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A Case Study: Data Transparency of Clinical Trial Data

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Titusville, New Jersey, U.S.A.**ABSTRACT**

Data Transparency (DT) of clinical trial data is in high demand in today's world of increasing research needs and new regulations across the globe, including US Food and Drug Administration Amendments Act of 2007 (FDAAA) regulations of protocol/result disclosure in clinicaltrials.gov; US California Consumer Privacy Act (CCPA); EU Clinical Trials Regulation 536/2014 (CTR) / EudraCT requirements; European Medicine Agency Policy on Publication of Clinical Data for Medicinal Products for Human Use (or, EMA Policy 0070); EU General Data Protection Regulation (GDPR); Health Canada's Public Release of Clinical Information (PRCI); and Japan Pharmaceutical Manufacturers Association (JPMA) Information on Japanese Regulatory Affairs. Recently, in 2019, the FDA has concluded the Clinical Data Summary Pilot Program and is proposing a new integrated review template. Therefore, a holistic DT process is needed to face the challenge of the complexity of different regulations and data utility needs. At Johnson & Johnson, the DT Group navigates the complexity with a responsible, efficient, and consistent approach. At the same time, the DT Group also contributes to PHUSE DT Workstream in establishing a Best Practices Guide. A case study from the DT Group of Johnson & Johnson demonstrates a real-world solution for whole spectrum activities: from sharing CSR and individual patient data, production of plain language summaries, to clinical trial result disclosure.

INTRODUCTION

In today's data-driven world, data is in high demand with its increasing values in our daily life. In the healthcare world, clinical trial data provides valuable information to patients and researchers in various disease areas. Therefore, it is a regulatory requirement to share the summary result and report in the following areas, especially in the US and EU:

1. Disclosure of the clinical trial summary results for required clinical trials in public domains: www.clinicaltrials.gov (for the US) and www.clinicaltrialsregister.eu (for EU).
2. Submission of Clinical Summary Reports (CSR):
 - a. EMA Policy 0070 requires redacted CSR
 - b. Health Canada's PRCI requires anonymized CSR

- c. JPMA Information on Japanese Regulatory Affairs requires redactions /anonymization of CSR

3. Plain Language Summary (or, Layperson's Summary): It is a planned requirement in EU CTR with an implementation timeline targeted in early 2022. In the Netherlands, although a public summary is required, the regulation does not clearly state if it is to be a layperson's summary. However, the User Manual for [Toetsing Online](#) states, "This final report will consist of a lay summary and a scientific summary with study results. This has to be submitted via the web portal Toetsing Online."

In the meantime, new regulatory programs are also under development. As a part of the FDA's efforts to enhance transparency around the drug approval decisions, recently, in 2019, the FDA has concluded the CSR Pilot program and is proposing a new integrated review template to enhance the new drug regulatory program.

In addition to the regulatory requirements, there are increasing demands in individual patient data from the research and academic communities for sharing clinical trial data and documents of the clinical trials. The data shared with the research community requires a reasonable data utility of individual patient data be kept to meet research needs.

However, with the increasing of data disclosure and sharing in the public domain and research communities, it is a crucial component in data transparency regulations to protect an individual's privacy. For clinical trial data, there are many regulations already in place to protect individual's patient data, such as the US Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule, to protect individually identifiable health information since the first effective date of 14 Apr 2003. Furthermore, regulatory authorities are also increasing the privacy requirements to protect individual's health information data and individual's data rights across the globe, such as the EU General Data Protection Regulation (GDPR) that became effective on 25 May 2018; the California Consumer Privacy Act (CCPA) with the effective date of 01 Jan 2020.

In facing the ever-changing landscape of data transparency, we also need to be able to balance the data utility and data privacy. Therefore, a holistic DT process is necessary to rise to the challenge of the complexity of different regulations and data utility needs.

In this paper, we will explore a case study demonstrating a real-world solution of data transparency of clinical data at Janssen in navigating the complexity of the requirements and demands in the fast-changing world.

METHOD

To meet the high demands and complexity of the data transparency requirements, we divided the data transparency activities into the following major areas:

- Protocol Registry and Disclosure of the Clinical Trial Summary Results
- Submission of Clinical Summary Reports
- Sharing of Individual Patient Data for Secondary Analysis and Beyond
- Protection of Individual's Patient Data
- Plain Language Summaries (or Layperson's Summaries)
- Future Requirements of Data Transparency in Clinical Trial Data

We will address the challenges and navigation methods for each area in the following sections.

