kinapse

Clinical Trial Transparency

14 March 2015

Pooja Phogat
Global Head and Vice-President, Clinical Trial Disclosure, Kinapse

Learning Objective

By end of today's session you will know about:

- What is Clinical Trial Disclosure
- Global clinical trial disclosure landscape
- Insights about upcoming regulatory framework in terms of trial transparency and responsible data sharing

Agenda

- Why Clinical Trial Disclosure
- Brief history of Clinical Trial Disclosure
- Overview of current global Clinical Trial Disclosure requirements
  - Clincaltrials.gov
  - EudraCT
- Latest and Upcoming Key Regulatory Reforms Worldwide
  - EFPIA/PhRMA “Principles for Responsible Clinical Trial Data Sharing”
  - TransCelerate Approach to Protection of Personal Data
  - EMA Policy on Publication of Clinical Data
  - NLM notice of proposed rule making
  - IOM "Committee on Strategies for Responsible Sharing of Clinical Trial Data"
- Key messages
- Questions

Why Clinical Trial Disclosure

kinapse

The intention of clinical trial disclosure is to:

- Inform patients/investigators of research programs
- Inform healthcare professionals about ongoing trials
- Reduce unnecessary duplication of research & accelerate knowledge creation
- Improve trial participation
- Publish in peer-reviewed journals
- Transparency and build mutual trust
- Fulfill legal, statutory and ethical obligations

Events: Lack of Transparency in Clinical Research (1/3)

BBC NEWS

Negative drug research 'withheld'

Drug companies have been accused of failing to publish drug trials which do not give the "right" result.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

- People have suffered and resources have been wasted because disappointing results of research have not been reported

Events: Lack of Transparency in Clinical Research (2/3)

Annals of Internal Medicine | ARTICLE

The ADVANTAGE Seeding Trial: A Review of Internal Documents

Kevin P. Hill, MD, MHS; Joseph S. Ross, MD, MHS; David S. Egilman, MD, MPH; and Harlan M. Krumholz, MD, SM

Conclusion: Documentary evidence shows that ADVANTAGE is an example of marketing framed as science. The documents indicate that ADVANTAGE was a seeding trial developed by Merck's marketing division to promote prescription of Vioxx (rofecoxib) when it became available on the market in 1999.

Merck and Co., Inc., and *McDarby v Merck and Co., Inc.* The documents were created between 1998 and 2006.

Data Extraction: An iterative case-study process of review, discussion, and re-review of documents to identify themes relevant to the design and conduct of ADVANTAGE. To supplement the case-study review, the authors did a systematic review of the literature to identify published manuscripts focused on seeding trials and their conduct.

may have limited generalizability.

Conclusion: Documentary evidence shows that ADVANTAGE is an example of marketing framed as science. The documents indicate that ADVANTAGE was a seeding trial developed by Merck's marketing division to promote prescription of Vioxx (rofecoxib) when it became available on the market in 1999.

Ann Intern Med. 2008;149:251-258. www.annals.org

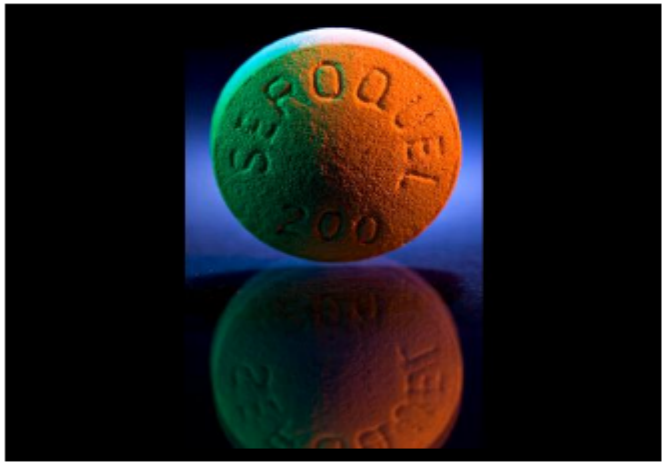
For author affiliations, see end of text.

