Paper DH11

Evolution of Clinical Data Disclosure and Transparency DH11

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ABSTRACT

The pharmaceutical industry has put greater focus on posting results of clinical trials for public disclosure. Data transparency is an important aspect of clinical research as it helps in enabling evidence-based decisions in medicine. Clinical data disclosure and transparency is of utmost importance due to legal obligations and compliance factors associated with data disclosure.

If sponsors or research organizations do not disclose clinical trial results on time or fail to post results at all, it may lead to misconduct or data fraud in clinical trials, also posing legal penalties to the organization. Publishing results from clinical trials helps in reducing the global costs of drug development.

In the past few years, there has been a significant change in the way clinical trial results are posted. We will briefly look at the evolution of clinical data disclosure and transparency as it pertains to US FDA (ClinicalTrials.gov) as well as EMA (EudraCT) and differences between the two registries.

INTRODUCTION

Clinical data disclosure, with its efforts to increase the transparency of data related to clinical trials, is an evolving topic for the pharmaceutical industry. The regions of the world particularly active regarding trial transparency are the European Union (EU), including countries of the European Economic Area (EEA), and the United States (US).

It has become a necessity for sponsor companies to post their clinical trial results for public disclosure in a timely manner and with accuracy.

This paper focuses on the evolution of clinical data disclosure and transparency as it pertains to the two main registries for results posting: ClinicalTrials.gov the US and EudraCT for the EU. We shall also look at the difference between these two registries and recent updates related to them.

REGISTRIES

ClinicalTrials.gov is a registry of privately and publicly funded clinical studies conducted around the world. The Web site is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH) in collaboration with the Food and Drug Administration (FDA), as a result of the FDA Modernization Act, which was passed into law in November 1997.

The following table lists major milestones related to the evolution of ClinicalTrials.gov:

DATE	MILESTONE
November 1997	The FDA Modernization Act of 1997 concentrates on reforming the regulation of food, medical products, and cosmetics in the United States. It also provides for an expanded database on clinical trials, which will be accessible by patients. With the sponsor's consent, the results of such clinical trials will be included in the database.
February 2000	The NIH website (ClinicalTrials.gov) is made available to the public after joint efforts by the NIH and the Food and Drug Administration (FDA).
September 2007	Congress passes the FDA Amendments Act of 2007 (FDAAA). The ClinicalTrials.gov registration requirements are expanded. Section 801 of FDAAA (FDAAA 801) requires more types of trials to be registered and additional trial registration information to be submitted. The law also requires the submission of results for certain trials.
September 2008	ClinicalTrials.gov results database, which contains summary information on study participants and study outcomes, including adverse events, is made available to the public.
September 2016	Health and Human Services (HHS) issues the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) clarifying and expanding the

	registration and results information submission requirements of FDAAA 801. This regulation takes effect in January 2017.
January 2017	As per the Final Rule, the release of results is mandatory within 12 months after final data collection of the prespecified primary outcome measure for all applicable trials, irrespective of the approval status for the medicinal product. Along with adverse event data, all-cause mortality data also must be disclosed.
January 2020	Initial results submissions for applicable clinical trials that do not meet quality control criteria will be publicly posted on ClinicalTrials.gov with brief standardized major comments. The National Library of Medicine (NLM) issues a Request for Information (RFI) seeking public input to guide ClinicalTrials.gov in planning infrastructure enhancements aimed at ClinicalTrials.gov users and submitters as part of a multi-year modernization initiative.

EudraCT (European Union Drug Regulating Authorities Clinical Trials) is the European clinical trials database of all clinical trials of investigational medicinal products with at least one site in the European Union commencing 1 May 2004 or later. The EudraCT database has been established in accordance with Directive 2001/20/EC. The European Union Drug Regulating Authorities Clinical Trials database (EUDRACT) is the European database for all interventional clinical trials on medicines conducted in the European Union (EU), or the European Economic Area (EEA) which started after 1 May 2004.

The following table lists major milestones related to the evolution of EudraCT:

DATE	**MILESTONE**
September 2010	EudraCT version 8.0 is launched with validation rules updated from previous version 7.0.
November 2013	EudraCT Version 9.0 is launched, allowing sponsors to create and save XML/PDF files of clinical trial applications locally. Locally saved clinical trial applications can be used to complete, validate, compare, or to prepare a package for submission to a National Competent Authority.

	Result users can create, update, validate and post result data sets, and load summary attachments to the EudraCT database and upload EudraCT XML files.
August 2014	EMA launches the EudraCT result training environment.
February 2019	As of 15 February 2019, sponsors/marketing authorization holders (MAHs)/third country data providers who wish to assign clinical trials to other parties are invited to use the clinical trial result request PDF form. The PDF form replaces the letter format, and its use is mandated starting on 1 March 2019.
July 2019	A new process for registering a new/development substance in EudraCT is in place, wherein instead of creating development substances directly in xEVMPD, sponsors of trials will need to request them in advance if they want to submit a clinical trial application in EudraCT, or an Investigational Medicinal Product in XEVMPD.
November 2019	The new version of Clinical Trial Application form launches, known as EudraLex, with updates related to the footnotes section.

We shall briefly have a look at the subtle differences between the two main registries widely used across the globe, i.e. ClinicalTrials.gov and EudraCT.

