Changing Scenarios of Disclosure and Transparency of Clinical Trials

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Agenda

Public Disclosure

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

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

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

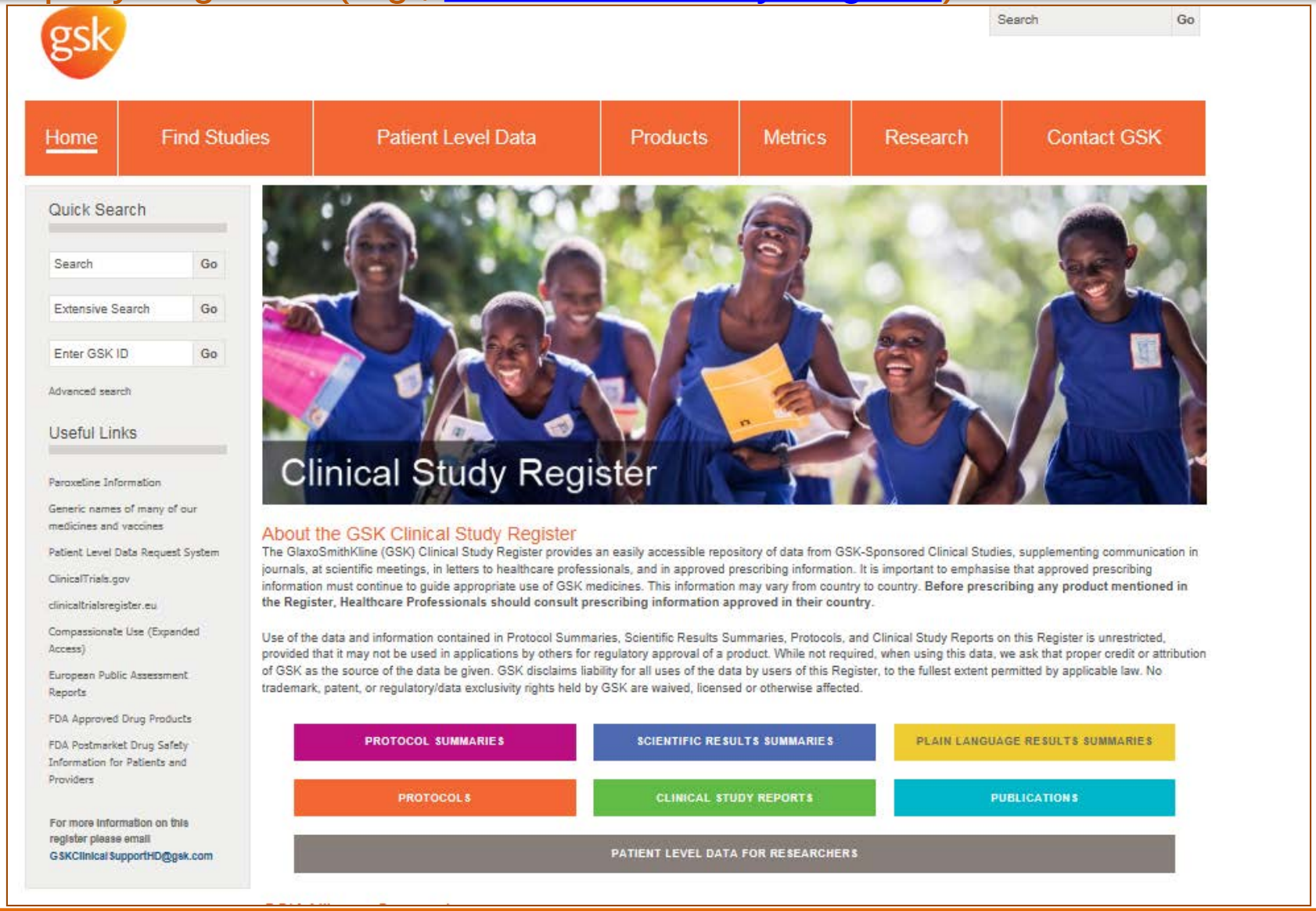
Scope of Disclosure and Transparency

Where?