Events: Lack of Transparency in Clinical Research (3/3)

AstraZeneca Seroquel Studies 'Buried,' Papers Show (Update3)

Email | Print | A A A

By Jef Feeley and Margaret Cronin Fisk

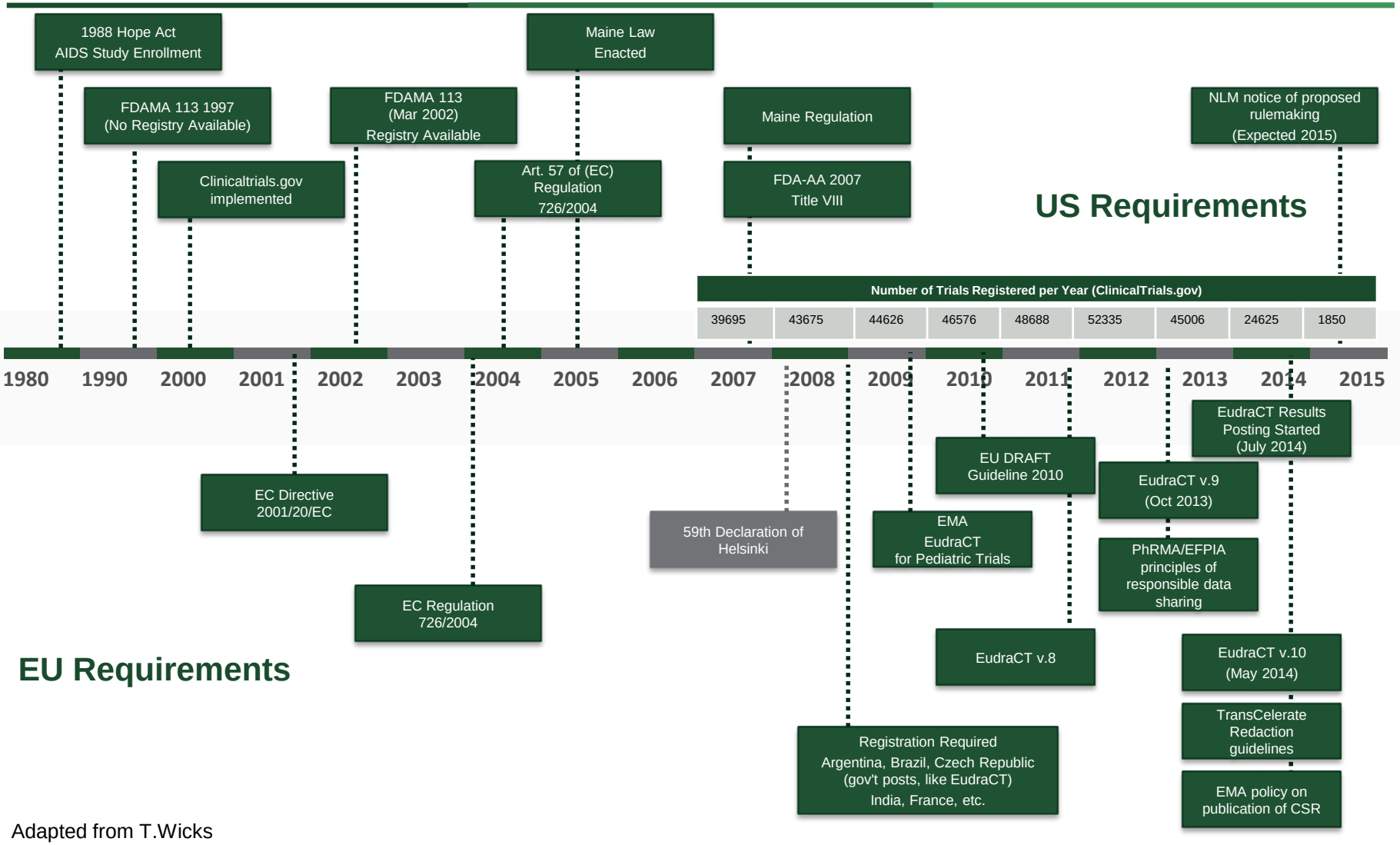


Feb. 27 (Bloomberg) -- **AstraZeneca Plc** "buried" unfavorable studies on its antipsychotic drug Seroquel, according to an internal e-mail unsealed as part of litigation over the medicine.

