Disclosure Writing

Module 11 Topic 7

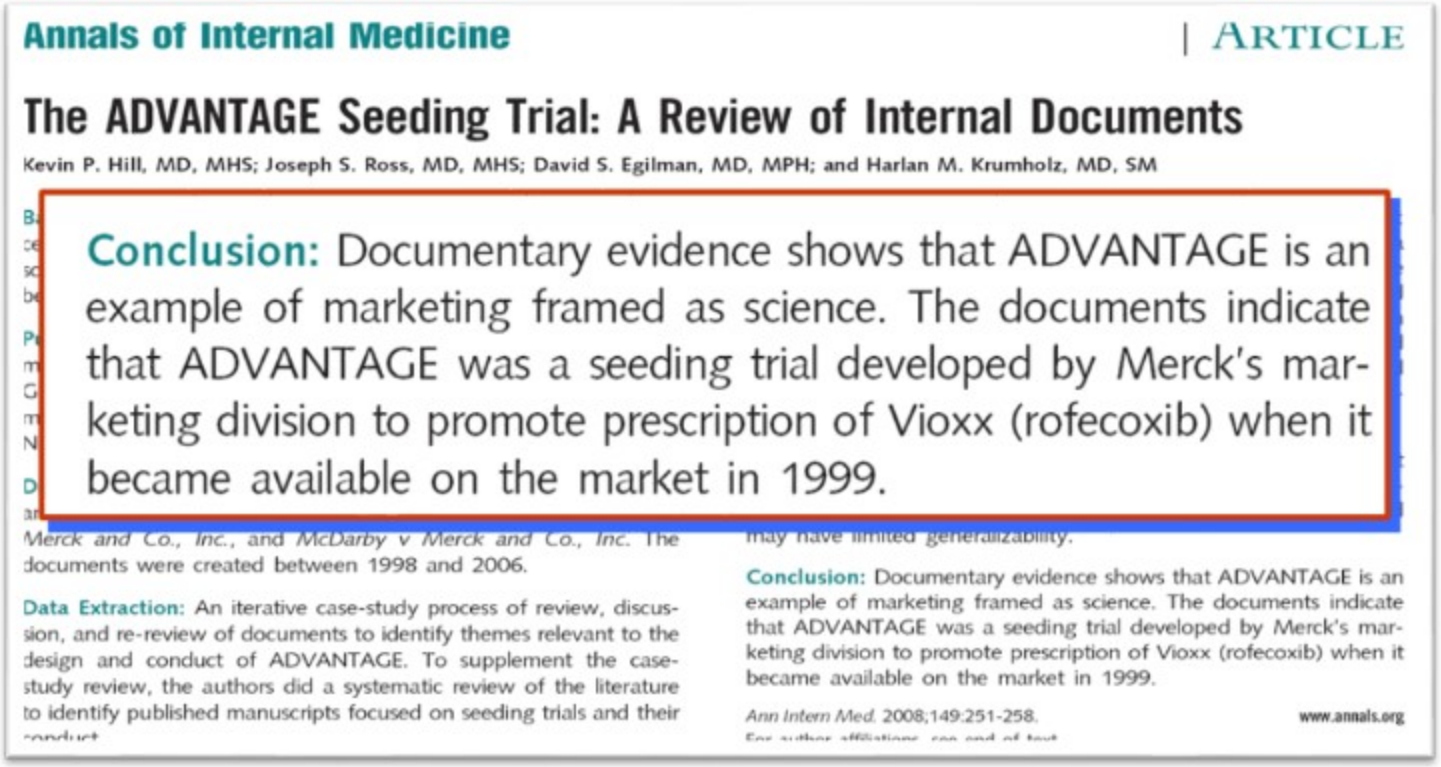
- Why Clinical Trial Disclosure
- Brief history of Clinical Trial Disclosure
- Overview of current global Clinical Trial Disclosure requirements
  - Clincaltrials.gov
  - EudraCT
- Latest and Upcoming Key Regulatory Reforms Worldwide
  - EFPIA/PhRMA "Principles for Responsible Clinical Trial Data Sharing"
  - EMA Policy on Publication of Clinical Data

Why Clinical Trial Disclosure?

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



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

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

Events: Lack of Transparency in Clinical Research (contd)

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.

Where to disclose?

- 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
- Peer reviewed Journals
- SHARE initiative (Clinicalstudydatarequest.com)

International Databases and National Registries

International registries

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

International Databases and National Registries

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&pag eName=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

