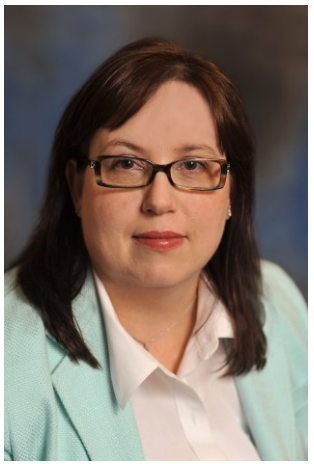
TrialScope®

# The Final Rule

## Challenges & Best Practices



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# Agenda

What is the Final Rule & Why is it Important?

Registrations Under the Final Rule

Results Under the Final Rule

QC Comments

Trial Data Updates

# What is the Final Rule

# What is the Final Rule

## In September 2016, the United States Department of Health and Human Services (HHS) issued 42 CFR Part 11 for Clinical Trials Registration and Results Information Submission, commonly known as the "Final Rule"

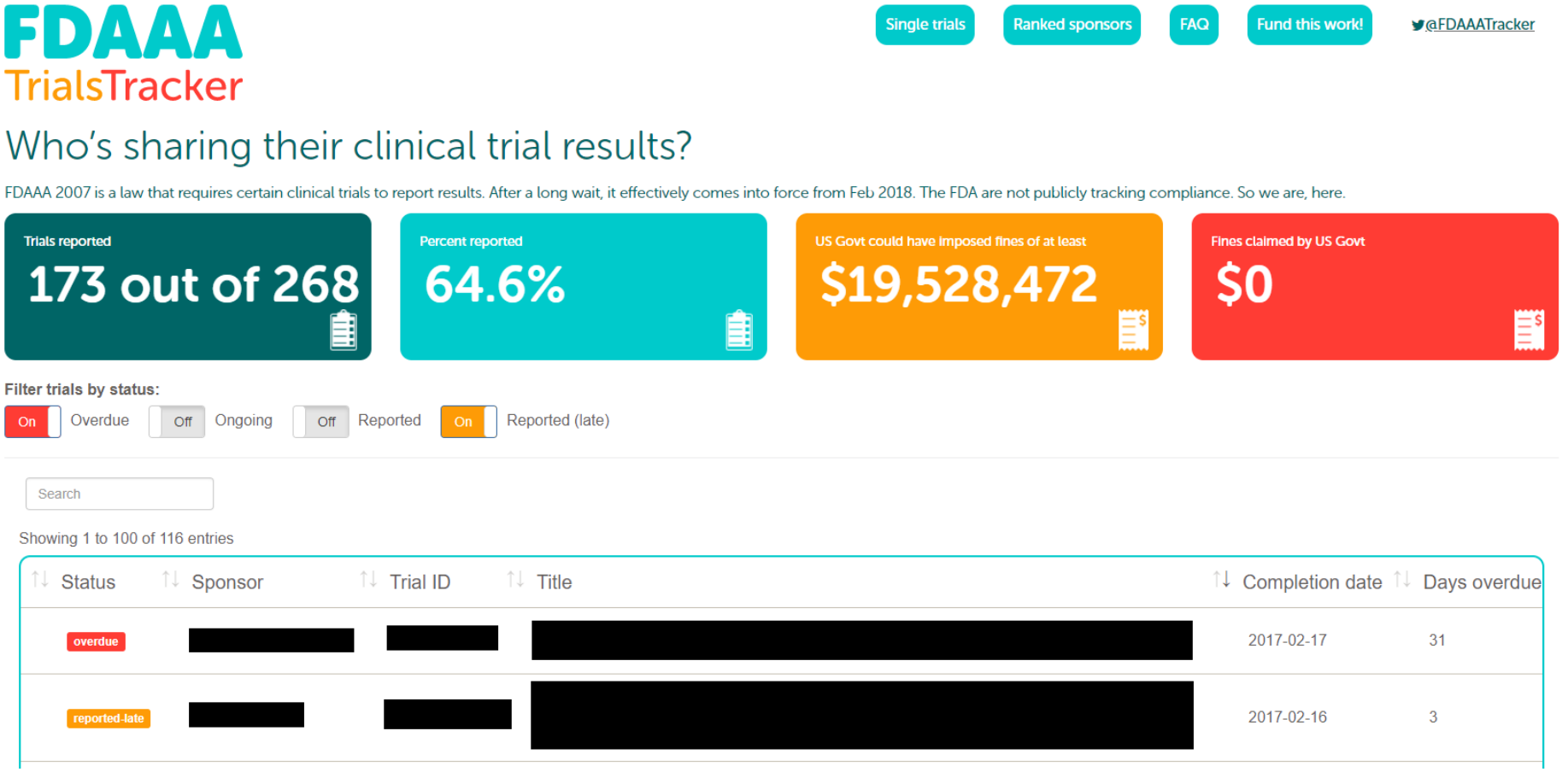
Required update to Title VIII of the Food and Drug Administration Amendments Act (FDAAA) of 2007

