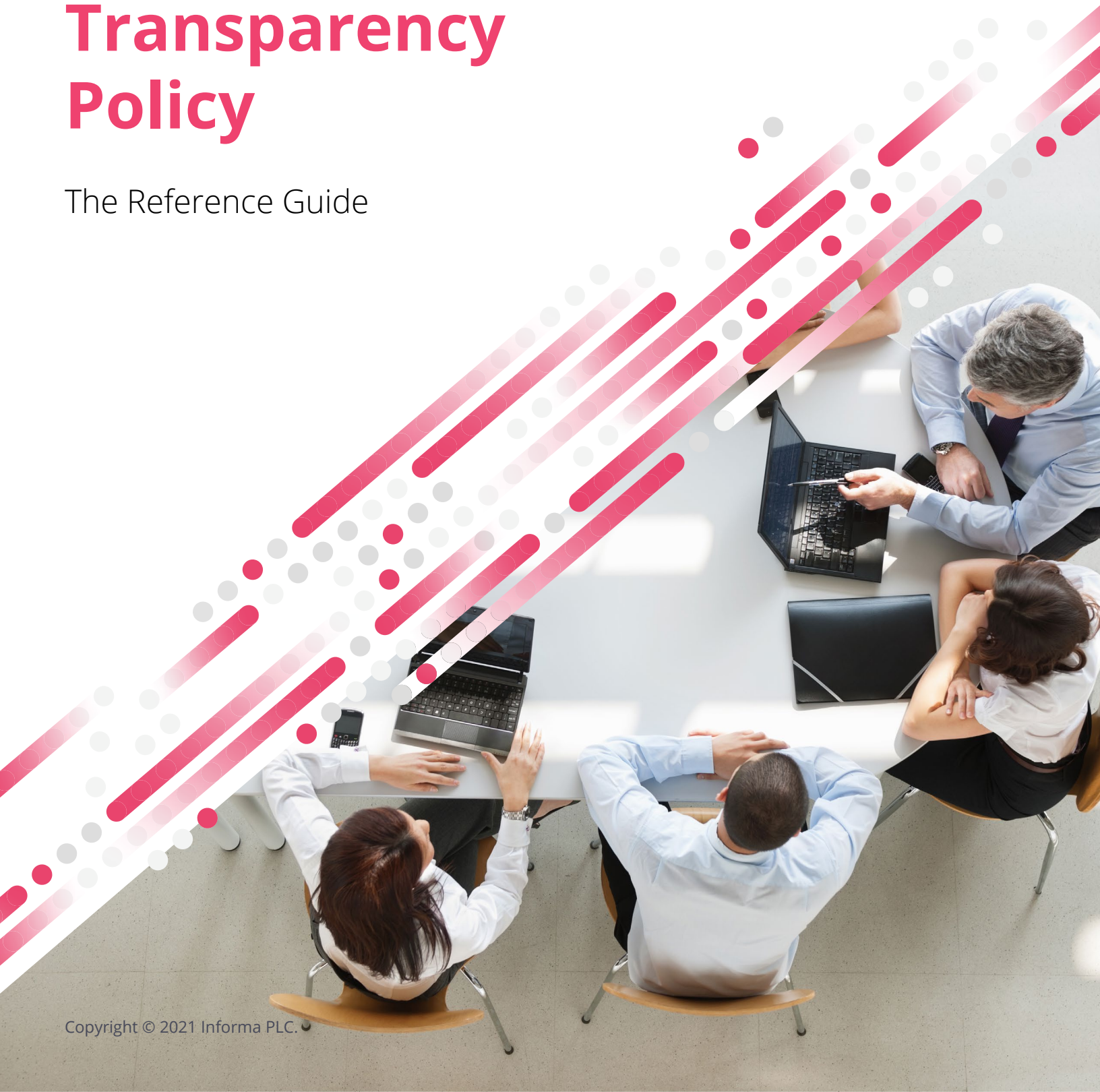
Clinical Trial Transparency Policy

The Reference Guide



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Overview

Clinical trials are conducted in almost every country in the world, each with its own health authority and regulations. Approximately 90 of these countries have requirements related to the disclosure of clinical trial data that are made publicly available on over 30 clinical trial registries. Complying with all regulations is the minimum disclosure requirement. However, there are no global standards for the scope and timing of these disclosure requirements, making it difficult for sponsors to obtain a consistent view of how their studies comply with local regulations. Adding to this complexity are the evolving expectations from transparency advocates and patient groups, as well as the general industry trend to disclose an ever-increasing scope of clinical data.