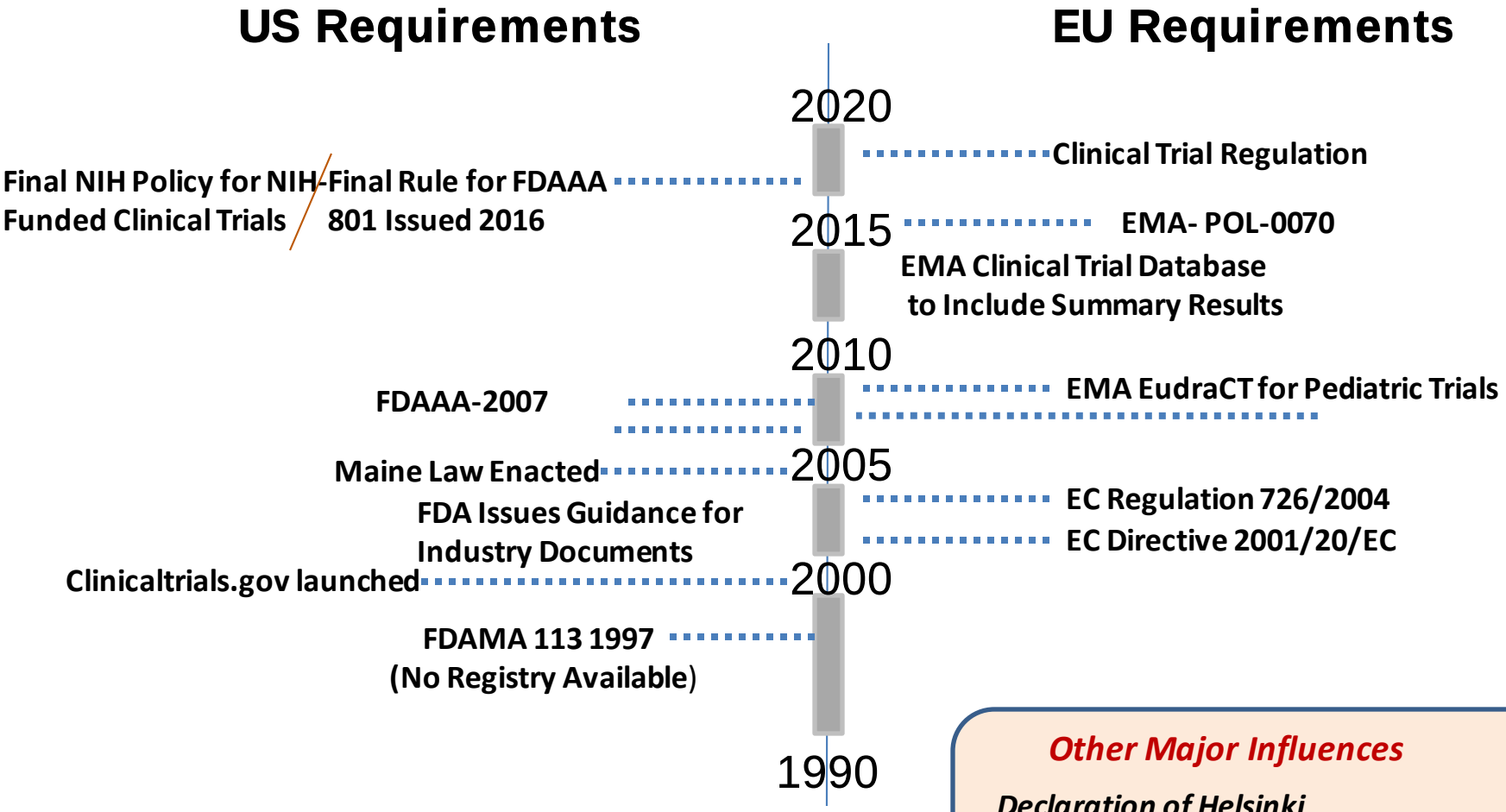
- National Registries - Clinical Trials.gov, EU Clinical Trial Registry, Pan African Clinical Trials Registry (PACTR), Clinical Trial Registry (India) to name a few.
- WHO International Clinical Trials Registry Platform
- Company Registries (e.g., GSK Clinical Study Register)
- Peer reviewed Journals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

