

Changing Scenarios of Disclosure and Transparency of Clinical Trials

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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)

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

EU 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>

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*

Study start

Results available

Publication accepted

PLAIN LANGUAGE SUMMARY

EU Register and Company Register
(Upcoming)

FULL PROTOCOL & ANALYSES PLAN

Are posted on external registers and/or Company register *

SHaring Anonymised REsearch Data (SHARE)

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

*As per GSK Public Policy

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](#))



[Home](#)[Find Studies](#)[Patient Level Data](#)[Products](#)[Metrics](#)[Research](#)[Contact GSK](#)

Quick Search

Advanced search

Useful Links

Paroxetine Information

Generic names of many of our medicines and vaccines

Patient Level Data Request System

ClinicalTrials.gov

clinicaltrialsregister.eu

Compassionate Use (Expanded Access)

European Public Assessment Reports

FDA Approved Drug Products

FDA Postmarket Drug Safety Information for Patients and Providers

For more information on this register please email GSKClinicalSupportHD@gsk.com



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 emphasise 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.

Use of the data and information contained in Protocol Summaries, Scientific Results Summaries, Protocols, and Clinical Study Reports on this Register is unrestricted, provided that it may not be used in applications by others for regulatory approval of a product. While not required, when using this data, we ask that proper credit or attribution of GSK as the source of the data be given. GSK disclaims liability for all uses of the data by users of this Register, to the fullest extent permitted by applicable law. No trademark, patent, or regulatory/data exclusivity rights held by GSK are waived, licensed or otherwise affected.

PROTOCOL SUMMARIES

SCIENTIFIC RESULTS SUMMARIES

PLAIN LANGUAGE RESULTS SUMMARIES

PROTOCOLS

CLINICAL STUDY REPORTS

PUBLICATIONS

PATIENT LEVEL DATA FOR RESEARCHERS

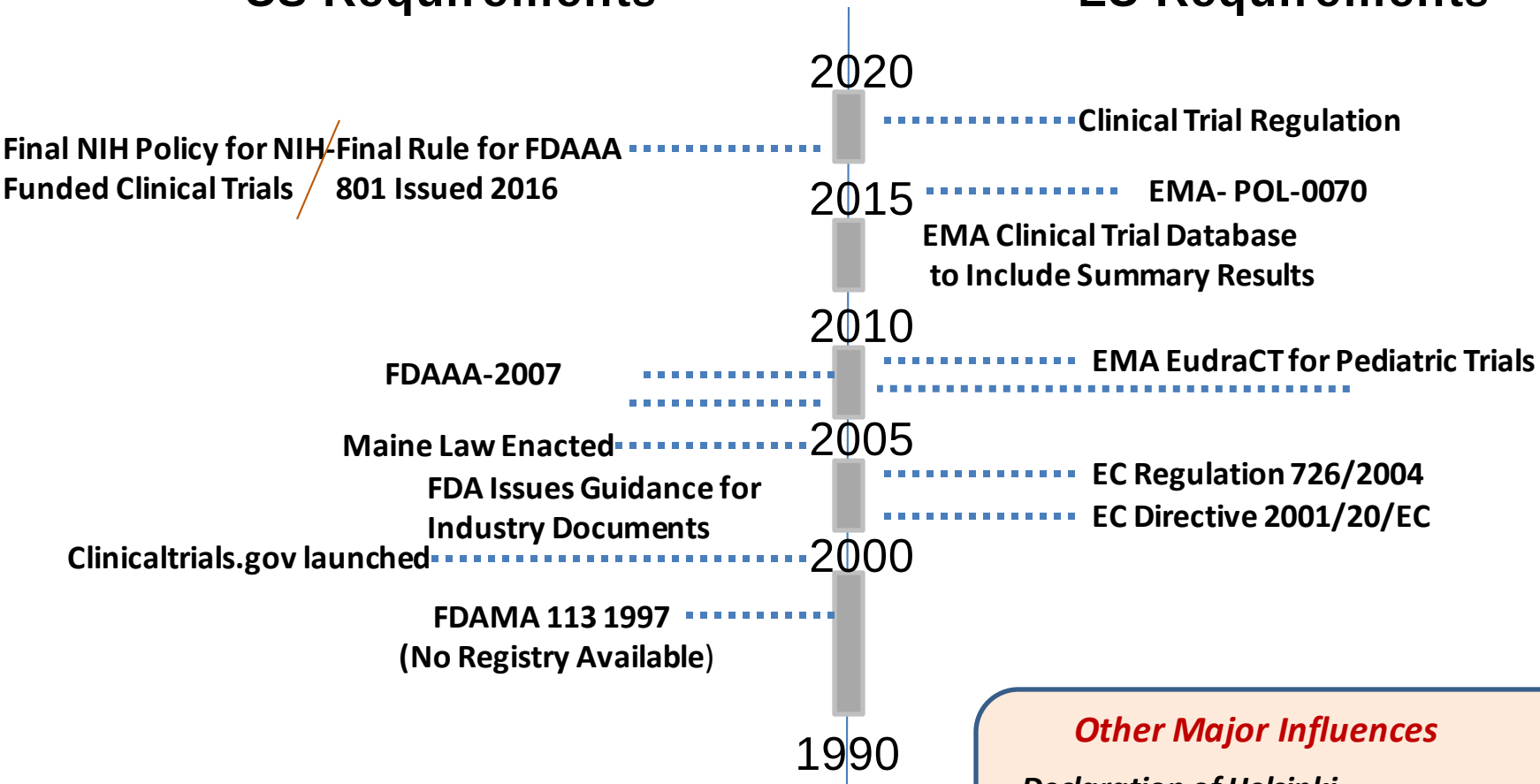
eSubmissions and Public Disclosures, Phuse SDE, Bangalore, India