The drugmaker failed to publicize results of at least three clinical trials of Seroquel and engaged in "cherry picking" of data from one of those studies for use in a presentation, an AstraZeneca official said in a December 1999 e-mail unsealed yesterday under an agreement between the company and lawyers for patients. The London-based company faces about 9,000 **lawsuits** claiming it failed to properly warn users that Seroquel can cause diabetes and other health problems.

"The larger issue is how we face the outside world when they begin to criticize us for suppressing data," John Tumas, an AstraZeneca publications manager, told colleagues in the e-mail.

Brief history of Clinical Trial Disclosure



Adapted from T.Wicks

Global Clinical Trial Disclosure Landscape

kinapse

EU regulations
EUCTR, EudraCT

Submission of CTA + substantial amendment + end of trial notifications + clinical study report to national competent authorities (NCA)

Create and post results in **EudraCT Database**

Sponsor

US regulations
ClinicalTrials.gov

Registration of protocol on ClinicalTrials.gov

Regular updates of protocol posted on public website (every 6 or 12 months)

Submission of summary results on ClinicalTrials.gov

Clinical trial information available on public domain
https://clinicaltrials.gov/
https://www.clinicaltrialsregister.eu

ClinicalTrials.gov: Regulatory Bodies and Laws

Laws/Acts/Regulations

FDAMA* 113 (1997)

FDAAA Section 801 (2007)**

Maine State Law

ICMJE* statement (2004)**

- **FDAMA* 113 (1997):** mandates registration of Investigational New Drug (IND) application trials for serious and life-threatening diseases or conditions
- **Maine State Law, ICMJE*** Statement (2004):** Emphasized on increased transparency of clinical trials
- **FDAAA** Section 801 (2007):** Expands registry and adds results reporting requirements

*Food and Drug Administration Modernization Act of 1997
**Food and Drug Administration Amendments Act of 2007
***International Committee of Medical Journal Editors

What Needs to be Disclosed on ClinicalTrials.gov?

kinapse

Prior to Trial Initiation

- Register the trial at ClinicalTrials.gov
- *Before 1st participant is enrolled (ICMJE)
- Within 21 days of 1st participant enrolled (FDAAA 801)

While the Trial is Ongoing

- Updates to ClinicalTrials.gov
  Required at least once every
  12 months (FDAAA 801)
- Update/verify “active” trials once every 6 months (ClinicalTrials.gov)
  Consider any protocol amendments that impact registration
- Recruitment status and (Primary) completion date must be updated within 30 days of a change (FDAAA 801)

After the Trial Completes

- Submit summary results (FDAAA 801)
- **When to submit?**
  <1 year after (Primary) completion date (or <30 days of approval or clearance)
- What to submit?
  Scientific information: Participant flow, baseline characteristics, outcome measures, adverse events
  Administrative information

*http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

Regulatory Bodies and Laws

Regulatory Bodies

- European Medicine Agency
- Member States (NCA) of the EU

Laws/Acts/Regulations

- Commission Guideline 2012/C 302/03
- Directive 2001/20/EC
- Pediatric Regulation (EC) No 1901/2006 (Art 41,45,46)
- Regulation (EC) No 726/2004

EudraCT V10: In Scope and Out of scope Activities

In Scope Activities

- Interventional trials (Approved and unapproved products)
- Phase 1 to 4
- Trials completed on or after 01 May 2004
- ICH E3 synopsis posting
  - Pediatric trials Art. 45 if not already submitted to EMA
  - Non-pediatric trials completed between 01 May 2004 to 20 Jul 2013 with at least one site in EU/ EEA
- Full dataset posting
  - All Pediatric trials acc. 2001/20/EC, Art 41 and Art 46 and Non -pediatric trials acc to 2001/20/EC completed on or after 21 Jul 2014
  - All pediatric trials, Art 41 and Art 46 completed before 21 Jul 2014