Scope of Disclosure and Transparency

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



Clinical Trial Disclosure – Changing Scenarios (Major)



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

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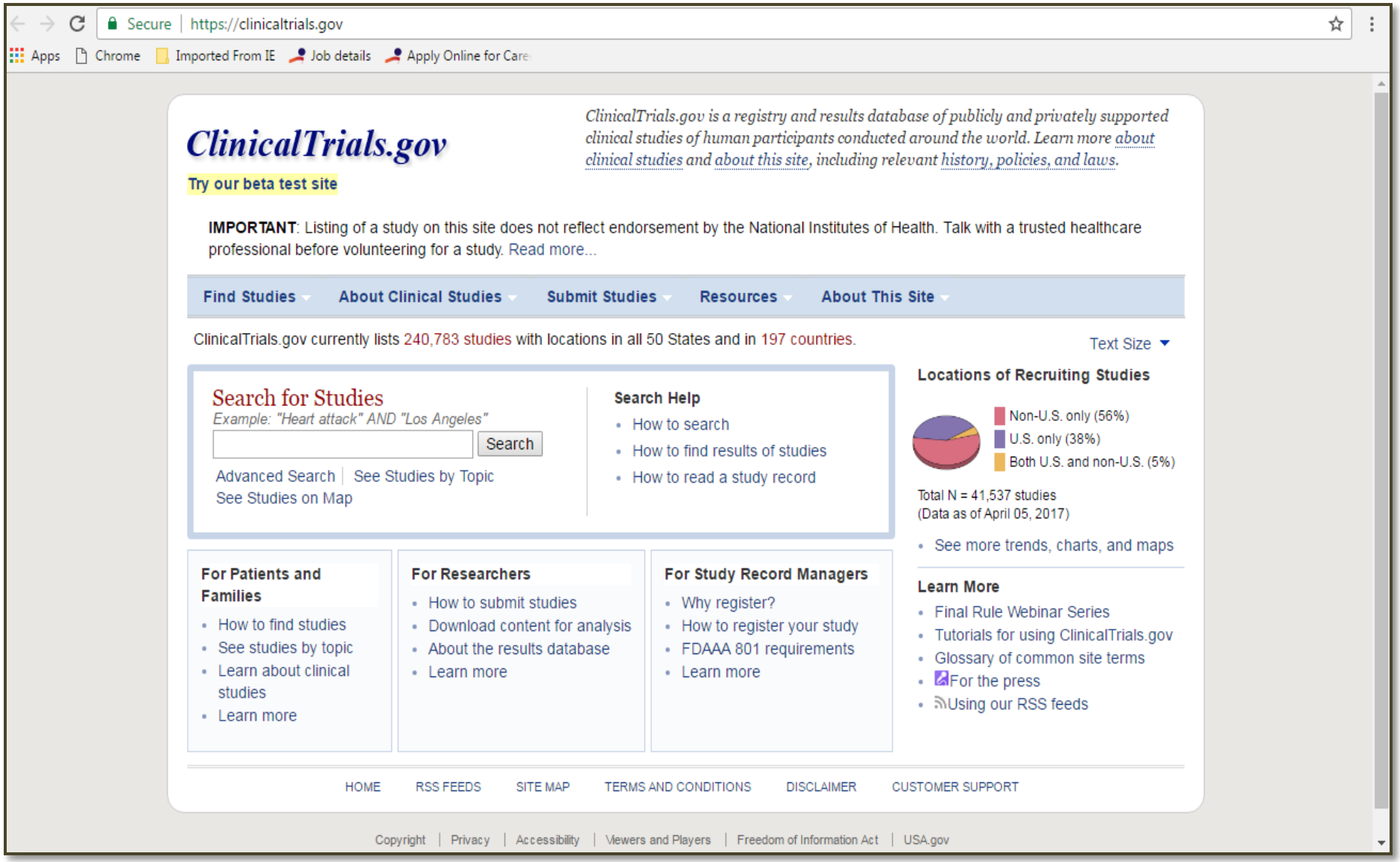
Introduction