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Clinical Trial Disclosure – Changing Scenarios (Major)

US Requirements

EU Requirements



Other Major Influences

Declaration of Helsinki

WHO Establishes Trial Registration Policy

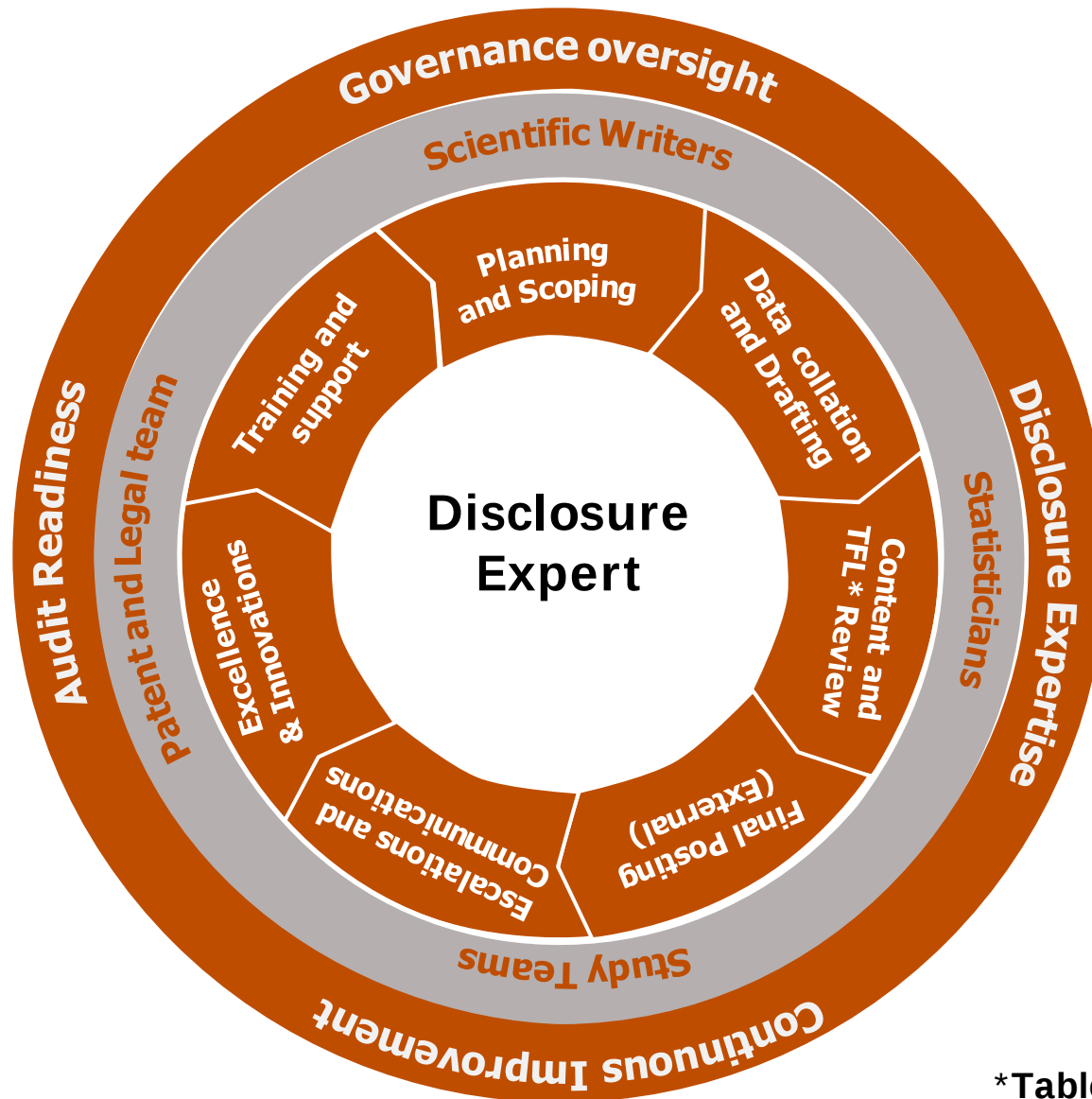
ICMJE Requires Trial Registration

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

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp

The Art and Science of Being a Disclosure Expert



*Tables, Figures & Listings

U.S. Regulations

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/>

Introduction

← → ↻

Secure | https://clinicaltrials.gov

☆ ⋮

Apps Chrome Imported From IE Job details Apply Online for Care

ClinicalTrials.gov

Try our beta test site

IMPORTANT: Listing of a study on this site does not reflect endorsement by the National Institutes of Health. Talk with a trusted healthcare professional before volunteering for a study. Read more...

Find Studies ▾ About Clinical Studies ▾ Submit Studies ▾ Resources ▾ About This Site ▾

ClinicalTrials.gov currently lists **240,783 studies** with locations in all 50 States and in **197 countries**. Text Size ▾

Search for Studies

Example: "Heart attack" AND "Los Angeles"

Search Help

- How to search
- How to find results of studies
- How to read a study record

Locations of Recruiting Studies



Non-U.S. only	(56%)
U.S. only	(38%)
Both U.S. and non-U.S.	(5%)

Total N = 41,537 studies
(Data as of April 05, 2017)

- See more trends, charts, and maps

For Patients and Families

- How to find studies
- See studies by topic
- Learn about clinical studies
- Learn more

For Researchers

- How to submit studies
- Download content for analysis
- About the results database
- Learn more

For Study Record Managers

- Why register?
- How to register your study
- FDAAA 801 requirements
- Learn more

Learn More

- Final Rule Webinar Series
- Tutorials for using ClinicalTrials.gov
- Glossary of common site terms
-  For the press
-  Using our RSS feeds

HOME RSS FEEDS SITE MAP TERMS AND CONDITIONS DISCLAIMER CUSTOMER SUPPORT

Copyright | Privacy | Accessibility | Viewers and Players | Freedom of Information Act | USA.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

Final rule - Summary of Key Provisions

Expands the scope of trials

- Result summary information of trials of unapproved products

One responsible party

- Submitting information about an applicable clinical trial.