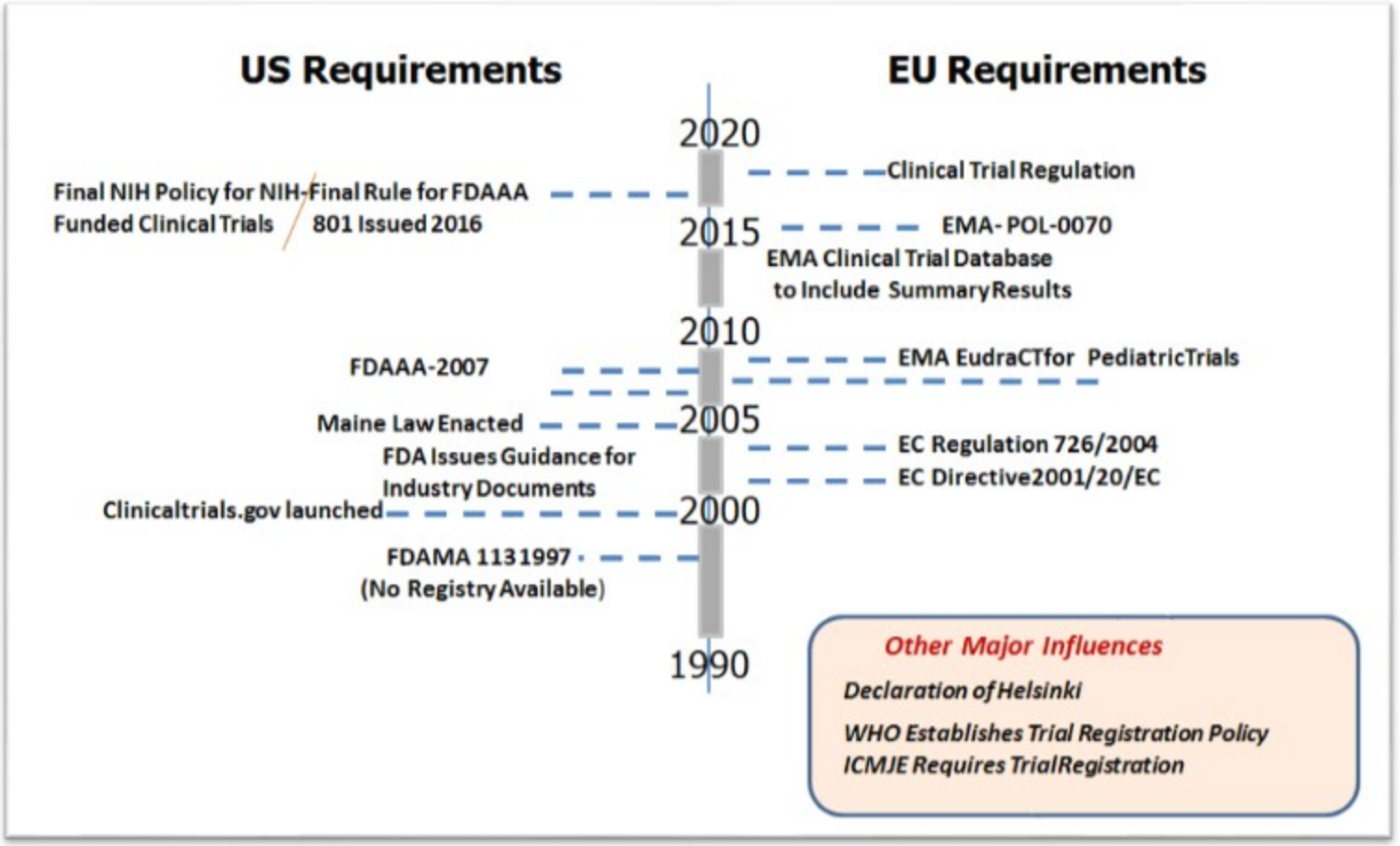
Importance of disclosure on public registry

- For those with medical conditions…
  - Finding a trial in which to participate
  - Finding an expanded access drug
  - Finding a center of research for a given condition/intervention
- For those concerned with human subjects protections…
  - Complete list of ongoing and completed trials of relevance
  - Assurance that information about the trial of interest
    - is in the public domain
    - results will become public