NIH/CT.GOV	**EUDRACT**
It was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA)	It has been a primary registry in the World Health Organization (WHO's) Registry Network since September 2011 and is a WHO Registry Network data provider.
Does not contain information about all clinical studies conducted in the United States because not all studies are required by law to be registered.	Register and disclose all interventional clinical trials conducted in the European Union (EU), or the European Economic Area (EEA).
Trial registration is performed by the sponsor within 21 days after enrolment of the first trial participant.	Applies to trials ongoing or started: • After May 2004 in adults • After May 2006 in children
Mandate to register all applicable clinical trials ongoing or started after September 2007 in the US or as part of a US regulatory application.	To register and disclose all interventional clinical trials conducted in the European region having EudraCT number

Timelines for disclosure of summary results: • For all applicable clinical trials within 12 months of LPLV (for primary endpoint)	Timelines for disclosure of summary results: • Trials in children within 6 months of last patient last visit (LPLV) (for primary endpoint) • Trials in adults within 12 months of LPLV (for primary endpoint)
The deliverables requested for NIH submission: • 0% Serious Adverse Events • >5% Non-serious Adverse Events • NIH XML	The deliverables requested for EUDRACT submission: • 0% Serious Adverse Events • >5% Non-serious Adverse Events • Serious Drug-Related Adverse Events • Serious Adverse Events Resulting in Death • Serious Drug-Related Adverse Events Resulting in Death • Adverse Event Summary • Subject Characteristics • Subjects Randomized by Investigator and Treatment Group • EudraCT XML
Recent update: All-Cause Mortality data (Number of deaths) in the NIH XML file to be uploaded on ctgov website	Recent update: Plain Language Summary Tables

EU REGULATION

The way clinical trials are conducted in the EU will undergo a major change when the Clinical Trial Regulation (Regulation (EU) No 536/2014) comes into application.

The Regulation harmonizes the assessment and supervision processes for clinical trials throughout the EU, via a Clinical Trials Information System (CTIS). CTIS will contain the centralized EU portal and database for clinical trials foreseen by the Regulation. EMA will set up and maintain CTIS, in collaboration with the Member States and the European Commission.

The Regulation was enforced in 2014, however, timing of its application to go-live depends on confirmation of full functionality of CTIS through an independent audit. This may possibly change the format of the EudraCT XML files as well which are posted along with the EudraCT reports. This may impact updates to the current tools/programs that are being used to generate EudraCT XML files.

Plain language summaries

In order to comply with requirements for greater transparency around clinical research as part of the EU Clinical Trials Regulation 536/2014 (EU CTR Article 37), sponsors will be expected to prepare plain language summaries (PLSs) for all Phase I through IV

interventional trials, which can be understood by patients, the general public, and experts.

It is the responsibility of the trial sponsor to ensure that the lay summary is developed and submitted to the EU database within the timelines required by applicable regulation.

Points to keep in mind relating to plain language summary tables

Keep simple and short descriptions to meet the needs of the general public. Use simple everyday language to ensure ease of reading and understanding. Explain technical terms in simple language. Unambiguous information to be reported.

There should be no assumption of trial data and no promotional content included in the plain language summary tables. Also, the numeric data should be represented such that it is easily understandable by the target audience.

Plain language summaries act as a complement to the clinical study disclosure results and support in understanding the results in case of complex study designs. They initially started as a result of EU Clinical Trial Regulation, however, with the evolution of regulations and policies across the globe, clinical data disclosure and transparency is also undergoing a radical change.

THE IMPACT OF BREXIT ON EUDRACT POSTINGS

The European Commission published a notice to stakeholders on September 6th, reminding pharmaceutical companies of some unexpected impacts of Brexit in multiple areas, including the submission of clinical trial information to EudraCT.

The notice states that protocol-related information from clinical trials conducted in the UK will no longer have to be submitted to EudraCT except when the trial is part of an agreed Pediatric Investigation Plan and the UK is the only country in which the protocol has been submitted.

Results of completed clinical trials conducted in the UK before the withdrawal date must still be submitted to EudraCT if the reporting of these results is due.

CHALLENGES DUE TO THE INCREASE IN SCOPE

Due to the recent trend of acquisitions and mergers in the pharmaceutical industry, clinical trials data is handled by multiple vendors/contract research organizations (CROs), adding to the overall complexity of drug development. This, at times, results in data issues in locked studies or discrepancies in the clinical study report (CSR) as well.

In addition, format issues when the input datasets are in non-standard format and needs additional programming effort to generate the disclosure deliverables. All of this puts a

strain on regulatory compliance deadlines for disclosure.

If trial results are not posted as required, sponsor companies may be held responsible for any penalties, including a potential effect on their reputation.

TIPS TO OVERCOME THE HURDLES

Service providers can support sponsors in various ways to ensure smooth data disclosure and meet submission deadlines. They need to work towards and achieve consensus amongst different stakeholders on the clinical data and results analyzed.

Also, they should be able to troubleshoot issues with the help of available data without external support from sponsor companies/vendors as and when required. They need to communicate quickly and clearly as and when there is an issue encountered, being sure to quickly loop in a disclosure team to ensure that regulatory compliance is met. This is in hand with the need to also collaborate with study teams, medical writers and programmers.

Discuss the discrepancies (if any) with the disclosure teams and document the same before posting the results (rather than getting it from the NIH/EudraCT reviewers as review comment).

CONCLUSION

We have covered few important aspects regarding the evolution of Clinical data disclosure and transparency considering the two main registries NIH and EudraCT.
The paper also talks about the subtle differences between these two main registries. Also tried to include recent developments with respect to disclosure submissions like EU Regulation and Brexit impact, Plain Language summary tables, the challenges faced due to the expansion in scope of data disclosure and some tips and tricks to overcome these hurdles.

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