Clarifies and completes requirements for registering clinical trials and disclosing clinical trial results

Applicable Clinical Trials (ACTs) that start on or after January 18, 2017 or with a Primary Completion Date on or after January 18, 2017 are subject to the Final Rule requirements

## As of January 18, 2018, all provisions of the Final Rule are in full effect

# Transparency Advocates Are Watching




Source: http:// FDAAA.trialstracker.net

# Key Changes in the Final Rule

# Defining an ACT

| Drug Trials | Device Trials | FDAAA (pre-Final Rule) |
|---|---|---|
| **Study Type:** Interventional | | |
| **Study Phase:** not Phase I or Early Phase I | **Primary Purpose:** not Device Feasibility | **Study Phase:** not Phase I or Early Phase I |
| | | **Intervention Type:** Drug, Device, Biological/Vaccine, Radiation, Genetic, Combination Product, or Diagnostic Test |
| *Any of the following apply:*<br>• **Facility Location(s):** At least 1 U.S. location or locations not specified, or<br>• **U.S. FDA IND or IDE:** Yes, or<br>• **Product Manufactured in and Exported from the U.S.:** Yes | | *Any of the following apply:*<br>• **Facility Location(s):** At least 1 U.S. location or locations not specified, or<br>• **U.S. FDA IND or IDE:** Yes |
| **Study Start Date:** On or after January 18, 2017 | | **Study Start Date:** Before January 18, 2017 |
| **Primary Completion Date:** On or after January 18, 2017 | | **Primary Completion Date:** On or after January 2008 or not specified, or<br>**Study Completion Date:** On or after January 2008, if Primary Completion Date not specified |
| **Overall Recruitment Status:** Not Withdrawn | | |




Source: PRS Users Guide

# Drug/Device Manufactured in US and Exported

## Need to know if any drug/device studied was manufactured in the US and exported

Comparators, placebos, and shams are considered products that are ‘studied’

Relevant to any stage of the manufacturing process, including device components, active ingredients, labeling, packaging

### Challenges

- May be difficult to find out where internally acquired products are manufactured, much less externally acquired

### Best Practice

- Eliminate the easy answers first; if the study has a US location or is conducted under IND/IDE, not necessary to determine manufacturing location
- Establish formal communications with groups that source products
- When in doubt, say YES

# Post Registration Data For Unapproved Devices

New options to post these studies prior to approval/clearance that was not possible to under the statute

## Challenges

- Balancing transparency trends with patent/intellectual property concerns

## Best Practices

- Include position on unapproved device trials in **Transparency Policy** and related processes
- Establish a formal review process with legal teams about risks to intellectual property and patent protections

# Results Under the Final Rule

# Scope of Results Disclosure

## Results are required for all ACTs, regardless of approval status

The Final Rule expands result disclosure to include unapproved products and indications

Results are due within 12 months of Primary Completion Date unless a delay is requested

### Challenges

- Notification of approval status
- Communication/buy-in of new requirements

### Best Practice

- Include position on unapproved products in **Transparency Policy** and related processes
- Keep it simple – complex decision trees are confusing and may not be consistently followed

# Formal Request to Delay Results for an ACT

## Must be submitted **before** results are due (i.e. PCD + 12 months)

New (initial) product or new indication approval, results are due the earlier of

- 30 days after FDA approval or FDA issues letter ending regulatory review cycle without approval
- 210 days after marketing application is withdrawn without resubmission
- 2 years after submission of delay request

Extension (i.e. good cause extension) is due on the date submitted

## Challenges

- Notification of approval status
- Manage results timeliness with regards to certification expirations, extension dates, and marketing application status, FDA letters & approvals

## Best Practice

- Include position delay requests in **Transparency Policy** and related processes
- Establish formal process to share information about marketing application status, FDA communications and approvals

# Statistical Analyses

## Statistical analyses are required

**Pre-specified** in the protocol /stat plan and was performed

**Made public** by responsible party prior to disclosure of the primary outcome measures(s)

**Requested by FDA** prior to disclosure of the primary outcome measure(s)

## Challenges

- Statistical analyses no longer optional
- Notification when analyses are made public prior to disclosure
- Notification on FDA requests for additional analyses prior to disclosure

## Best Practice

- Close communication with study teams, publication, and regulatory groups
- Establish formal process for making results public prior to disclosure
- Establish formal process to share information on FDA communications

# Protocol & Stat Plan

## Protocol & statistical analysis plan must be submitted and will be published on ClinicalTrials.gov

Include amendments requiring IRB/EC approval

May be redacted

### Challenges

- Alignment with EMA Policy 70 redactions
- OPEN QUESTIONS WITH NIH
  - If appendices are required

### Best Practice

- Comprehensive process on timing and redactions of protocols to include EU and US requirements
- Use the ICH E3 Clinical Study Report to provide the protocol and statistical analysis plan data for both US and EU