Timelines & data elements

- Clarification & specification - registration and results information submission.
- Some data elements must be updated more frequently than the standard 12 months.

Full protocol and statistical analysis plan

- Submission required

Adverse event information

- Required to be submitted by arm or group

Narrative summaries

- Submission NOT required

Expanded Access record

- Required if an investigational drug product studied in an applicable drug clinical trial is available through an expanded access program.

Definition of ACT

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



ACT Definition &
Checklist

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)

Source: <https://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf> ; https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

Determination of ACT

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

- ✓ Study Type = Interventional*
- ✓ Studies a U.S. FDA Regulated Drug Product? OR Studies a U.S. FDA Regulated Device Product= Yes [\[new data element\]](#)
- ✓ 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

Source: https://prsinfo.clinicaltrials.gov/webinars/finalrule/resources/Final_Rule_Webinar_One_Sept_27_2016.pdf

Final rule – Scope and Timelines

Trigger	Timeline	Activity
Protocol finalization	•Within 21 days of first subject enrolled •Before first subject is enrolled (ICMJE)	Protocol registration
Protocol summary QA comments & correction of errors	15 calendar days	Update of Protocol summary record
Change in data elements (intervention name, study status, milestones, site status, responsible party contact details)	30 calendar days	Update of Protocol summary record
Protocol amendment(s) finalization	30 calendar days	Update of Protocol summary record impacted by protocol amendment
-	At least once every 12 months for ongoing studies	Record verification date