Importance of disclosure on public registry

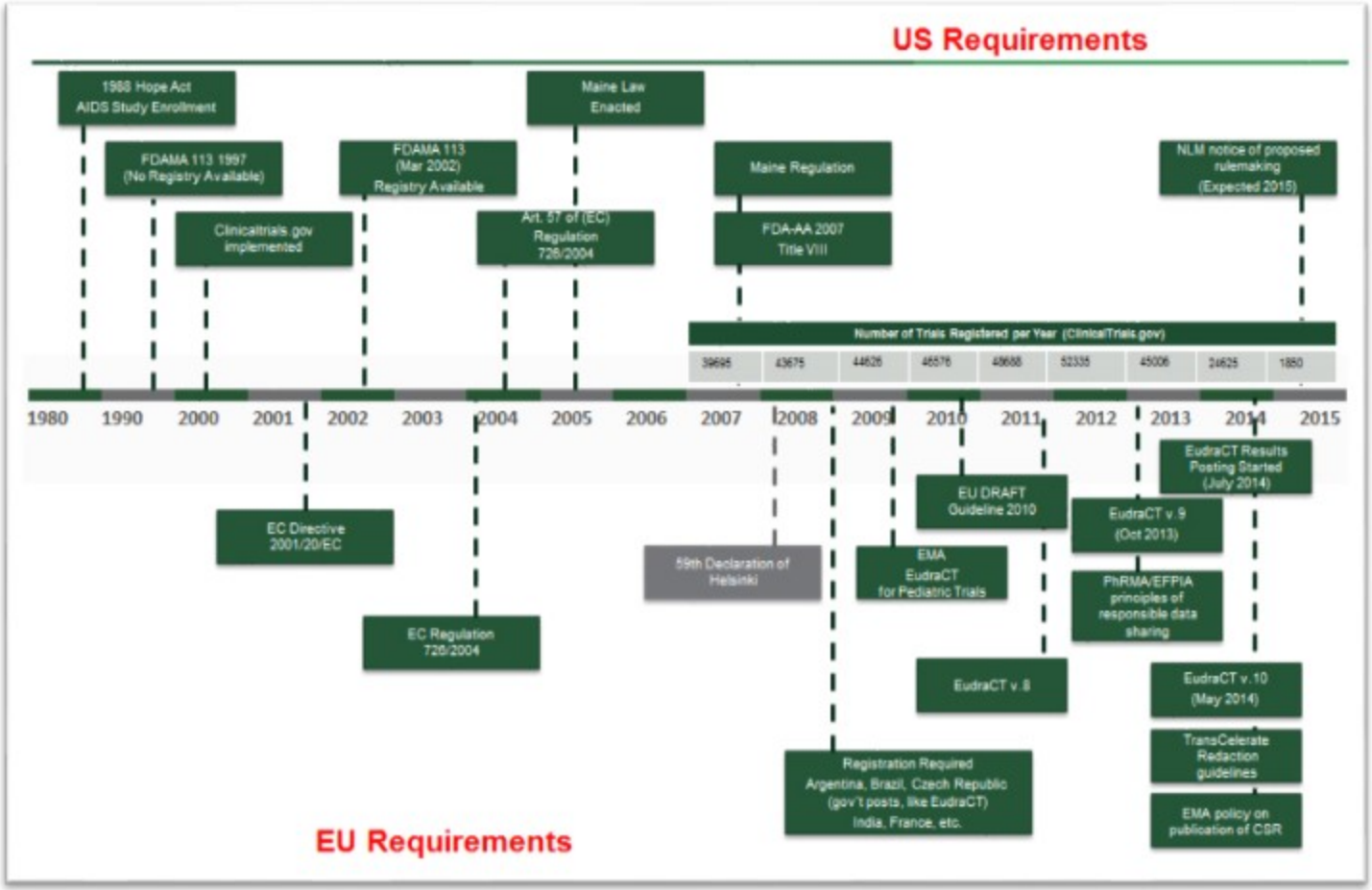
- For those concerned with research integrity…
  - Relatively complete list of trials
  - Description of protocol
  - Tracking of changes to protocols
  - Identifying all outcome measures
  - Providing results, regardless of journal publication status
- For those seeking study results…
  - Linkages to PubMed
  - Summary Results in database
  - Results for all pre-specified outcome measures
  - Standardized format facilitating comparisons

Brief history of Clinical Trial Disclosure (Major milestones)