- 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



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

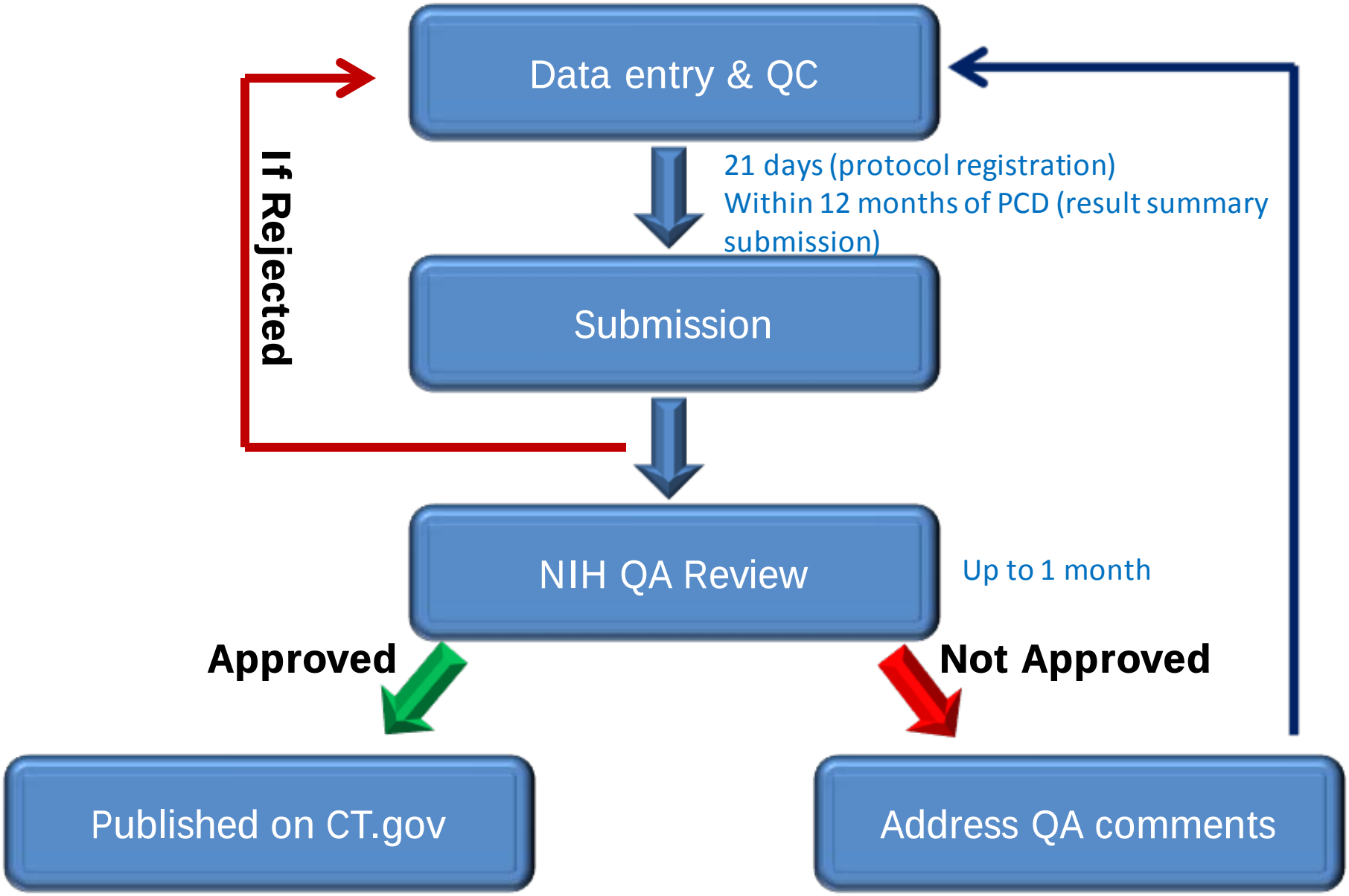
Final rule – Scope and Timelines

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

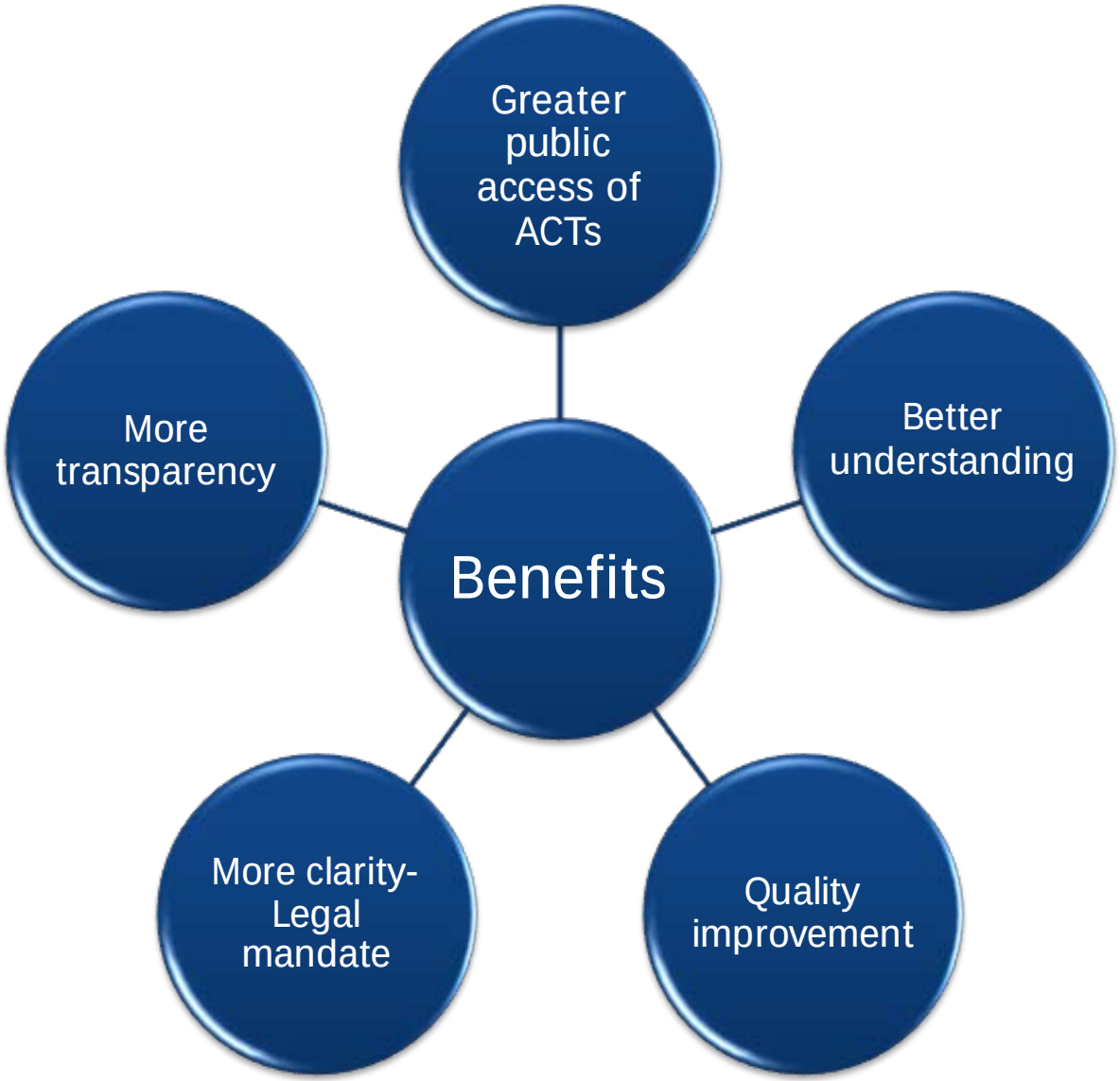
*Results information submission could be delayed for up to 2 additional years from the date of submission of a certification that either an unapproved, unlicensed, or uncleared product studied in the trial is still under development by the manufacturer or that approval will be sought within 1 year after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