Responsible data sharing advances scientific understanding and supports better research decisions, leading to faster insights that, in turn, help patients. Additionally, greater transparency holds the promise of:

- **Improved trust in the industry**
- **Better relationships with patients, patient groups, and researchers**
- **Positive investor evaluations of companies based on their commitment to transparency, which is perceived to reduce certain risks and reflects a company's ethics**

Approximately

90

countries

have requirements related to the disclosure of clinical trial data

Transparency Policy Scope

To satisfy the changing regulatory requirements, and to address the evolving expectations of patient groups, transparency advocates, and industry trends, a transparency policy must clearly define the following commitments related to disclosure, transparency, and data sharing:

- Protocol registration
- Results disclosure
- Clinical Study Report (CSR) synopses
- Full Clinical Study Reports (CSRs)
- Plain (Lay) Language Summaries (PLS)
- Individual Patient-level Data (IPD)

Summary of Requirements and Expectations

In order to develop a comprehensive transparency policy, it is essential to know the requirements of various international organizations.

International Committee of Medical Journal Editors (ICMJE)

The ICMJE requires that all protocols for trials included in a manuscript must be posted on a recognized public registry by the start of enrollment; otherwise, the manuscript will be rejected.

Additionally, the ICMJE requires that sponsors provide a "Data Sharing Statement" with the manuscript that describes in detail the commitment to sharing clinical data related to the trial(s) in the manuscript, including:

- Will individual patient data (IPD) be made available?
- What data will be shared, and what other documents will be made available?
- When will it be available?
- Who may request the data and for what types of analyses?
- How can the data be accessed?

Note: A lengthy list of journals that are not ICMJE members also follow these requirements.

The Declaration of Helsinki

The World Medical Association (WMA) Declaration of Helsinki requires that every research study involving human subjects be registered in a publicly accessible database before recruitment of the first subject and states that researchers have a duty to make publicly available the results of their research. In effect, this means that all trials in humans (including Phase 1 healthy volunteer trials) must be registered and results must be disclosed. Additionally, the declaration now requires that all medical research subjects should be given the option of being informed about the general outcome and results of the study, which is generally understood to mean providing trial participants with plain (lay) language summary of results.

In order to develop a comprehensive transparency policy, it is essential to know the requirements of various international organizations.

Industry groups

Industry groups such as the Biotechnology Innovation Organization (BIO), the Pharmaceutical Research and Manufacturers of America (PhRMA), the European Federation of Pharmaceutical Industries and Associations (efpia), and the Association of the British Pharmaceutical Industry (ABPI) have made disclosure commitments on behalf of their members.

The PhRMA/efpia principles for responsible data sharing include:

- Sharing clinical trial data and documents with qualified scientific and medical researchers upon request
- Working with regulators to provide a factual summary of clinical trial results to patients who participate in clinical trials
- Making the synopses of clinical study reports for clinical trials in patients submitted to the Food and Drug Administration, European Medicines Agency, or national authorities of EU member publicly available upon the approval of a new medicine or new indication
- Publishing clinical trial results regardless of the outcome; at a minimum, results from all Phase 3 clinical trials and clinical trial results of significant medical importance should be submitted for publication

For BIO members, the principles include:

- A commitment to register all company-sponsored clinical trials conducted on patients on an appropriate registry such as ClinicalTrials.gov or the European Clinical Trials Database (EudraCT)
- Disclosing results for approved products or after discontinuation of development
- Submitting for publication in the scientific literature, or otherwise make available to the scientific community, results of all Phase 3 trials and clinical studies of significant medical importance regardless of whether their outcomes are positive or negative
- For their approved medicines, sponsors will fulfill qualified requests from medical and scientific researchers for additional clinical trial data (e.g., clinical study reports, patient-level clinical datasets, clinical study designs, protocols, etc.) beyond those shared proactively with the public.
- Providing factual summaries of clinical trials to research participants

Transparency advocates

Regular publications in medical journals and articles in the general media assess and occasionally criticize the state of clinical trial disclosure. Increasingly, these publications analyze the disclosure practices of individual sponsors, and publish their findings with details of specific trials and companies.