Out of Scope Activities

- Non-interventional studies (NIS)
- Investigator sponsored trials (ISTs)
- Trials completed before 01 May 2004
- Non-pediatric trials outside EU/ EEA

International Databases and National Registries

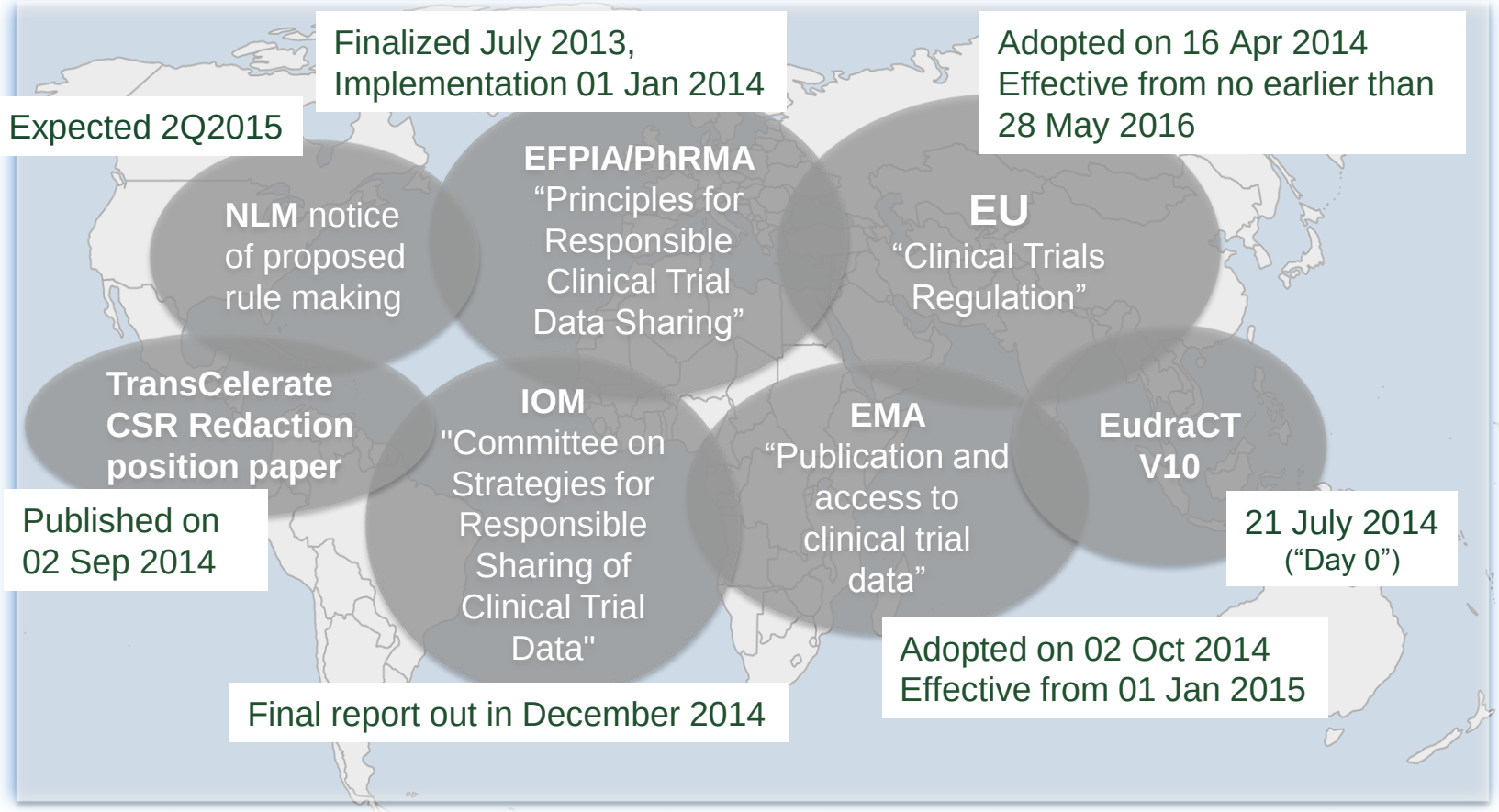
International registries

Country/Region	Regulatory Body	Clinical Trial Disclosure Database
US	National Institute of Health (NIH) Food and Drug Administration (FDA)	Clinicaltrials.gov, http://www.clinicaltrials.gov
European Economic Area (EEA)	European Medical Agency (EMA) European Clinical Trial Database (EudraCT)	EudraCT, https://www.clinicaltrialsregister.eu

