Changing Scenarios of Disclosure and Transparency of Clinical Trials

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Public Disclosure, GSK- Vaccines, Bangalore, India
22-April-2017
Agenda

- What is Clinical Trial Disclosure?
- Scope of Disclosure and Transparency
- Clinical Trial Disclosure – Changing scenarios
- The Art and Science of Being a Disclosure Expert

Public Disclosure

US Regulations

- Introduction
- History
- Final rule – Introduction, Summary of key provisions, ACT, Scope of Disclosure and timelines, Benefits
- Process flow (Brief)
- Then and now (FDAAA vs. NIH Final Rule)

EU Regulations

- Introduction and requirements
- History
- Scope of Disclosure and timelines
- EMA Policy 070 vs. Clinical Trial Regulation
- Impact of change in external regulations
What is Clinical Trial Disclosure?

Public disclosure of clinical trials is an integral part of an ongoing effort to improve transparency and be more patient focused through different registries.

**Changing Environment:** A wider umbrella of studies in scope of disclosure for mandatory registries (e.g., NIH Final Rule, EMA Pol - 0070 and EU Clinical Trial Regulation)

**Why?**

- Fulfill ethical and legal obligations to participants and the research community
- Transparency and build mutual trust
- Provide information to potential participants, referring clinicians, editors, etc
- Reduce publication bias and selective reporting

Ref: [https://clinicaltrials.gov/ct2/manage-recs/background](https://clinicaltrials.gov/ct2/manage-recs/background)
Scope of Disclosure & Transparency

**PROTOCOL SUMMARIES**
Are posted on external registers and/or Company register*

**RESULTS SUMMARIES**
Are posted on external registers and/or Company Register*

**FULL STUDY REPORTS**
Redacted and published on Company Register*

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**Study start**

**Results available**

**Publication accepted**

**FULL PROTOCOL & ANALYSES PLAN**
Are posted on external registers and/or Company register *

**PLAIN LANGUAGE SUMMARY**
EU Register and Company Register
(Upcoming)

**SHaring Anonymised REsearch Data (SHARE)**
Anonymised patient level data from GSK interventional studies evaluating products (investigational/ marketed) is made available on www.clinicalstudydatarequest.com*

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*As per GSK Public Policy

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Scope of Disclosure and Transparency

Where?

- National Registries - Clinical Trials.gov, EU Clinical Trial Registry, Pan African Clinical Trials Registry (PACTR), Clinical Trial Registry (India) to name a few.
- WHO International Clinical Trials Registry Platform
- Company Registries (e.g., GSK Clinical Study Register)
- Peer reviewed Journals
- SHARE initiative (Clinicalstudydatarequest.com)
Scope of Disclosure and Transparency

Company Registries (e.g., GSK Clinical Study Register)

About the GSK Clinical Study Register
The GlaxoSmithKline (GSK) Clinical Study Register provides an easily accessible repository of data from GSK-Sponsored Clinical Studies, supplementing communication in journals, at scientific meetings, in letters to healthcare professionals, and in approved prescribing information. It is important to emphasize that approved prescribing information must continue to guide appropriate use of GSK medicines. This information may vary from country to country. Before prescribing any product mentioned in the Register, Healthcare Professionals should consult prescribing information approved in their country.

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Clinical Trial Disclosure - Changing Scenarios (Major)

US Requirements

- 1990: FDAMA 113 1997
- 2000: Clinicaltrials.gov launched
- 2005: FDA Issues Guidance for Industry Documents
- 2010: Maine Law Enacted
- 2015: EMA Issues Guidance for Industry Documents
- 2020: Final NIH Policy for NIH-Funded Clinical Trials

EU Requirements

- 1990: (No Registry Available)
- 2007: EC Regulation 726/2004
- 2008: EC Directive 2001/20/EC
- 2010: EMA EudraCT for Pediatric Trials
- 2015: EMA Clinical Trial Database to Include Summary Results
- 2020: Clinical Trial Regulation

Other Major Influences

- Declaration of Helsinki
- WHO Establishes Trial Registration Policy
- ICMJE Requires Trial Registration

Ref: https://clinicaltrials.gov/ct2/about-site/history

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U.S. Regulations
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Introduction

- Clinicaltrials.gov is the largest clinical trials database that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions.

- It is run by the United States National Library of Medicine (NLM) at the National Institutes of Health.

- The registry currently has more than 224,000 study records, 23,000 of which display results information.

- Information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study.