The ongoing scrutiny of disclosure practices is shaping the transparency policies of a growing number of trial sponsors. By pointing out potentially noncompliant trials, these trackers are also informing inspections and compliance audits, as well as impacting public perception and reputation.

Patient groups

While no single advocacy group represents all patients, common clinical transparency expectations include the public disclosure of:

- Protocol summary information for all trials conducted in patients
- Plain (lay) Language Summaries (PLS) for all interventional trials
- Study synopses (CSRs) or basic results for all interventional trials
- Informed consent forms
- Links to publications

Transparency Policy Considerations

Following are basic requirements and trends shaping the six key elements of a clinical trial transparency policy:

1. Protocols

US

Protocol information for Phase 2, 3, and 4 interventional clinical trials that have a site in the US or involve a product regulated by the Food & Drug Administration (FDA) must be submitted to the Protocol Registration System (PRS) no later than 21 days after study start and are then made public on ClinicalTrials.gov.

EU

Similarly, all Phase 2, 3, and 4 interventional trials with sites in EU, or that are part of an EU pediatric investigation plan (PIP), are made public on EU CTR based on the clinical trial application (CTA) submitted to EudraCT. Additionally, the EU requires Phase 1 trials to be submitted, though currently only those with pediatric populations or that are part of a PIP are made public.

ICMJE

The International Committee of Journal Editors (ICMJE) requires that all protocols for trials included in a manuscript must be posted on a recognized public registry by the start of enrollment; otherwise, the manuscript will be rejected. This requirement suggests that any protocol that may ever be referenced in a manuscript should be registered by study start.

The Declaration of Helsinki

The Declaration of Helsinki requires that protocol information for every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

Transparency advocates

While there is no single set of protocol posting standards established and shared by all transparency advocates, the main requirements are:

- For new trials, post protocols for all trials by study start, with a special emphasis on all Phase 2, 3, and 4 trials regardless of whether disclosure is required by law.
- At minimum, post all trials on ClinicalTrials.gov and other registries as required.
- For older trials where protocols have not yet been posted and where there was no legal requirement to do so, there is less agreement how far back the disclosure should go, though there are four main perspectives:

1. All trials for products currently in the market should be posted.

> **Note:** Because this could require the public disclosure of trials that occurred many decades ago, this is not a standard that any major company has adopted.

2. Post all trials conducted since the introduction of the Guideline for Good Clinical Practice E6 (introduced in June 1996). ICH E6 established standards for the recording and reporting of trials, which makes assessing and comparing trials more practical.
3. Post protocols for all trials in humans that are included in an NDA/BLA submission made since 2014, irrespective of when these trials were initiated.
4. Post protocols for all Phase 2–4 trials irrespective of regulatory requirements that have started since 1990.

> **Note:** The trend is to post all protocols for Phase 2–4 trials that started since 2005.

Patient groups

Protocol summary information for all trials conducted on patients.

Industry trends for posting protocols

The industry trend is to post all Phase 2–4 interventional trials on ClinicalTrials.gov whether or not these are required by US regulations, in addition to other registries where required. There are six main reasons for this trend:

1. By limiting the policy to protocols that must be posted by law and ICMJE, instead of committing to disclosing all protocols, transparency advocates that rank these commitments will reduce the company's score significantly.
2. ClinicalTrials.gov is by far the largest global trial registry with about nine times the number of trials publicly available compared to the next largest registry, which means it is the main registry used by researchers, patients, transparency advocates, investors, etc. to locate trial information.
3. The Good Pharma Scorecard[2] requires that any trial included in an NDA or BLA should be publicly available.
4. The Declaration of Helsinki requires the posting of all trials in humans.

Note: Because the Declaration is usually understood to require the disclosure of Phase 1 and healthy volunteer studies, consider extending the policy to include these as well.