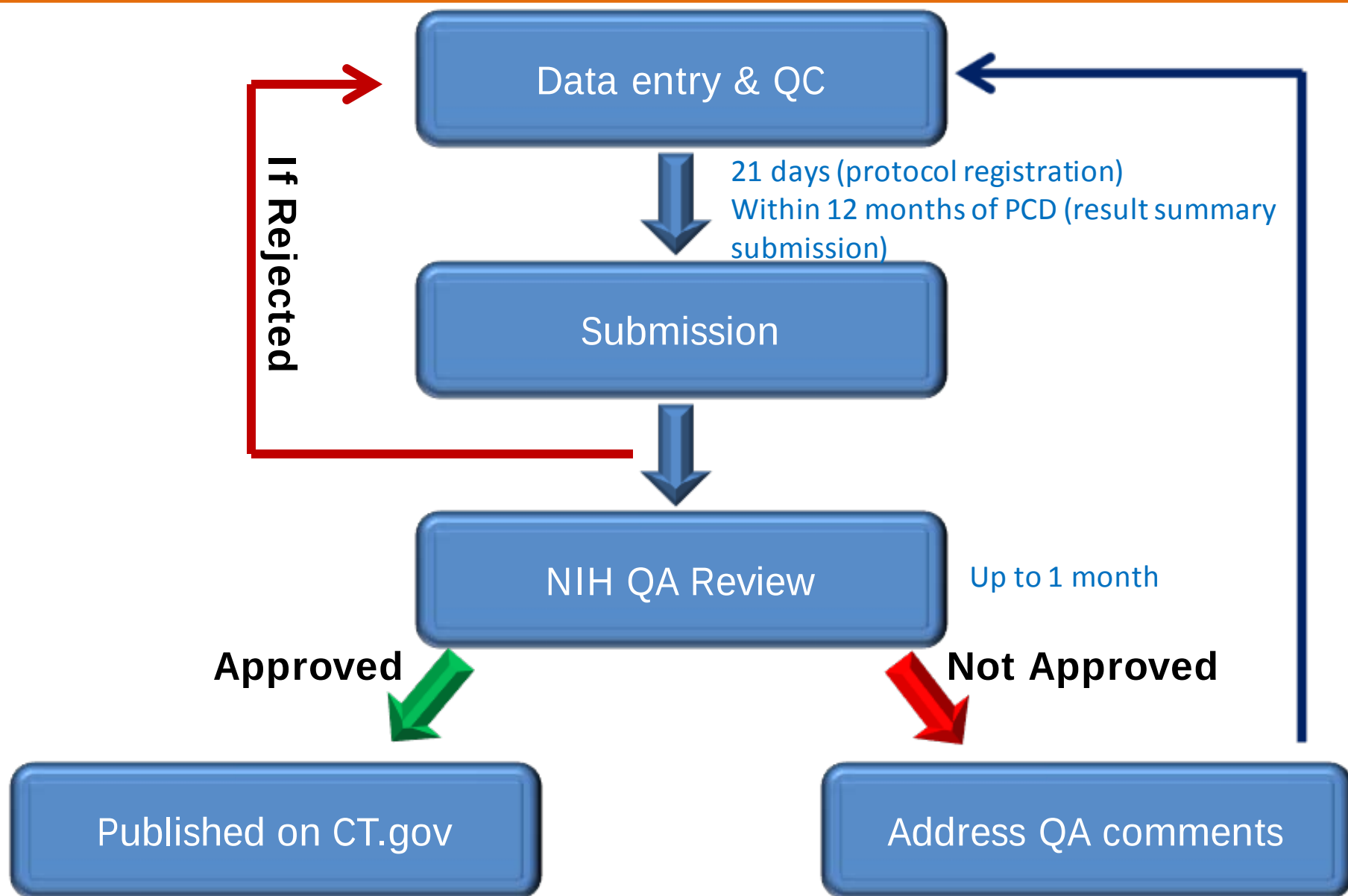
Final rule – Scope and Timelines

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

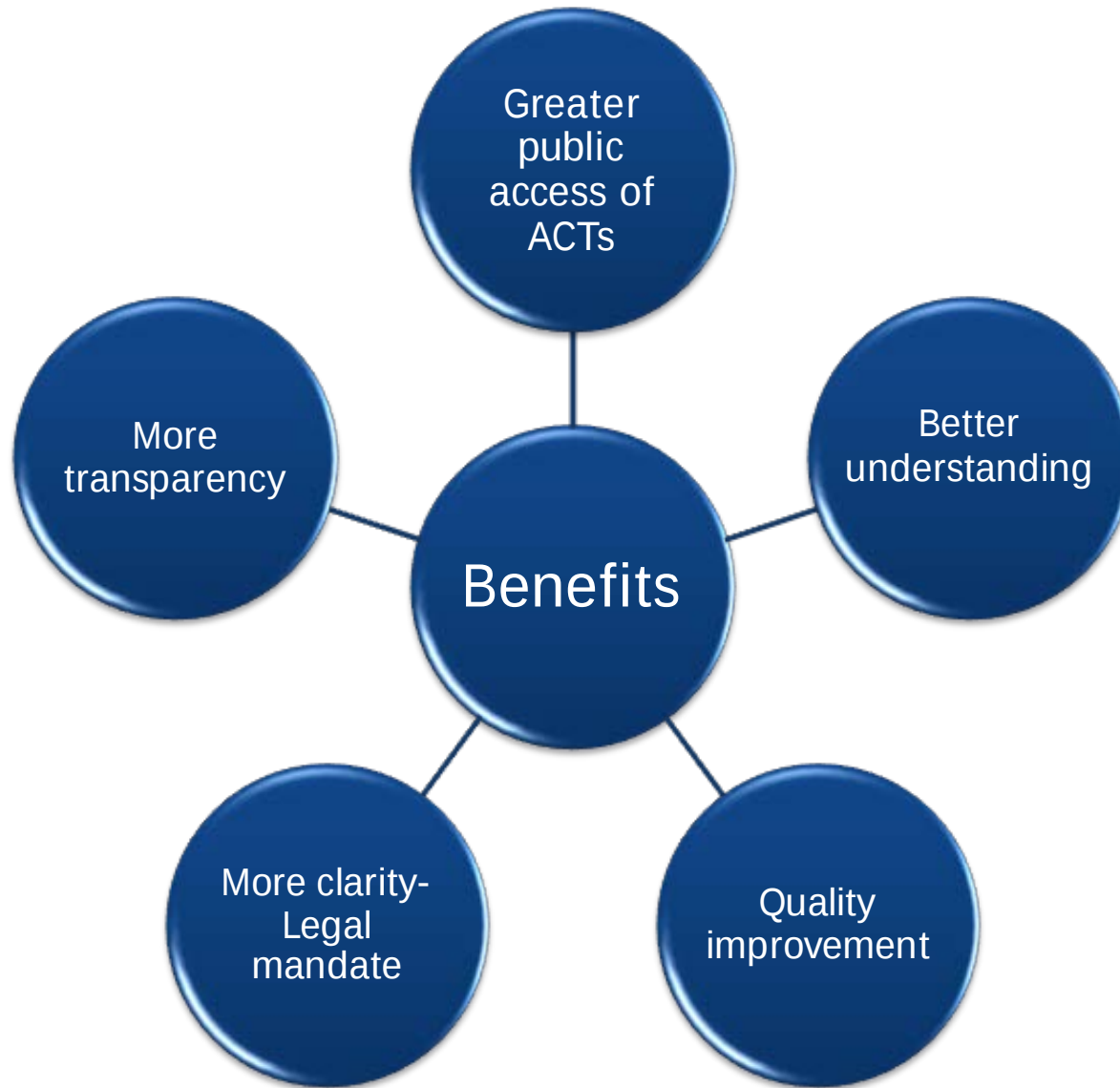
*Results information submission could be delayed for up to 2 additional years from the date of submission of a certification that either an unapproved, unlicensed, or uncleared product studied in the trial is still under development by the manufacturer or that approval will be sought within 1 year after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