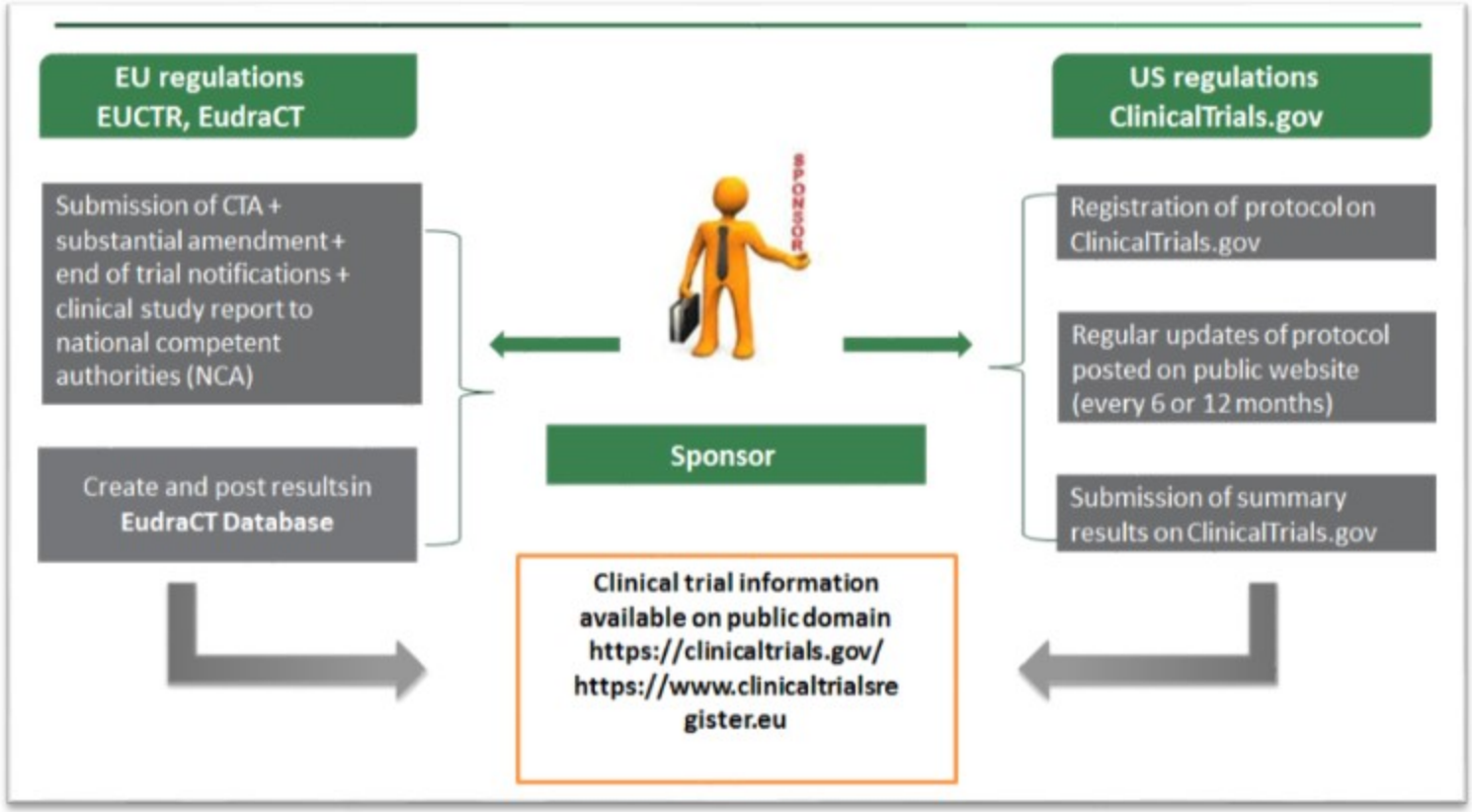
Ref: https://clinicaltrials.gov/ct2/about-site/history
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp

Brief history of Clinical Trial Disclosure (Detailed view)



Adapted from T.Wicks

Global Clinical Trial Disclosure Landscape



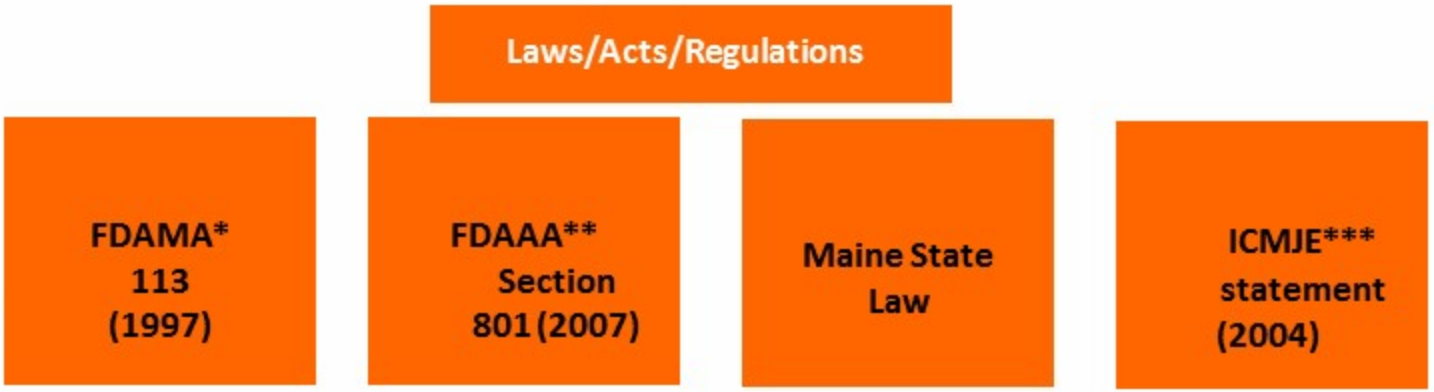
Clinicaltrials.gov (US Registry)