5. Certain industry associations have committed their members to posting protocols of all trials in patients on an appropriate public registry, such as ClinicalTrials.gov or EudraCT.
6. Under the US regulations, few Phase 2, 3, and 4 trials are excluded from the protocol registration requirement, especially for US companies, which means this commitment typically requires little additional work.

2. Results

US

Results for Phase 2, 3, and 4 interventional clinical trials that have a site in the US or study a product that is regulated by the FDA must be submitted to the PRS no later than 1 year after the primary completion date and are then made public on ClinicalTrials.gov, though it may be possible to request a delay for up to 24 months beyond that.

EU

Similarly, results for all Phase 2, 3, and 4 interventional trials with sites in EU, or that are part of an EU pediatric investigation plan (PIP), are made public on EU CTR within 1 year of the study completion date or within 6 months for trials with pediatric participants. Additionally, the EU requires results for Phase 1 trials to be submitted, though currently only those with pediatric populations or that are part of a PIP are made public.

The Declaration of Helsinki

The Declaration of Helsinki requires that results information for all trials in humans (including healthy volunteer studies) should be posted publicly after study completion.

Transparency advocates

While there is no single set of results disclosure standards established and shared by all transparency advocates, the main requirements are:

- For new trials, disclose results for all trials within 12 months of study completion or within 30 days of product approval — whichever is earlier.
- At minimum, post results for all trials on ClinicalTrials.gov and other registries as required.
- For older trials where results have not yet been disclosed and where there was no legal requirement to do so, there is less agreement how far back the disclosure should go, though there are four main perspectives:

1. Results for all trials for products currently in the market should be posted.

> **Note:** Because this could require the public disclosure of trials that occurred many decades ago, this is not a standard that any major company has adopted.

2. Disclose results for all trials that started since the introduction of the Guideline for Good Clinical Practice E6 (introduced in June 1996). ICH E6 established standards for the recording and reporting of trials, which makes assessing and comparing trials more practical.

> **Note:** A small number of sponsors have committed to disclose results for all Phase 2–4 interventional trials back to their adoption of the E6 standards, which means trials that completed since approximately 1998.

3. Disclose results for all trials in humans that are included in an NDA/BLA submission made since 2014, irrespective of how long ago these trials were initiated. This disclosure is a requirement to score well in the Good Pharma Scorecard.[2]

4. Disclose results for all Phase 2–4 trials irrespective of regulatory requirements that have started since 1990.

> **Note:** The trend is to post all results for Phase 2–4 trials started since 2007.

Patient groups

Results summary information for all trials in patients.

IOM (Institute of Medicine)

IOM recommends that the summary results of clinical trials should be publicly available within 12 months after study completion.

Industry trends for posting protocols

The industry trend is to disclose results for all Phase 2–4 interventional trials on ClinicalTrials.gov whether or not these are required by US regulations, in addition to other registries where required. There are six main reasons for this trend:

1. By limiting the policy to results that must be disclosed by regulations, transparency advocates that rank these commitments will reduce the company's score significantly.
2. Under the US regulations, very few Phase 2, 3, and 4 trials are excluded from the results disclosure requirement, especially for US companies, which means that this commitment typically requires little additional work.
3. ClinicalTrials.gov is by far the largest global trial registry with about nine times the number of trials publicly available compared to the next largest registry, which means it is the main registry used by researchers, patients, transparency advocates, investors, etc. to locate trial information.
4. The Good Pharma Scorecard[2] requires that results for any trial that is included in an NDA or BLA of an approved product should be publicly available.
5. The Declaration of Helsinki requires the disclosure of results of all trials in humans.

   Note: Because the Declaration is usually understood to require the disclosure of Phase 1 and healthy volunteer studies, consider extending to policy to include these as well.

6. Certain industry associations have committed their members to disclosing the results of approved products for all companysponsored clinical trials testing both safety and efficacy in patients, regardless of whether their outcomes are positive or negative. Additionally, sponsors will disclose results of trials for pivotal company-sponsored clinical trials testing both safety and efficacy in patients for products discontinued in development for all indications because of safety concerns.