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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 s
  - ✓sponsored by a m
    medicinal product
    population includi
  - ✓which forms a par
    those where the i

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.

the use of a
n in the pediatric
(PIP) including

- 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).

Ref: http://www.ema.europa.eu/ema/

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)

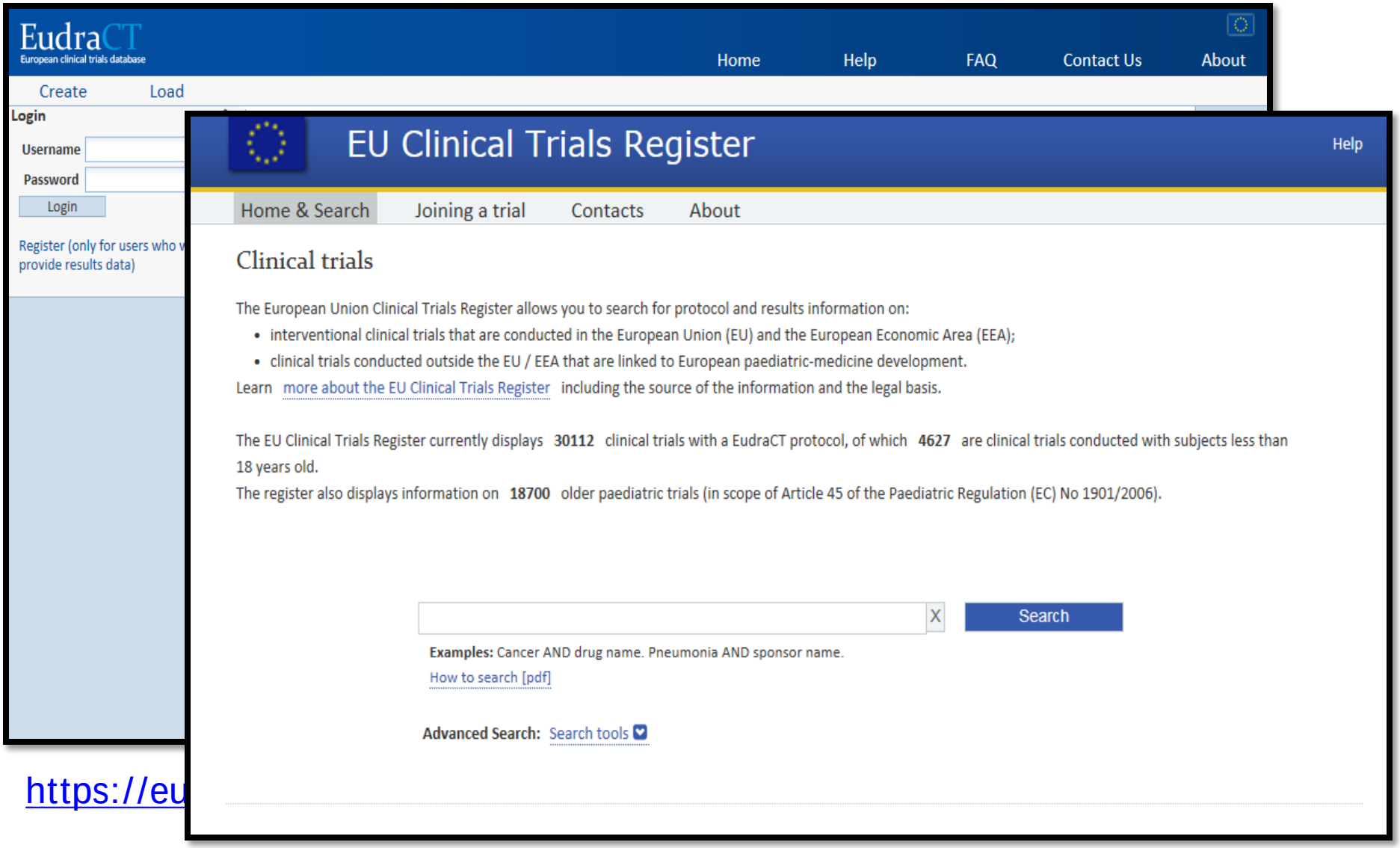
Result summaries to be disclosed :