Final rule - Benefits



Ref: <https://www.gpo.gov/fdsys/pkg/FR-2016-09-21/pdf/2016-22129.pdf>

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

EU Regulations

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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.

Ref: <http://www.ema.europa.eu/ema/>
<https://eudract.ema.europa.eu/>

EU Regulation- User end information

- 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 for a medicinal product in the EU/EEA
 - ✓ which forms a part of a paediatric investigation plan (PIP) including those where the information is provided for the use of a medicinal product in the pediatric population
- 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
- Regulation (EC) No 536/[2014](#) on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC
- EMA Policy-070 on publication of clinical data for medicinal products for human use ([2015](#))

EU Regulation- History and Scoping

Studies in scope

Interventional phase I – IV studies

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

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

Studies that fall within Article 45 of Regulation (EC) No 1901/2006, including those where the investigator sites are outside the EU

Studies that fall within Article 46 of Regulation (EC) No 1901/2006, including those where the investigator sites are outside the EU

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)

EU Regulation

The image shows two overlapping web browser windows. The background window is the EudraCT (European clinical trials database) homepage, featuring a blue header with the EudraCT logo and navigation links: Home, Help, FAQ, Contact Us, and About. Below the header are buttons for 'Create' and 'Load', and a 'Login' section with fields for 'Username' and 'Password' and a 'Login' button. A note states: 'Register (only for users who provide results data)'. The foreground window is the 'EU Clinical Trials Register' homepage, also with a blue header and the European Union flag. It has a 'Help' link and a navigation bar with 'Home & Search', 'Joining a trial', 'Contacts', and 'About'. The main content area is titled 'Clinical trials' and explains that the register allows searching 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.

 It includes a link to 'Learn more about the EU Clinical Trials Register' and states that the register currently displays 30112 clinical trials with a EudraCT protocol, of which 4627 are clinical trials conducted with subjects less than 18 years old. It also mentions 18700 older paediatric trials. At the bottom, there is a search bar with a placeholder 'X' and a 'Search' button. Below the search bar, it provides examples: 'Cancer AND drug name. Pneumonia AND sponsor name.' and a link to 'How to search [pdf]'. There is also an 'Advanced Search' section with a link to 'Search tools' and a dropdown arrow.