- 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/

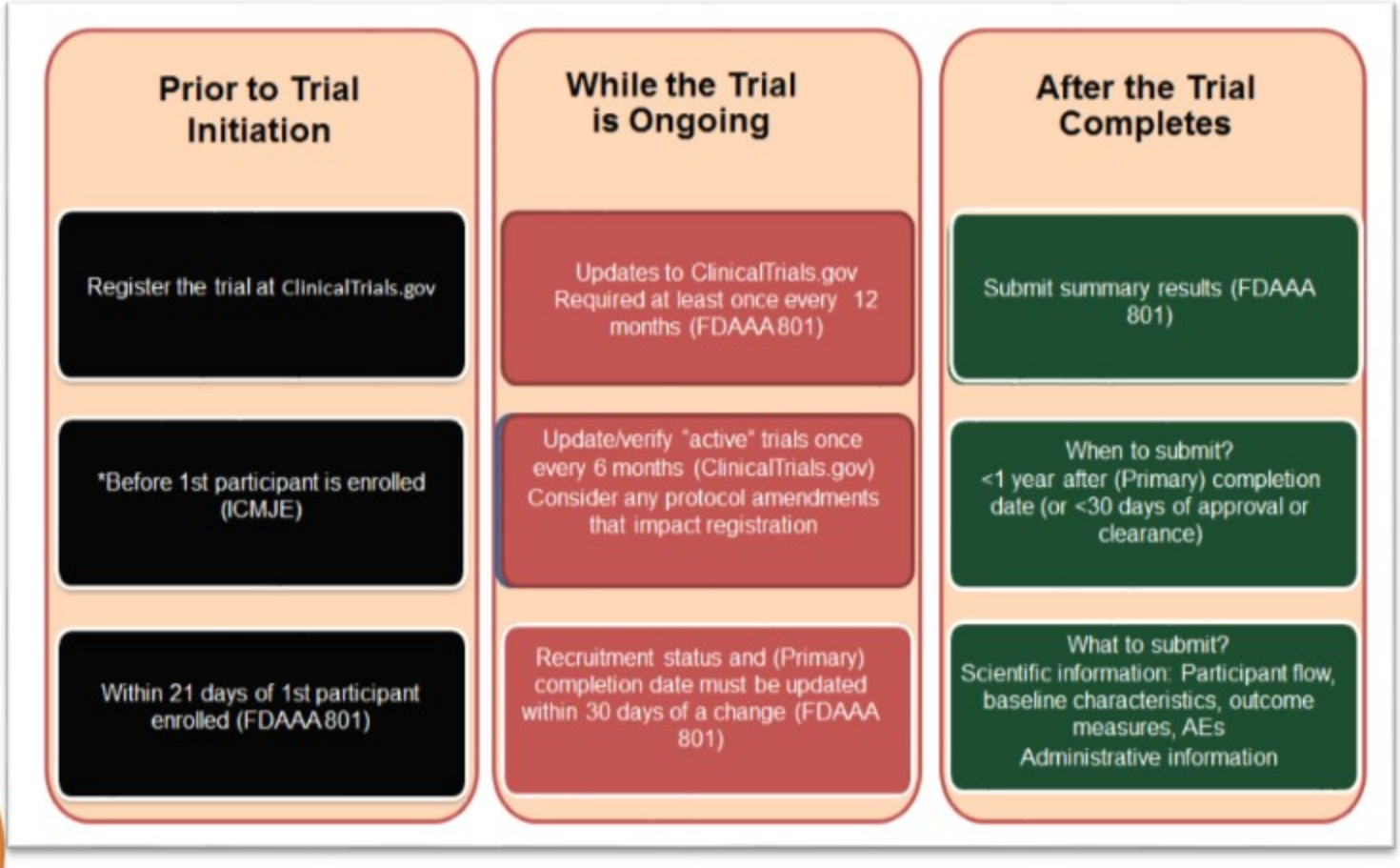
ClinicalTrials.gov: Regulatory Bodies and Laws

- 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?



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

New regulation- Final Rule

- **Final Rule** - Regulation issued by the US Department of Health and Human Services on Sept 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
  - Applicable Clinical Trial (ACT) determination approach
  - Enhance the public availability of information about specified trials

New regulation- Final Rule (contd)

- 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

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

European Union (EU) Clinical Trial Register

- Provides access to information on interventional clinical trials
- The information available dates from 1st 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 22nd March 2011, enables users to search for information that has been included in the EudraCT database

European Union (EU) Clinical Trial Register

- 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 paediatric investigation plan

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

EudraCT V10: In Scope and Out of scope Activities

Out of Scope Activities

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

EudraCT V10: In Scope and Out of scope Activities

In Scope Activities

- Interventional trials
  - Approved as well as unapproved products
- Phase 1 to 4
- Trials completed on or after 01 May 2004

EudraCT V10: In Scope and Out of scope Activities

- ICH E3 synopsis posting
  - Paediatric trials Art. 45 if not already
- submitted to EMA
  - Non-paediatric trials completed between 01 May 2004 to 20 Jul 2013 with at least one site in EU/ EEA
- Full dataset posting
  - All Paediatric trials acc. 2001/20/EC, Art 41 and Art 46 and Non -paediatric trials act to 2001/20/EC completed on or after 21 Jul 2014
  - All paediatric trials, Art 41 and Art 46 completed before 21 Jul 2014