National registries

Country/Region	Regulatory Body	Clinical Trial Disclosure Database
India	Drugs Controller General of India (DCGI)	Clinical Trial Register of India http://www.ctri.in/
Germany	Federal Ministry of Education and Research (BMBF) University Medical Centre Freiburg: German Clinical Trials Register (DRKS)	University Medical Centre Freiburg: German Clinical Trials Register (DRKS) http://www.germanctr.de
China	Center for Drug Evaluation (CDE) Chinese Clinical Trial Register (ChiCTR)	Chinese Clinical Trial Register (ChiCTR) http://www.cde.org.cn/news.do?method=changePage&pageName=serviceLcsy&frameStr=126
Japan	Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Database	Clinical Trials Information /JapicCTI http://www.clinicaltrials.jp/user/cte_main.jsp

Latest and Upcoming Key Regulatory Reforms Worldwide



kinapse

EFPIA/PhRMA “Principles for Responsible Clinical Trial Data Sharing”

EFPIA/PhRMA Principles - Effective January 2014

1 Enhancing Data Sharing with Researchers

"Commit to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the US and the EU as necessary for conducting legitimate research."

2 Enhancing Public Access to Clinical Study Information

"Make publicly available, at a minimum, the synopses of clinical study reports (CSRs) for clinical trials in patients submitted to the Food and Drug Administration (FDA), European Medicines Agency (EMA), or national competent authorities of EU Member States."

3 Sharing Results with Patients Who Participate in Trials

"Work with regulators to adopt mechanisms for providing a factual summary of clinical trial results and make the summaries available to research participants."

4 Certifying Procedures for Sharing Trial Information

"Certify on a publicly available web site that they have established policies and procedures to implement these data sharing commitments."

5 Reaffirming Commitments to Publish Trial Results

""At a minimum, results from all Phase 3 clinical trials and any clinical trial results of significant medical importance should be submitted for publication."

Pharmaceutical Research and Manufacturers of America (PhRMA), founded in 1958, is a trade group representing the pharmaceutical research and biopharmaceutical companies in the United States.

Its mission is to conduct effective advocacy for public policies that encourage discovery of important new medicines for patients by pharmaceutical and biotechnology research companies.

The **European Federation of Pharmaceutical Industries and Associations** (**EFPIA**) is a Brussel based trade association founded in 1978 representing the research-based pharmaceutical industry operating in Europe.

Its mission is to promote pharmaceutical research & development and the best conditions in Europe for companies to bring to patients new medicines that improve human health and the quality of life around the world.

kinapse

EMA Policy on Publication of Clinical Data

EMA Policy 70 - Publication and Access to Clinical Trial Data (1/3)

- Allows external parties (researchers or lay public) access to CT data held by the Agency
- EMA policy finalized and applicable as per Jan 2015
- Mandates the publication of CSRs
  - Prospectively – includes clinical trial data submitted after policy comes into effect
  - Retrospectively – CSRs will be made available upon request

*Publication and Access to Clinical Trial Data

EMA Policy 70 - Publication and Access to Clinical Trial Data (2/3)

Categories content of Clinical Trial Dossier into 3 groups:

- Open Access – will be proactively disclosed
  - Most of the clinical dossier – Clinical Overview, Clinical Summaries and Clinical Study Reports (CSRs)

- Closed Access – will be publicly available through a controlled access process
  - Patient level data in CSR line listings, Case Report Forms (CRFs)

- Commercial Confidential Information (CCI) – will not be disclosed through this process (may still be sought under traditional 'reactive' process)
  - Summary of Biopharm studies
  - Biopharm and PK CSRs

EMA Policy 70 Draft – Redaction Policy (3/3)