12
months

Summary results must be publicly available within a year of study completion

3. CSR synopses

Key legal requirements

Certain national health authorities, such as the German Federal Institute for Drugs and Medical Devices (BfArM), require the submission of a CSR synopsis, typically in the ICH E3 format for products. The timing of this submission may vary by health authority but is usually associated with approved products.

The emerging trend is to make CSR synopses available on corporate trial websites concurrently with the release of results information on public registries.

Transparency advocates

AllTrials: The disclosure of CSRs was an element of the 2017 AllTrials Policy Audit.[1] To earn the highest score for this section would require a commitment to share the full CSR prospectively (rather than on request) for all Phase 2–4 interventional trials, irrespective of product approval status. In 2017, no sponsor had agreed to this level of transparency, but a number of sponsors did agree to the prospective sharing of CSR synopses for approved and unapproved products/indications.

Bioethics International: The 2019 Good Pharma Scorecard[2] includes an assessment of the data-sharing commitment. To receive a positive rating requires either that the company's data-sharing policy provide access to the analysis-ready dataset and CSR for all of the following: the statistical analysis plan (SAP), the study protocol, the dataset codebook, and the CSR synopses.

Industry associations

PhRMA/efpia members have committed to making the analysis-ready dataset available, with the full CSR and study protocol, within a "reasonable period after drug approval." There is no specific guidance for the availability of CSR synopses.

BIO members are committed to making CSRs of approved products available upon request. There is no specific guidance for the availability of CSR synopses.

Patient groups

A number of patient groups are requesting the public availability of the CSR synopses after study completion, irrespective of the product's approval status. While the CSR synopsis is not a lay language document, patient representatives and advocates find the format useful in understanding the results of a trial and often prefer it to the tabular result summaries on registries such as ClinicalTrials.gov and EU CTR.

4. Full CSRs

Key legal requirements

The EU clinical trial regulation (EU) No 536/2014 and Policy 0070 require that sponsors make the full CSR public after the commission's granting or refusing a product's market authorization. Health Canada requires the disclosure of CSRs under the Public Release of Clinical Information in Drug Submissions and Medical Device Applications.

ICMJE

The ICMJE data-sharing statement that must accompany manuscripts submitted since July 2018 includes the question "what other documents will be available?" which can include the CSR. While the ICMJE currently has no formal data-sharing requirements, an overly restrictive data-sharing statement may lead to the manuscript being rejected.

Transparency advocates

AllTrials: The disclosure of CSRs was an element of the 2017 AllTrials Policy Audit.[1] To earn the highest score for this section would require a commitment to share the full CSR prospectively (rather than on request) for all Phase 2–4 interventional trials, irrespective of product approval status.

Bioethics International: The 2019 Good Pharma Scorecard[2] includes an assessment of the data-sharing commitment. To receive a positive rating requires either that the company's data-sharing policy provides access to the analysis-ready dataset and CSR for all the following: the statistical analysis plan (SAP), the study protocol, the dataset codebook, and the CSR synopses.

Industry associations

PhRMA/efpia members have committed to making the analysis-ready dataset available, with the full CSR and study protocol, within a "reasonable period after drug approval."

BIO members are committed to making CSRs of approved products available upon request.

IOM (Institute of Medicine)

IOM recommends that the full data package should be shared within 18 months of study completion (unless the trial supports a regulatory application). The full data package includes the analyzable data set, the full protocol (original protocol, any modifications, and the final protocol), the full statistical analysis plan, and the analytic code.

5. Plain (Lay) Language Summaries (PLS)

Key legal requirements

The EU clinical Trials regulation (EU) No 536/2014 that is expected to go into effect in late 2020 or early 2021 requires that a plain (lay) language summary be submitted at the same time as the results records. The Dutch CCMO does not require, but does accept, submissions of PLS to its ToetsingOnline web portal for publication on its CCMO trial registry.

The Declaration of Helsinki

The Declaration of Helsinki requires that all medical research subjects should be given the option of being informed about the general outcome and results of the study, which can be understood to mean providing trial participants with PLS.

Industry associations

PhRMA/efpia are working with regulators to "to adopt mechanisms for the preparation and distribution of lay summaries to research participants."