1. Protocol Registry and Disclosure of the Clinical Trial Summary Results

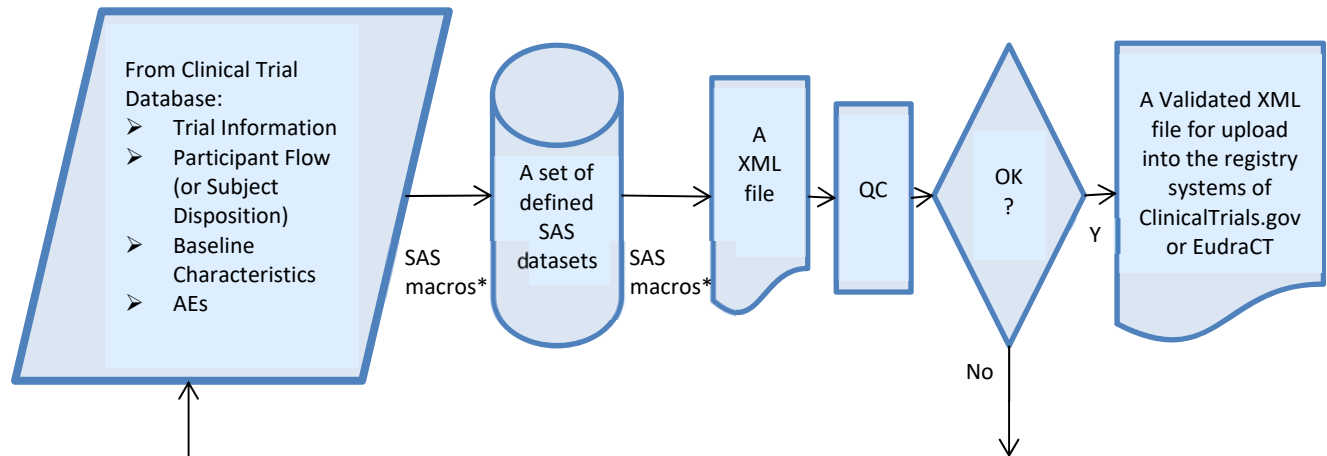
Protocol Registry Disclosure of the clinical trial summary results for required clinical trials in public domains is required for both the US and the EU.

In the US, Protocol Registry and Disclosure of the clinical Trial Result in [ClinicalTrials.gov](https://clinicaltrials.gov) has been mandated since 27 Sept 2007, according to the US Public Law 110-85 (Food and Drug Administration Amendments Act of 2007, or FDAAA), Title VIII, Section 801. It requires that a “responsible party” (i.e., the sponsor or designated principal investigator) to register and disclose trial basic result of “applicable clinical trials” if it is a Phase 2 to 4 trial conducted for a product that must be approved in the United States (per policy)), and has been initiated or ongoing as of 27 Sept 2007 per FDAAA (2007). On January 18, 2017, the Final Rule for Clinical Trials Registry and Results Information Submission (42CFR Part 11) became effective. It requires that sponsors need to: (1) post results for all applicable trials, including for non-licensed products, and (2) disclose the full protocol, statistical analysis plan, and all amendments (with redaction, as required) when results are posted. For clinical trial protocol registration, an applicable clinical trial must be submitted with the required information within 21 days after the first patient is enrolled. For disclosure of the results, applicable clinical trial results must be posted with the required information within one year of "primary completion date." If the product or indication is not yet marketed, or blind has not yet been removed at this time, then a delayed submission must be filed. The Data Element Definitions of Result Disclosure and more details of the requirements can be found in the PRS (Protocol Registration and Results System) website <https://prsinfo.clinicaltrials.gov>. A quality review process will be completed before the protocol registry and result posted to the public via a website: <https://clinicaltrials.gov/>.