- Redaction of publicly disclosed documents allowed only for removal of Patient Privacy Information

- For Investigators and Study Personnel
  - Section contains personal data, such as list of investigators; individual investigators' names, addresses, appointments, qualifications and clinical duties
  - In light of the overriding public interest, these personnel are considered exempt from Protection of Personal Data (PPD) considerations

- No redaction of publicly disclosed documents for CCI in EMA Draft Policy

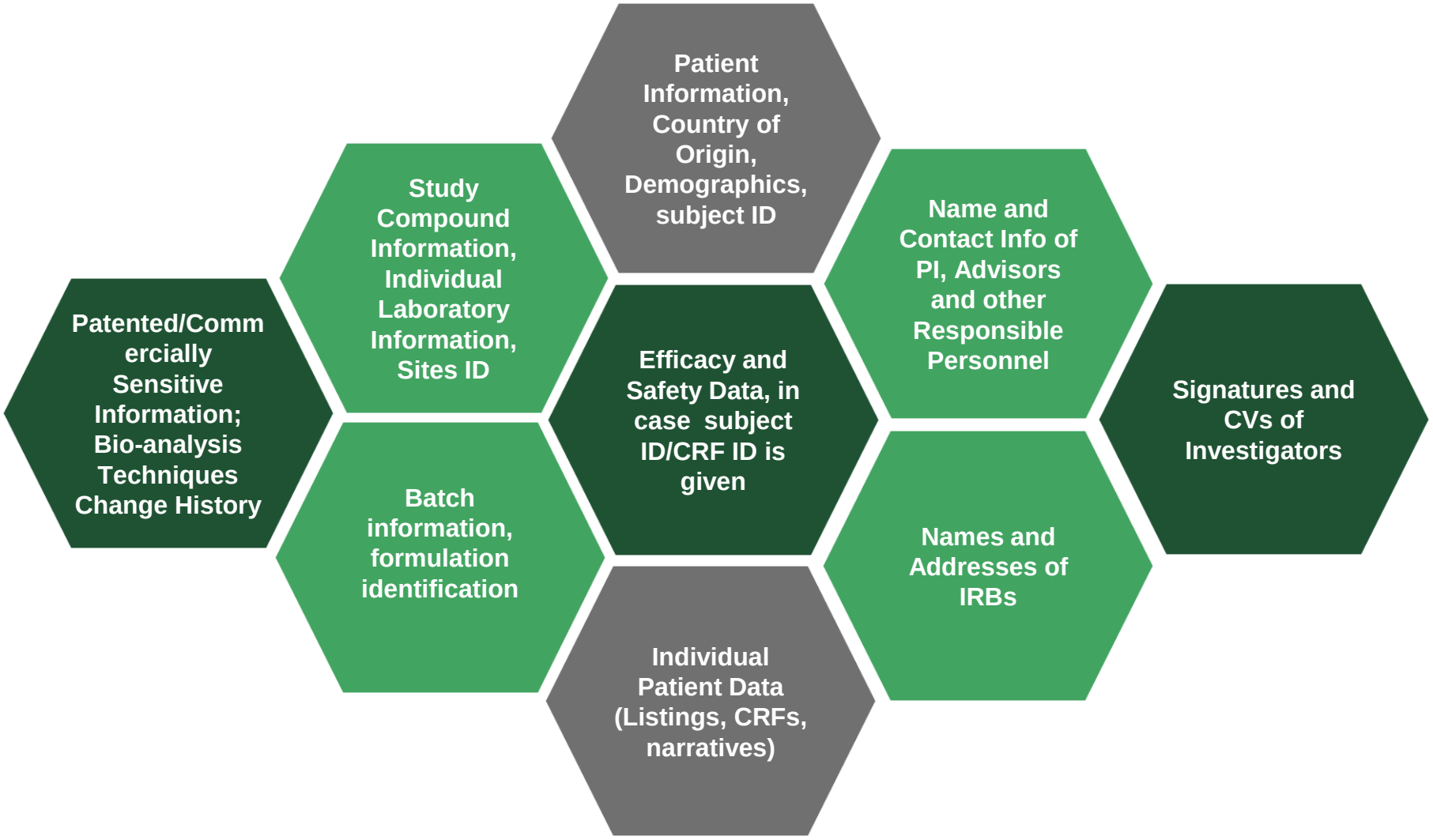
kinapse

TransCelerate Approach to Protection of Personal Data

Background

- TransCelerate BioPharma Inc., a non-profit organization of biopharmaceutical companies
- Focused on advancing innovation in R&D, identifying and solving common R&D challenges, thus increasing the quality of clinical studies
- Committed to enhancing public health, medical and scientific knowledge through sharing and transparency of clinical trial information