Patient groups

Patient advocacy groups expect that trial participants have access to PLS written in the same language as the informed consent form after the completion of the trial and welcome the public availability of PLS to all patients, not just trial participants.

Note: While the EU legal requirement to provide these PLS is not expected to be in effect until late 2020/early 2021, sponsors that have started to provide these summaries report that their first PLS required up to 18 months to produce when using internal resources. These sponsors have found that the process for authoring the PLS, reviewing them internally for scientific accuracy and with patient panels for usability, often required significantly more time than originally estimated. Whatever PLS policy is defined, we recommend selecting two or three trials to pilot the authoring process well before these become a regulatory requirement.

6. Individual Patient-Level Data (IPD)

Key legal requirements

Phase II of the (EU) No 536/2014 clinical trial regulation will require the sharing of anonymized IPD, though the implementation timeline and details for Phase II have not been established. Health Canada's Public Release of Clinical Information (PRCI) does not currently include the public release of IPD.

ICMJE

The ICMJE data-sharing statement that must accompany manuscripts submitted since July 2018 includes the question "will individual participant data be available (including data dictionaries)?" While the ICMJE currently has no formal requirement to share IPD, an overly restrictive data-sharing statement may lead to the manuscript being rejected.

Transparency advocates

AllTrials: The sharing of IPD was an element of the 2017 AllTrials Policy Audit.[1] To earn the highest score for this section would require a commitment to share the IPD for all trials Phase 2–4, irrespective of product approval status.

Bioethics International: The 2019 Good Pharma Scorecard[2] includes an assessment of the data-sharing commitment. To receive a positive rating requires either that the company's data-sharing policy provides access to the analysis-ready dataset and CSR for all the following; the statistical analysis plan (SAP), the study protocol, the dataset codebook, and the CSR synopses.

Industry associations

PhRMA/efpia The biopharmaceutical industry is committed to sharing patient-level data, study-level data, and clinical study designs and protocols with qualified medical and scientific researchers.

BIO For approved medicines, each BIO member company will fulfill qualified requests from medical and scientific researchers for additional clinical trial data (e.g., clinical study reports, patient-level clinical datasets, clinical study designs and protocols, etc.) beyond those shared proactively with the public.

Patient groups

Generally, patient advocacy groups support the sharing of de-identified individual patient data, provided there are the appropriate privacy and re-identification protections.

IOM (Institute of Medicine)

IOM recommends that the full data package should be shared within 18 months of study completion (unless the trial supports a regulatory application). The full data package includes the analyzable data set, the full protocol (original protocol, any modifications, and the final protocol), the full statistical analysis plan, and the analytic code. The trend is for sponsors to accept data requests for Phase 2–4 interventional trials of approved products/indications. An increasing number of sponsors are joining data-sharing platforms like Vivli and Clinical Study Data Request, typically agreeing to have an independent third-party review panel (instead of the sponsor) assess data requests.

Summary of Requirements and Expectations

Many sponsors see transparency not merely as a regulatory requirement but as a strategic advantage. In this era of mergers and acquisitions in the pharmaceutical industry, a company's commitment to transparency is viewed as a positive by investors. And at a time when the public's perception of pharmaceutical companies is less than favorable, a solid transparency policy can go a long way toward building trust and enhancing a company's brand reputation.

Let's not forget the patients, upon whom clinical trials depend. Patients will be more likely to join a clinical trial conducted by a company they trust, and transparency is the first step in earning that trust.

1. Goldacre, B., Lane, S., Mahtani, K.R,, Heneghan, C., Onakpoya, I., & Bushfield, I., et al. 2017. Pharmaceutical companies' policies on access to trial data, results, and methods: audit study. London, England. British Medical Journal. https://www.bmj.com/content/358/bmj.j3334

2. Miller, J., Ross, J.S., Wilenzick, M., Mello, M.M. 2019. Sharing of clinical trial data and results reporting practices among large pharmaceutical companies: cross sectional descriptive study and pilot of a tool to improve company practices. London, England. British Medical Journal. https://www.bmj.com/content/366/bmj.l4217