In the EU, [EU Clinical Trials Register](https://www.clinicaltrialsregister.eu) uses [EudraCT](https://eudract.ema.europa.eu/) (European Union Drug Regulating Authorities Clinical Trials) database for its protocol registry and result posting of all interventional clinical trials (Phase I to IV) of medical products commencing in the European Union from 1 May 2004 onwards. The EudraCT database has been established in accordance with Directive 2001/20/EC. On 21 July 2014, the European Medicines Agency (EMA) has mandated the disclosure of the result for all interventional clinical trials (Phase I to IV) conducted in the EEA and all Pediatric studies irrespective of location. For non-pediatric trials, the trial results are required to be uploaded to EudraCT database within 12 months after the end of the trial (LPLV); For pediatric trials, the trial results are required to be uploaded to EudraCT database within six months after the end of the trial (LPLV). The result data dictionary and more details of the requirement can be found on the EudraCT website: <https://eudract.ema.europa.eu/index.html>. Based on applicable business rules within EudraCT, Information of clinical trials in the EudraCT database is posted to the public via a website of the EU Clinical Trials Register: www.clinicaltrialsregister.eu.

One of the challenges in result disclosure is a large number of studies that need to be disclosed to meet both the US and the EU requirements. At Janssen, a team of automation group developed an automation method to extract the information needed for result disclosure from the clinical trial database and create required XML files to meet both the US and the EU requirements. Figure 1 below is a data flow of the automation method.

Figure 1: Data Flow of the Automation Process:



*SAS macros are developed in two sets of macros: one set is based on the requirement of ClinicalTrials.gov; the other set is based on the requirement of EudraCT.

The automation process can generate an XML file that can be directly loaded into the registry system of ClinicalTrials.gov and EudraCT. The source data may be from a clinical trial database with various types of trial designs and different data modules from different companies. The automation process provides accuracy, efficiency, and consistency in aggregated result posting required by FDAAA and EMA. The set of SAS macros, developed by the Automation Working Group, reads the input source SAS clinical trial datasets that are used in many pharmaceutical companies and generates a validated XML file that meets requirements of ClinicalTrials.gov and EudraCT.

2. Submission of Clinical Study Reports

[EMA Policy 0070](#) and [Health Canada' PRCI \(Public Release of Clinical Information\)](#) requires redacted/anonymized Clinical Study Reports (CSRs) being submitted as part of an application. Both EMA and Health Canada encourages adopting a 9% (or, 0.09) re-identification risk threshold for redacted/anonymized CSRs. At the same time, EMA and Health Canada have different timelines for the submission of the redacted/anonymized CSRs. As it currently stands, EMA has temporarily suspended all new activities related to clinical data publication since 01 Aug 2018. This is a result of the implementation of the third phase of [EMA's business continuity plan](#). EMA will continue to publish clinical data submitted by the end of July 2018, but no new data packages will be processed until further notice.

In Japan, Japan Pharmaceutical Manufacturers Association (JPMA) released Information on Japanese Regulatory Affairs in 2018, and it requires sponsors to submit the redacted/anonymized CSR per request.

To proactively navigate through different health authority requirements across the globe, at Janssen, we applied the most restrictive requirements, such as adopting a 9% re-identification risk threshold encouraged by both EMA and Health Canada, to all CSR redaction/anonymization package starting in 2019. This way, we can keep consistency and efficacy; reduce potential data leakage in CSR redaction/anonymization package across different CSR publications across the globe.

3. Sharing of Individual Patient Data for Secondary Analysis and Beyond

Disclosure of Individual Patient Data (IPD) has not required yet by the current EMA Policy 0070 Phase I nor Health Canada' PRCI requirement. Still, in the research community, many researchers would like to have individual patient data to conduct secondary analysis for their research needs. In the meantime, we must protect individual patient data. Both US HIPAA privacy rule and EMA Policy 0070 Phase II require the data de-identification/anonymization of clinical data for data sharing/publication. To meet both research and data privacy needs, at Janssen, we developed create de-identified/anonymized data package; established a clinical data sharing platform YODA Project where research can request and access anonymization package including both anonymized CSR report and anonymized individual patient data.

One of the challenges in preparing the anonymization package is how to balance data privacy and utility. One of the solutions we came up is to prepare both anonymized CSR and anonymized data together with consistency, such as to keep the same anonymized subject ID between anonymized CSR and anonymized data, and at the same time to keep the same re-identification risk threshold between anonymized CSR and anonymized data (such as 9% as encouraged by both EMA and Health Canada). Additionally, to maximized data utility while the re-identification threshold is maintained, at Janssen, we have been working closely with both internal and external industry experts in developing a methodology to increase data utility for value-added anonymization packages to meet research needs.