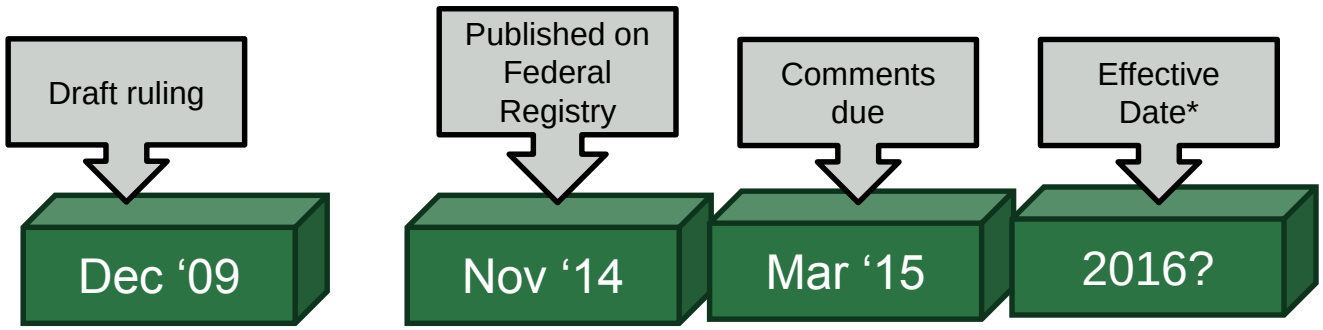
What to redact in the CSRs?



kinapse

NLM notice of proposed rule making

Notice of Proposed Rulemaking (NPRM)



* being challenged ”45 days after published in the Federal Register”

What to expect from the ruling:

- Results for **“unapproved products”** includes drug, biologics and devices
- “Lay” and non-technical **summaries**
- Copy of “full” **protocol** when results are submitted
- “Such **other categories** as the Secretary determines appropriate”
- **Increasing the timeline** for submitting results from 12 to 18 months after the earlier of the estimated completion date of the trial or the actual date of completion

kinapse

IOM "Committee on Strategies for Responsible Sharing of Clinical Trial Data"