<https://europa.eu/eudract/index.htm>

<https://www.clinicaltrialsregister.eu/ctr-search/search>

EMA protocol posting

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

EMA result posting

	≤ 6 months of end of trial	≤ 12 months of end of trial
Studies ongoing or initiated after 21 July 2014	Pediatric studies (Art 46 & PIP & other)	Non-pediatric studies

2018

EMA Plain Language Summary

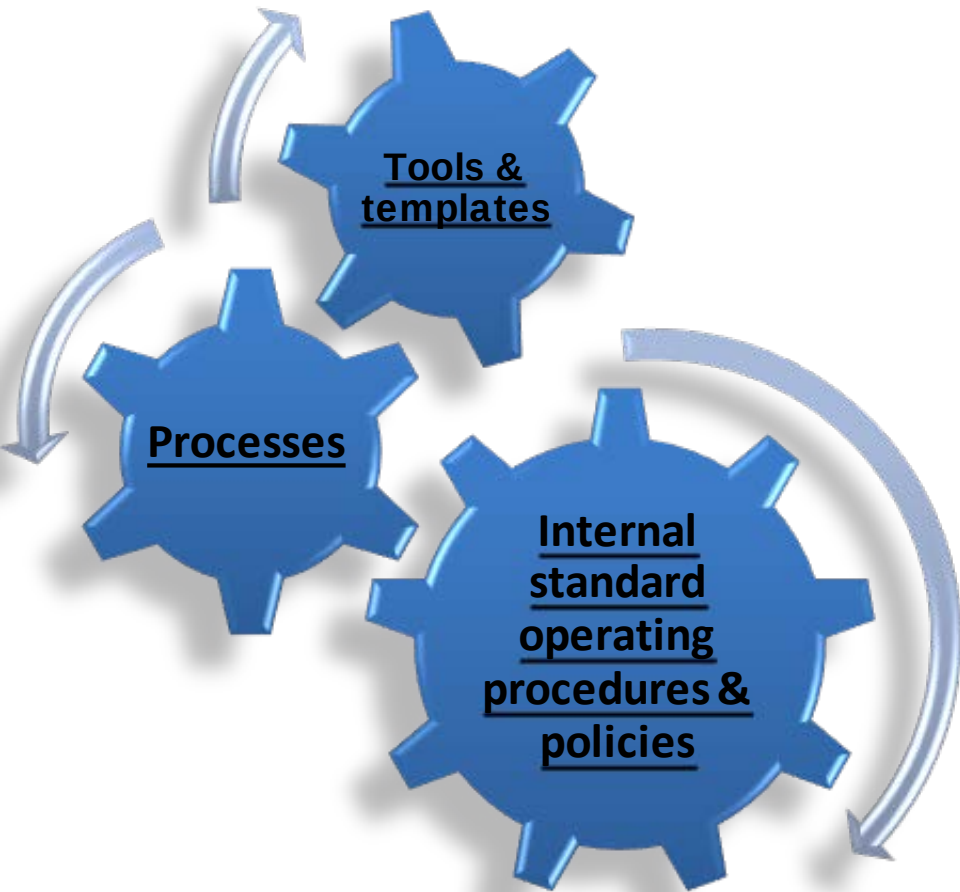
Plain Language Summaries will have to be posted on EU portal within 12 months of end of trial

EU Regulation- EMA Policy 070 vs. Clinical Trial Regulation

	Clinical data publication policy (EMA- POL-0070)	Clinical Trial Regulation
Medicinal products covered	Centrally authorised products only	Investigational medicinal products regardless of whether they have a marketing authorisation
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

Ref: http://www.ema.europa.eu/ema/?curl=pages/special_topics/general/general_content_000555.jsp

Impact of change in external regulations on clinical trial disclosure



Review and Approval of updates

Finalization process

Implementation after effective date

Contacts



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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