EU 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

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

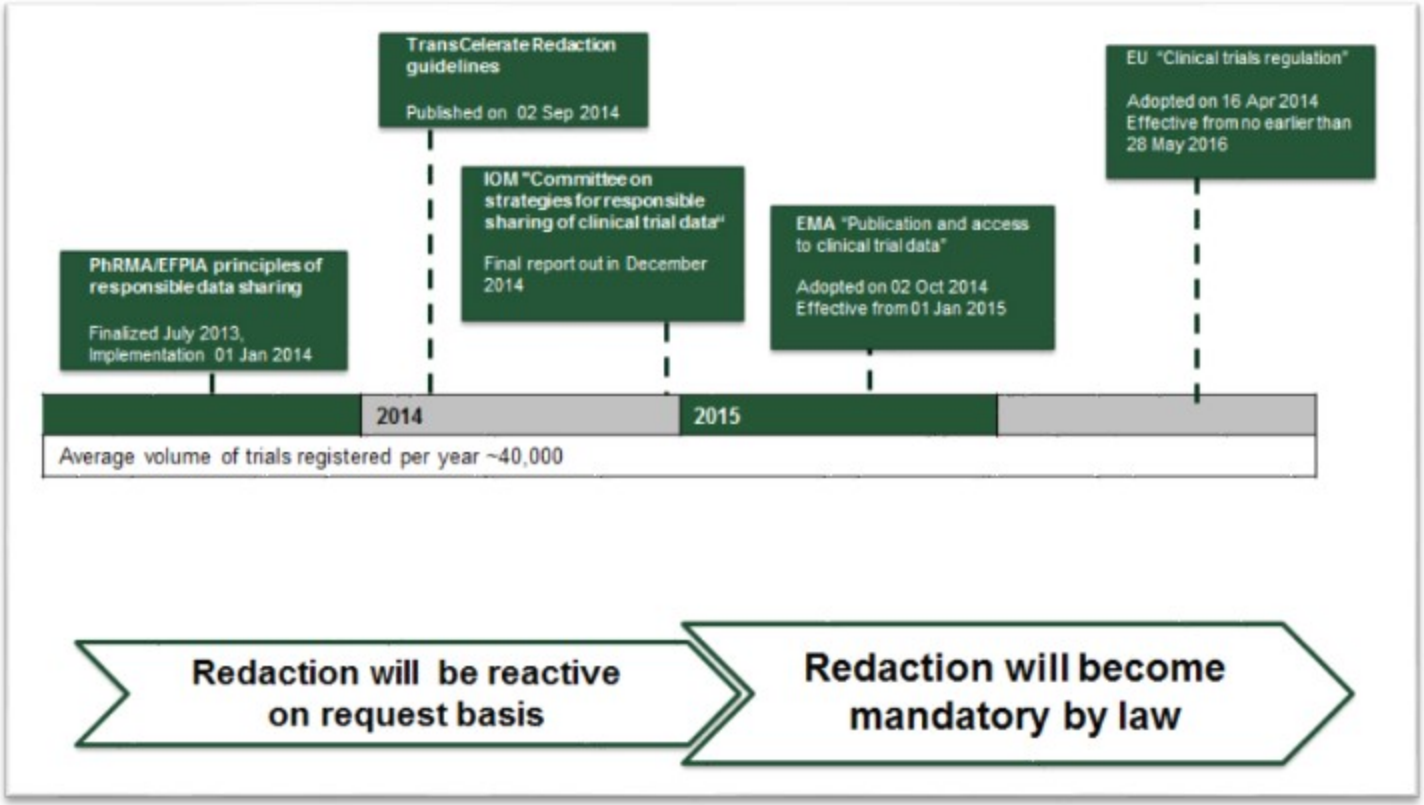
For Investigators and Study Personnel

- 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

What to redact in the CSRs?

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



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

Scope of Disclosure & Transparency

Major Disclosure documents

- Protocol Summary
- Result Summary
- Plain Language Summary

Protocol Summary

Protocol Summary

- Summarises the protocol briefly in a defined format
- Needs to be prepared after finalization of the protocol but before starting the actual trial.
- Needs to be concise but should cover all important and mandatory elements of the protocol
- Intended for understanding of layman and patients/volunteers who want to know more about the clinical trials.
- Should clearly outline the benefits and the risks associated with the trial.

Basic Protocol summary Modules

Basic Protocol Module	Summary Description
Brief Summary	A short description of the clinical study, including a brief statement of the clinical study's hypothesis, written in language intended for the lay public.
Study Design	A description of the manner in which the clinical trial will be conducted, including the following information: Primary Purpose: The main objective of the intervention(s) being evaluated by the clinical trial. Interventional Study Model: The strategy for assigning interventions to participants. Number of Arms *§ Definition: The number of arms in the clinical trial. Masking *§ Definition: The party or parties involved in the clinical trial who are prevented from having knowledge of the interventions assigned to individual participants. Select all that apply.

Basic Protocol summary Modules

Basic Protocol Module	Summary Description
Arms, Groups and Interventions	Arm Information * (For interventional studies only) Definition: A description of each arm of the clinical trial that indicates its role in the clinical trial; provides an informative title; and, if necessary, additional descriptive information (including which interventions are administered in each arm) to differentiate each arm from other arms in the clinical trial. Group/Cohort Information (For observational studies only) Definition: Specify the predefined participant groups (cohorts) to be studied, corresponding to Number of Groups specified under Study Design (for single-group studies, the following data elements are optional). Interventions * Definition: Specify the intervention(s) associated with each arm or group; at least one intervention must be specified for interventional studies.