# Voluntary Disclosure & Trigger Trials

## Voluntary disclosure may trigger additional disclosures

- Interventional clinical trial disclosed on ClinicalTrials.gov
- Included on a marketing application (MA) to the FDA on or after September 27, 2007
- Studies same indication as the MA
- Responsible party of trial is also manufacturer submitting the MA

## All ACTs on MA must be disclosed at same level as voluntary

### Challenges

- Notification of all trials on MA
- Determining if any voluntary disclosures trigger additional disclosures
- Determining which additional ACTs must be disclosed

### Best Practice

- Include position on voluntary disclosure in Transparency Policy and related processes
- Keep it simple – complex decision trees are confusing and may not be consistently followed

# Secondary OM & Additional AEs

## Data not collected for secondary outcome measures or adverse events by Primary Completion Date must be submitted by the earlier of

One year after data for that secondary outcome or adverse event is collected

If delay requested, then the date that primary outcome measure data is due

### Challenges

- Tracking dates of data collection completion for each secondary outcome measure or adverse events
- Not generally captured in source system feeding disclosure (e.g. CTMS)
- Interim amendments to protocol must be submitted

### Best Practice

- Align milestone dates for collecting secondary outcome and adverse events data if possible
- Update CTMS to capture new milestone dates
- Close communication with study teams

# Trial Data Updates

# Trial Updates

## Updates required at least once per year

More frequent updates:

- 1 data element within 15 days of change
- 13 data elements within 30 days of change
- Global protocol amendments within 30 days of IRB/EC approval
- When results are submitted

**Both ACTs and voluntary submissions** need to be updated

**Obligation ends** when all required information has been submitted and corrections have been made or addressed

Some data elements may need to be **updated after trial ends**

# Trial Updates:  Responsible Party

Requires update within **30 days** of change in responsible party, including a change to the official title of the responsible party or the contact information of the responsible party.

## Challenges

- Timely notification of responsible party changes
- Disclosure may not be centralized or notification of PI changes not normalized

## Best Practice

- Establish central group to oversee disclosure compliance
- Create/include disclosure on checklists:
  - On- and off-boarding PIs and other key personnel on projects
  - Acquire/divest products or businesses

# Trial Updates:  Product Changes

## Device Approval or Clearance Status

Approval or clearance requires update within 15 days of status change

## Intervention Name

Requires update within 30 days of proprietary name being established

## Challenges

- Timely notification of product changes
- Not generally captured in source system feeding disclosure (e.g. CTMS)
- Informal notification is the norm

## Best Practice

- Establish formal process to get information about product naming and approval/clearance status and dates

# Trial Updates:  Expanded Access

Expanded access record requires creation/update within 30 days of expanded access availability

ACT requires update within 30 days of the NCT ID assignment for the expanded access record

## Challenges

- Timely notification of expanded access program availability and/or NCT ID assignment
- No formal responsibility for registering expanded access programs

## Best Practice

- Establish formal process to get information about expanded access programs
- Establish formal responsibility and guidelines for registering and maintaining expanded access records

# QC Comments

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## Major comments must be addressed within:

15 days for protocol registration

25 days for results information

## Challenges

- Timely action on major QC comments
- Performance is on display

## Best Practice

- Communicate importance of timely update/review/approvals
- Establish formal process to manage QC comments

# QC Comments

## New submission dates now published on ClinicalTrials.gov

NIH U.S. National Library of Medicine

ClinicalTrials.gov

**Key Record Dates**

| | |
|---|---|
| **ClinicalTrials.gov Identifier:** | NCT01287013 |
| **Brief Title:** | Comparing Xperguide vs. Conventional Methods During Percutaneous Image Guided Procedures |
| **First Submitted** : | January 25, 2011 |
| **First Submitted that Met QC Criteria** : | January 31, 2011 |
| **First Posted** : | February 1, 2011 (Estimate) |
| **Results First Submitted** : | August 4, 2016 |
| **Results First Submitted that Met QC Criteria** : | December 4, 2017 |
| **Results First Posted** : | January 5, 2018 (Estimate) |
| **Last Update Submitted** : | December 4, 2017 |
| **Last Update Submitted that Met QC Criteria** : | December 4, 2017 |
| **Last Update Posted** : | January 5, 2018 (Estimate) |

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# In Summary

## Final Rule may impact many areas of an organization

## Transparency advocates are watching and waiting for the FDA to start levying fines for non-compliance

## Challenges around timely and correct data

## Best practices include

Robust Transparency Policy that is shared internally and externally

Formalized processes to gather data

Better and/or formalized communication between stakeholders

Dedicated oversight of disclosure compliance

Simplify decisions and lean towards more generous disclosure to align with transparency trends and ethical expectations

# Next Steps

## Consider

Conduct a formal review of policies, SOPs, guidelines, or other documents that are relevant to disclosure to confirm they support and ensure compliance

- Verify that relevant stakeholders are included in documents
- Identify source systems and how data is shared
- Confirm that disclosure is appropriately addressed in policies, procedures, and processes

Create a transparency oversight board

Conduct disclosure training for relevant stakeholders

Perform internal audit for Final Rule readiness

# Thank you!

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