Source: https://clinicaltrials.gov/
History

- Food and Drug Administration Modernization Act (FDAMA) (1997)
- Clinicaltrials.gov site released by NIH (2000)
- International Committee of Medical Journal Editors (ICMJE) began requiring trial registration as a condition of publication (2005)
- Maine State Law (2005)
- FDA Amendments Act (FDAAA) Section 801 (2007)
- Clinicaltrials.gov releases results database (2008)
- Notice of Proposed Rulemaking (NPRM) for FDAAA 801 Issued for Public Comment (2014)
- Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) (2016)

Source: https://clinicaltrials.gov/ct2/about-site/history
Introduction to Final rule

What is Final Rule?

- Regulation issued by the US Department of Health and Human Services on Sep 16th 2016, which implements Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801).
  - Specifies & expands the requirements for submission of clinical trial registration and submitting summary results information to ClinicalTrials.gov
  - Applicable Clinical Trial (ACT) determination approach
  - Enhance the public availability of information about specified trials.

What are the potential consequences of Non-compliance?

- Criminal proceedings and civil penalties of up to $10,000/day
- For federally funded trials, grant funding can be withheld if required reporting cannot be verified.
- Notices of non-compliance included in the public record on ClinicalTrials.gov
<table>
<thead>
<tr>
<th>Final rule - Summary of Key Provisions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expands the scope of trials</strong></td>
</tr>
<tr>
<td>• Result summary information of trials of unapproved products</td>
</tr>
<tr>
<td><strong>One responsible party</strong></td>
</tr>
<tr>
<td>• Submitting information about an applicable clinical trial.</td>
</tr>
<tr>
<td><strong>Timelines &amp; data elements</strong></td>
</tr>
<tr>
<td>• Clarification &amp; specification - registration and results information submission.</td>
</tr>
<tr>
<td>• Some data elements must be updated more frequently than the standard 12 months.</td>
</tr>
<tr>
<td><strong>Full protocol and statistical analysis plan</strong></td>
</tr>
<tr>
<td>• Submission required</td>
</tr>
<tr>
<td><strong>Adverse event information</strong></td>
</tr>
<tr>
<td>• Required to be submitted by arm or group</td>
</tr>
<tr>
<td><strong>Narrative summaries</strong></td>
</tr>
<tr>
<td>• Submission NOT required</td>
</tr>
<tr>
<td><strong>Expanded Access record</strong></td>
</tr>
<tr>
<td>• Required if an investigational drug product studied in an applicable drug clinical trial is available through an expanded access program.</td>
</tr>
</tbody>
</table>
Definition of ACT

Under the Final Rule, two types of ACTs are defined:

1. **Applicable drug clinical trial:**
   - It is a controlled clinical investigation,
   - Other than a phase 1 clinical investigation
   - Drug product subject to section 505 of the FD&C Act (21 U.S.C. 355) or a biological product subject to section 351 of the Public Health Service Act (PHS Act).

2. **Applicable device clinical trial:**
   - It is a prospective clinical study of health outcomes
   - Compares an intervention with a device product against a control in human subjects
   - The studied device is subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
   - It is other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes except in case of a pediatric postmarket surveillance of a device product as required under section 522 of the FD&C Act (21 U.S.C. 3601)

Determination of ACT

For a study initiated on or after January 18, 2017 (42 CFR 11.22):

- Study Type = Intervventional*


- Study Phase ≠ Phase 1 (drug and biological products) OR Primary Purpose ≠ Device feasibility (device products) [new menu option]

- Any of the following apply:
  - Facility Location Country = U.S. (or U.S. territory); OR
  - U.S. FDA IND or IDE Number = Yes; OR
  - Product Manufactured in and Exported from the U.S. = Yes [new element]

* 42 CFR 11.22(b); If the study is a pediatric postmarket surveillance of a device product as required by FDA under Section 522 of the Federal Food, Drug, and Cosmetic Act, it meets the definition of an applicable device clinical trial.