Basic Protocol summary Modules

Basic Protocol Module	Summary Description
Outcome measures	Primary Outcome Measure Information * Definition: A description of each primary outcome measure (or for observational studies, specific key measurement[s] or observation[s] used to describe patterns of diseases or traits or associations with exposures, risk factors or treatment). Secondary Outcome Measure Information [*] Definition: A description of each secondary outcome measure (or for observational studies, specific secondary measurement[s] or observation[s] used to describe patterns of diseases or traits or associations with exposures, risk factors or treatment).

Basic Protocol summary Modules

Basic Protocol Module	Summary Description
Eligibility	Sex/Gender * Definition: The sex and, if applicable, gender of the participants eligible to participate in the clinical study. Age Limits * Definition: The minimum and maximum age of potential participants eligible for the clinical study, provided in relevant units of time. Eligibility Criteria * Definition: A limited list of criteria for selection of participants in the clinical study, provided in terms of inclusion and exclusion criteria and suitable for assisting potential participants in identifying clinical studies of interest. Use a bulleted list for each criterion below the headers "Inclusion Criteria" and "Exclusion Criteria". Sampling Method * (For observational studies only) Definition: Indicate the method used for the sampling approach and explain in the Detailed Description

Result summary

- Summarises the outcome of the clinical trial in a structured tabular form with neutral and non interpretative way of presentation.
- The results section consists of the following:
  - scientific information, consisting of discrete modules that represent information in a series of data tables with supporting notes
  - administrative information, consisting of semi-structured fields

Result summary (contd)

- The scientific information requires the sponsor or PI to define the rows (i.e., “measures”) and columns (i.e. “arms/groups”) of tables before populating the cells with results data
- For each table, the measures and arms/groups need to be labelled with meaningful titles and descriptions to allow viewers to understand the data

Basic Results Reporting Requirements

- Results of FDA-*approved/cleared* products
- Generally, submission within 12 months of the *earlier* of estimated/actual primary completion date
- Delayed Submission of Results
  - Seeking initial approval
  - Seeking approval of a new use
  - Extensions for "good cause"

Basic Results Modules

- Participant Flow
- Baseline and Demographic Characteristics
- Outcome Measures
- Adverse Events (summary data)
- Other Information
  - "Certain Agreements" *Restricting Results Disclosure*
  - Overall Limitations and Caveats
  - Results Point of Contact

Basic Results Modules

Basic Results Module	Summary Description	Overview of Minimum Required Information
Participant flow	Description of the No. of research participants starting and completing the study, including exclusions and dropouts, for each arm or comparison group (frequently reported as a CONSORT diagram in a journal article)	No. of participants who entered study; and No. of participants who completed study
Baseline characteristics	Demographic and baseline data for the study population and each arm or comparison group	Overall No. of participants analysed; age; gender; for all other measures reported: name (and description); unit of measurement; and summary data, total and by arm
Outcome measures and statistical analyses	Table of outcome measure values for each arm/comparison group, including appropriate statistical analyses	For all pre-specified primary and secondary outcome measures: name and description; unit of measurement; time frame; analysis population; and summary data, total and by arm
Adverse events (optional prior to September 2009)	Number and frequency of all serious adverse events and other adverse events exceeding a specified frequency threshold in each arm/group, grouped by organ system	For all adverse events reported: adverse event term; organ system; type of assessment (spontaneous vs systematic); and No. of participants affected, No. of participants at risk, and total No. affected, by arm

Plain Language Summary

- ‘A plain English summary is a brief summary that has been written for members of the public, rather than researchers or professionals. It should be written clearly and simply, without jargon and with an explanation of any technical terms that have to be included
- Plain English summaries support the dissemination of research to patients, participants, other scientists, health professionals and policy makers. Plain English is something that the intended audience can read, understand and act upon the first time they read it. It is crucial to minimise the use of jargon, technical terms and acronyms, and where this is unavoidable, provide explanations

Plain Language Summary

- The key principles of layperson summaries are:
  - ensuring the information is accessible:
    - not using jargon or medical terms (where these must be used, giving a full explanation),
    - keeping in mind literacy levels and
    - how use of formatting can help people understand

- Develop the summary for a general public audience and do not assume any prior knowledge of the trial
- Develop the layout and content for each section in terms of style, language and literacy level to meet the needs of the general public
- Keep the document as short as possible
- Focus on unambiguous, factual information

- Ensure that no promotional content is included
- Research across Europe suggests that text for the public should be aimed at a literacy proficiency level of 2 -3
- Communications written for the public should use simple everyday language to ensure ease of reading and understanding
- Avoid long and complex sentences that include many clauses as these are difficult to understand
- Use simple vocabulary familiar to non-medical people

- Numeracy
  - Study results summaries are likely to include a variety of numerical data that should be easily understandable by the target audience
- Visuals
  - Well-chosen and clearly designed visual aids can help enhance understanding of text
  - Patient friendly summaries of clinical trial results which combine clear infographics with explanatory text can be a good way of presenting complex information