- 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



https://eu

https://www.clinicaltrialsregister.euctr-search/search

EU linked timelines

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

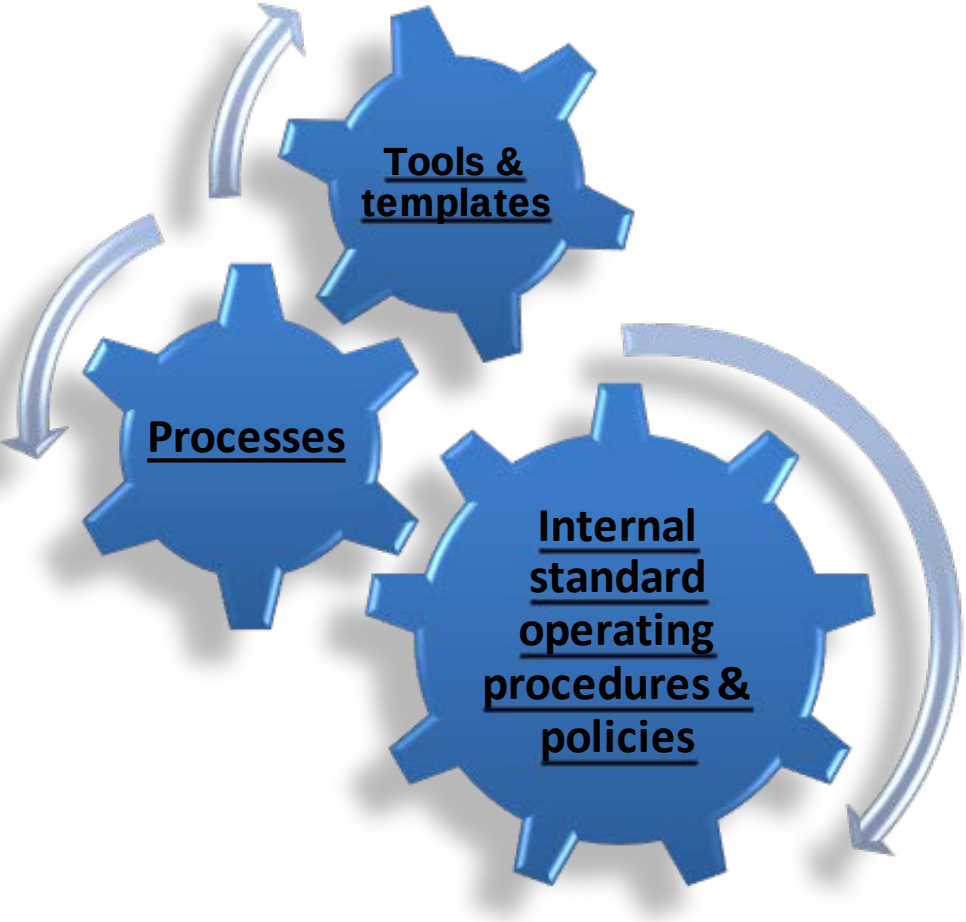
EMA Plain Language Summary
Plain Language Summaries will have to be posted on EU portal within 12 months of end of trial

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