To help research development in new systems and data-driven technology in clinical trial research, at Janssen, we also investigated in synthetic data approach by working with both internal and external experts with better data utility and efficiency while an individual's identification information is protected.

In section 4 below, it provides further details of the protection of the individual's patient data besides data de-identification/anonymization.

4. Protection of Individual's Patient Data

To protect an individual's data privacy and rights, the EU released the General Data Protection Regulation (GDPR) rule with an effective date of 25 May 2018. GDPR gives stronger rights to individuals/study participants, including the "right to be forgotten" to have his/her data removed from data sharing of the clinical trial data. GDPR also enforces the data transparency that sponsors will be able to collect and process data only for a well-defined purpose. Sponsors will have to inform the study participants about new purposes for processing, such as secondary data use

needed to be included in ICF. To meet the new GDPR requirements, at Janssen, we developed the following company standards:

1. Developed a standard process to systematically track records of study participants who made GDPR request to have his/her data removed from required studies, so we can probably implement the GDPR request for those individuals' data.
2. We worked with cross-functional teams, including legal and clinical trial teams, to have a well-defined ICF in place to collect and process data only for a well-defined purpose to have better control of the data use.

In the US, besides the HIPAA Privacy Rule, to protect individually identifiable health information since the first effective date of 14 Apr 2003, the California Consumer Privacy Act (CCPA) was passed in 2018 with the effective date of 01 Jan 2020. The regulation of CCPA requires us to continually update our privacy process/policy to meet ever-changing regulations and requirements.

5. Plain Language Summaries (or Layperson's Summaries)

EU requires the publication of Plain Language Summaries (or Layperson's Summaries) per [Clinical Trial Regulation \(Regulation \(EU\) No 536/2014\)](#). The planned implementation timeline is targeted for early 2022. It requires sponsors to share with trial participants and the general public a trial summary of results written in non-scientific, easy-to-understand language. This trial summary of results is commonly referred to as "Plain Language Summaries" (PLS) or "Layperson's Summaries" in the EU. It requires PLS provision for all Phase I – Phase IV interventional studies conducted in the EU. The delivery timeline follows the same timeframe of the disclosure of trial results in the EU Clinical Trial Register: For non-pediatric trials, delivery within 12 months after the end of the trial (LPLV); For pediatric trials, delivery within six months after the end of the trial (LPLV).

Planning for the PLS should begin before the study starts, and the provision of PLS should be communicated to study participants via Informed Consent Form (ICF).

PLSs are required to be written in a manner that the trial participants can understand. At a minimum, the summary is expected to be provided in the local language of each of the EU countries where the trial took place.

To prepare for the upcoming implementation of EU CTR, at Janssen, we proactively started a PLS initiative to develop a policy, standard process, and template for all therapeutic areas across Phase I to IV trials, including a volume forecast of studies with planned PLSs to feed resource and budget planning. A standard PLS template is developed for each required study to maintain efficiency and consistency across all studies. A standard process safeguards participant's privacy and ensures a clear understanding of the various published results, including disclosures of trial results in EudraCT and Clinicaltrials.gov that is described in section 1 above.

6. Future Requirements of Data Transparency in Clinical Trial Data

To prepare for the future requirements of Data transparency in clinical trial data, we have been proactively preparing ourselves with the active participation in many industry and health authorities initiatives, such as PHUSE Data Transparency

Working Group with development of De-identification Standard for CDISC SDTM 3.2; publication of Clinical Trial Transparency and Disclosure: A Global View; participation in FDA's Clinical Data Summary Pilot Program; contributions to PHUSE Data Transparency Workstream: A Global View of the Clinical Transparency Landscape - Best Practices Guide; and participation in EFGCP-EFPIA Roadmap Initiative to Good Lay Summary Practice. Through the active involvement in industry and health authorities' initiatives, we prepare ourselves and help the industry shape the future of data transparency in clinical trial data.

CONCLUSION

With the increasing demand of data transparency in clinical trial data and the complexity of regulatory requirements, we need to find value-added solutions to address many challenges with a holistic view to protect the privacy of data with a maximum utility to ultimately, protect our patients and benefit our patient with innovative and effective solutions.

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