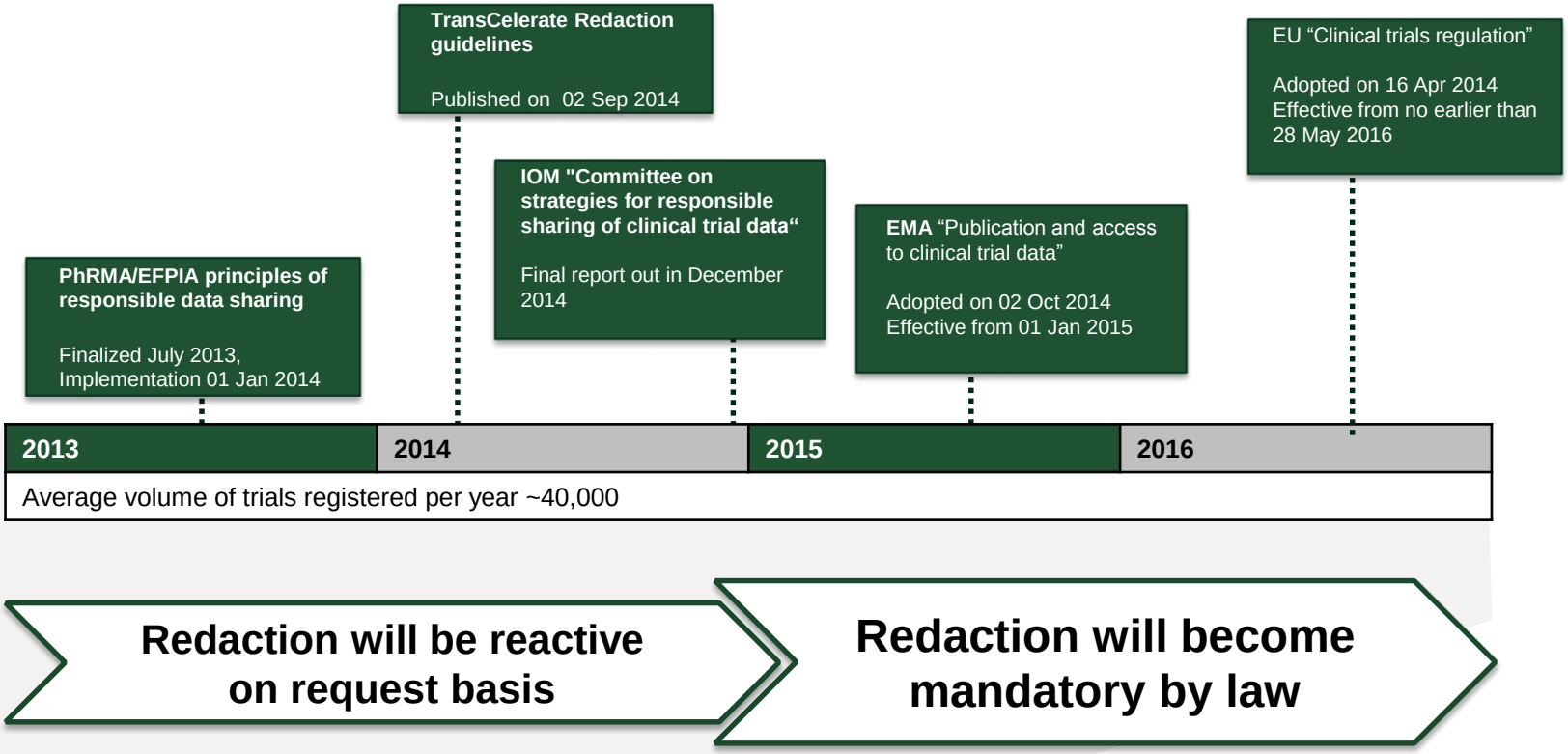
IOM Sharing Clinical Trial Data Report – Jan 2015

Intent: to balance the interests of different stakeholders with the public interest of having the best information possible regarding the effectiveness and safety of therapies

The report lays out specific plans for sharing data

- Granting access through third-party web sites
- Adopting recommended timetables for releasing both summary and complete data packages
- Summary level results (including AEs), should be publicly available within 1 year after trial completion
- A complete data package (i.e. full protocol and statistical analysis plan) should be shared within 18 months after trial completion

Based on upcoming regulation, Redaction is key to disclosure, between 2013 – 2016



Key messages

- Disclosure a significant step towards more transparent pharmaceutical world
- Disclosure is essential for human subjects protection, research integrity, evidence based medicine and legal obligation
- As more organizations and governments shape the bars for which transparency looks like, it is imperative to keep up with current thinking
- In order to match up with the current and upcoming regulatory requirements in EU and US, companies need to make sure that they have sufficient and appropriate resources in order to be par with their competitors as well as country regulations
- **'Good Disclosure Practices'** are as important as **'Good Clinical Practice'** 

kinapse

Thank you…

Questions

kinapse

Contact Details

Pooja Phogat
Head of CTD
+91 981 088 9208, pooja.phogat@kinapse.com

Web site: www.kinapse.com
General enquiries: info@kinapse.com

kinapse

Back-up slides

Clinical Trial Data and Transparency

- Introduction of new legislation & regulations and the evolution of clinical trial disclosure and data transparency in the pharmaceutical industry
- Guidelines regarding clinical trial disclosure exists in >40 countries globally
- Augmented regulatory requirements in regions like US, EU and EEA in last 5 years

Regions/Countries Mandating Clinical Trial Disclosure