IND = Investigational New Drug application; IDE = Investigational Device Exemption

## Final rule – Scope and Timelines

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Timeline</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol finalization</td>
<td>• Within 21 days of first subject enrolled</td>
<td>Protocol registration</td>
</tr>
<tr>
<td></td>
<td>• Before first subject is enrolled (ICMJE)</td>
<td></td>
</tr>
<tr>
<td>Protocol summary QA comments &amp; correction of errors</td>
<td>15 calendar days</td>
<td>Update of Protocol summary record</td>
</tr>
<tr>
<td>Change in data elements (intervention name, study status, milestones, site status, responsible party contact details)</td>
<td>30 calendar days</td>
<td>Update of Protocol summary record</td>
</tr>
<tr>
<td>Protocol amendment(s) finalization</td>
<td>30 calendar days</td>
<td>Update of Protocol summary record impacted by protocol amendment</td>
</tr>
<tr>
<td>-</td>
<td>At least once every 12 months for ongoing studies</td>
<td>Record verification date</td>
</tr>
</tbody>
</table>
**Final rule – Scope and Timelines**

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Timeline</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Completion date (PCD)</td>
<td>Within 12 months of PCD</td>
<td>Submission of result summary*</td>
</tr>
<tr>
<td>Availability of data after PCD</td>
<td>Within 12 months of availability of data</td>
<td>Submission of partial results ** (Update of result summary record)</td>
</tr>
<tr>
<td>Missing information</td>
<td>At least once every 12 months</td>
<td>Update of result summary record</td>
</tr>
<tr>
<td>Result summary QA comments and correction of errors</td>
<td>Within 25 calendar days</td>
<td>Update of result summary record</td>
</tr>
<tr>
<td>Submission of result summary</td>
<td>Within 12 months of PCD</td>
<td>Submission of Full Protocol and Statistical analysis plan</td>
</tr>
</tbody>
</table>

*Results information submission could be delayed for up to 2 additional years from the date of submission of a certification that either an unapproved, unlicensed, or uncleared product studied in the trial is still under development by the manufacturer or that approval will be sought within 1 year after the primary completion date of the trial for a new use of an approved, licensed, or cleared product that is being studied in the trial.

**Submission of results information for a secondary outcome measure or additional adverse events that was not available by the PCD.
Process flow

Data entry & QC

Submission

NIH QA Review

Approved

Not Approved

Published on CT.gov

Address QA comments

21 days (protocol registration)
Within 12 months of PCD (result summary submission)

Up to 1 month

If Rejected

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Final rule - Benefits

- Greater public access of ACTs
- More transparency
- More clarity - Legal mandate
- Quality improvement
- Better understanding

Then & Now (FDAAA Vs Final rule)

FDAAA enacted - September 27, 2007
- Study Start Date before Jan 18, 2017: FDAAA registration requirements
- Primary Completion Date before Jan 18, 2017: FDAAA results requirements
- Result summary submission of unapproved, unlicensed & uncleared products – Not in scope

Final Rule Published - September 21, 2016
- Study Start Date on or after Jan 18, 2017: Final rule registration requirements
- Primary Completion Date on or after Jan 18, 2017: Final rule results requirements
- Result summary submission of unapproved, unlicensed & uncleared products – In scope

Effective Date - January 18, 2017 (~ 4 months after publication)
Compliance date - April 18, 2017 (90 days after effective date)
EU Regulations
Introduction to EU Clinical Trial Register & EudraCT

The What, Where and How of European Union (EU) Clinical Trial Register

- Provides access to information on interventional clinical trials.
- The information available dates from 1 May 2004, when national medicine regulatory authorities began populating EudraCT, the application that is used by national medicines regulatory authorities to enter clinical trial data.
- The website, launched on 22 March 2011, enables users to search for information that has been included in the EudraCT database.
- The EU Clinical Trials Register currently displays 30159 clinical trials with a EudraCT protocol.

EudraCT- A database that includes information on clinical trials taking place in the European Union and clinical studies conducted worldwide in accordance with a pediatric investigation plan.

• Phase II to IV adult clinical trials where the investigator sites are in the EU/EEA.

• Any pediatric clinical trial
  ✓ with investigator sites in the EU/EEA
  ✓ sponsored by a marketing authorization holder
  ✓ which forms a part of an agreed pediatric investigation plan (PIP) including those where the investigator sites are outside the EU/EEA.

• Summary results of the clinical trials mentioned above and of pediatric trials completed by 26 January 2007 covered by an EU marketing authorization.

• Download up to 50 results (per request) in a text file (.txt).


The information on EU Clinical Trials Register is provided by the Company or organization responsible for the clinical trial, and is a component of its application to a national medicine regulatory authority for authorization to conduct a trial.
EU Regulation - Requirements

- Directive 2001/20/EC & CT-1 JO C82-1 (30-MAR-2010)
- Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
- Regulation (EC) No 1901/2006 on medicinal product for pediatric use
- Commission Guideline 2012/C 302/03 on posting and publication of results-related information on clinical trials in relation to implementation of Art 57(2) of Regulation (EC) No 726/2004 and Art 41(2) of Regulation (EC) No 1901/2006
- EMA Policy-070 on publication of clinical data for medicinal products for human use (2015)
# EU Regulation - History and Scoping

## Studies in scope

<table>
<thead>
<tr>
<th>Studies regulated by Directive 2001/20/EC i.e. studies with at least one investigator site located in the EU or in a contracting State of the European Economic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies that are part of a PIP (Art. 41 Regulation (EC) No 1901/2006) of including those where the investigator sites are outside the EU</td>
</tr>
<tr>
<td>Studies that fall within Article 45 of Regulation (EC) No 1901/2006, including those where the investigator sites are outside the EU</td>
</tr>
<tr>
<td>Studies that fall within Article 46 of Regulation (EC) No 1901/2006, including those where the investigator sites are outside the EU</td>
</tr>
</tbody>
</table>

## Protocol information to be disclosed:

- as of 01 May 2004 according to Directive 2001/20/EC
- as of 2012 for non-EU studies part of a PIP according to Regulation (EC) No 1901/2006 (retrospective & prospective)
- as of 2014 for non-EU Art. 46 studies (retrospective & prospective)

## Result summaries to be disclosed:

- as of 21 July 2014 according to Commission Guideline 2012/C 302/0

Retrospective posting of results for studies that ended before 21 July 2014:

- Due date 21 July 2015 (Art 46 & PIP & studies that ended after 21 July 2013)
- Due date 21 Dec 2016 (other pediatric and non-pediatric studies that ended before 21 July 2013)
The EU Clinical Trials Register allows you to search for protocol and results information on:

- interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA);
- clinical trials conducted outside the EU / EEA that are linked to European paediatric medicine development.

Learn more about the EU Clinical Trials Register including the source of the information and the legal basis.

The EU Clinical Trials Register currently displays 30112 clinical trials with a EudraCT protocol, of which 4627 are clinical trials conducted with subjects less than 18 years old.

The register also displays information on 18700 older paediatric trials (in scope of Article 45 of the Paediatric Regulation (EC) No 1901/2006).
## EU linked timelines

### EMA protocol posting

Protocol information to be submitted as part of Clinical Trial Application (CTA) before study start

### EMA result posting

<table>
<thead>
<tr>
<th>Studies ongoing or initiated after 21 July 2014</th>
<th>Pediatric studies (Art 46 &amp; PIP &amp; other)</th>
<th>Non-pediatric studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6 months of end of trial</td>
<td>≤ 12 months of end of trial</td>
<td></td>
</tr>
</tbody>
</table>

### 2018

#### EMA Plain Language Summary

Plain Language Summaries will have to be posted on EU portal within 12 months of end of trial
### EU Regulation - EMA Policy 070 vs. Clinical Trial Regulation

<table>
<thead>
<tr>
<th>Medicinal products covered</th>
<th>Clinical data publication policy (EMA- POL-0070)</th>
<th>Clinical Trial Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrally authorised products only</td>
<td>Investigational medicinal products regardless of whether they have a marketing authorisation</td>
<td></td>
</tr>
</tbody>
</table>

| Clinical studies covered | Clinical studies submitted to the Agency in the context of a Marketing Authorisation Application (MAA), Art 58 procedure, line extension or new indication, regardless of where the study was conducted | Clinical trials conducted in the EU and pediatric trials conducted outside the EU that are part of pediatric investigation plans |

| Documents published | Clinical data (clinical overview, clinical summaries and clinical study reports) and the anonymisation report | All clinical trial-related information generated during the life cycle of a clinical trial (e.g. protocol, assessment and decision on trial conduct, summary of trial results including a lay summary, study reports, inspections, etc.) |

| Publication channel | EMA clinical data publication website | Future EU portal and database |

| Date it applies | 1 January 2015 (MAA or Art 58 procedure) or 1 July 2015 (line extension or new indication) | Expected October 2018 |

| Publication from | October 2016 | Expected in 2019 |

Impact of change in external regulations on clinical trial disclosure

- Processes
- Internal standard operating procedures & policies
- Tools & templates

- Review and Approval of updates
- Finalization process
- Implementation after effective date
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“When people participate in clinical trials, they are volunteering to create generalizable knowledge to help others in the future and we want their participation honored by ensuring that the existence of trials and their results are available to all patients and their healthcare providers, as well as researchers” – Robert M. Califf