- Using Microsoft Word, writers can test the readability of writing in English by using the Flesch Reading Ease Test or the Flesch-Kincaid Grade Level Test based on counting syllables and sentence length
- The Flesch Reading Ease Test assesses readability on a scale from 1 to 100
  - The higher the Flesch Reading Ease test score, the easier the text is to read
  - Anything that scores 70 and above is easy to read
  - An ideal reading grade level is 6th grade which is close to the literacy level of the general population
  - Even if the writer cannot achieve this, strive to get as close to this as possible

The Art and Science of Being a Disclosure Expert

*Tables, Figures & Listings

Key messages

- Disclosure is essential for human subjects protection, research integrity, evidence based medicine and legal obligation
- Disclosure a significant step towards more transparent clinical research world
- In order to match up with upcoming regulatory requirements world wide, companies need to invest more time and resources to ensure proper and timely public disclosures
- 'Good Disclosure Practices' are as important as 'Good Clinical Practice'

Safety Writing

Aggregate study reports (ASR)

- DSUR
- RMP
- PSUR
- PBRER
- PADER
- SmPC

Aggregate Safety Reports

Aggregate Reports refers to those safety reports that focus not so much on individual cases, but rather on overview, assessment of the safety profile and benefit-risk-evaluation. They comprise e.g.

- Periodic Safety Update Reports (PSURs) / Periodic Benefit Risk Evaluation Reports (PBRERs),
- Periodic Adverse (Drug) Experience Reports (US),
- Development Safety Update Reports (DSURs),
- Integrated Summaries of Safety (US), or
- Clinical Summaries of Safety (EU)

These reports need special diligence and attention to detail on the one hand, overview and a sense of what is essential on the other hand.

Development Safety Update Report (DSUR)

- Objective of DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed.
- DSUR provides safety information from all ongoing clinical trials or completed trails using an investigational drug whether with or without a marketing approval.

DSUR

- DSUR provides safety information from all Clinical trials conducted using marketed drugs in approved indication which requires additional monitoring.
- Other therapeutic use of an investigational drug and comparability trials.
- The first DSUR period should not be longer than 1 year.
- The DSUR is always submitted on a yearly basis.

What Is a Risk Management Plan (RMP)?

- A Risk Management Plan (RMP) is the document submitted as part of the Marketing Authorization Application that describes the activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those interventions and document post-authorization obligations that have been imposed as a condition of the marketing authorization updated throughout the lifetime of the medicine as new information becomes available.

What are the objectives of a Safety RMP?

The specific objectives of RMPs are three-fold:

- To specify what is and is not known about safety of a drug at the time of submission drug (Safety Specification)
- To further characterize the safety risks post authorization (Pharmacovigilance Plan)
- Where necessary, to define appropriate measures to minimize known risks to patients and to monitor the success of those measures (Risk Minimization Plan and Evaluation of Effectiveness)

Risk Management System in the European Union

- The concept of RMP is specific to EU/EEA region. For medicines that do not have an RMP, it is likely that one will be required with any application involving a significant change to the marketing authorisation.
- In addition, any national competent authority (NCA) in the EU can request an RMP whenever there is a concern about a risk affecting the benefit-risk balance of the medicine. The RMPs are continually modified.

Risk Management System in the USA

- In the USA, a REMS will be required if the Food and Drug Administration (FDA) determines that a REMS is necessary to ensure the benefits of the drug or biological product outweigh its risks.
- A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage a known or potential serious risk associated with a drug or biological product and can be comprised of: Medication Guide, Patient Package Insert, including a communication plan elements to assure safe use, and an implementation system.

WHAT IS A PERIODIC SAFETY REPORT (PSUR)

- Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation holders at defined time points during the post-authorisation phase.

OBJECTIVES OF THE PSUR

1. To present a comprehensive and critical analysis of new or emerging information on the risks and, where pertinent, new evidence of benefit to enable an appraisal of overall benefit risk.
2. This evaluation of risk-benefit assessment should be undertaken in the context of ongoing pharmacovigilance and risk management: Module VII: Post-authorization safety studies Module V: Risk management systems

OBJECTIVES OF THE PSUR

3. To contain an evaluation of new relevant information that became available to the MAH during the reporting interval, in the context of cumulative information:

1. Examine whether new information is in accord with previous knowledge of the benefit risk profile
2. Summarises relevant new safety information that may impact the benefit risk profile
3. Summarises any important new efficacy and effectiveness information
4. Conduct an integrated Benefit/Risk evaluation (where new important safety information has emerged)

PERIODICITY OF PSUR

1. PSUR must be prepared at the following intervals:
    1. Immediately upon request
    2. Every six months from authorisation until product placed on the market
    3. Every six months for first two years on the market
    4. Annually for the next two years
    5. Thereafter every 3 years Exception – frequency and dates of submission are laid down as a condition of the MA or determined otherwise in the list of Union Reference Dates (EURD List).
    6. Submit: • By day 70 for intervals up to 12 months • By day 90 for intervals in excess of 12 months

PSUR Vs PADER

- Approved worldwide. •
- Adverse events occurring around the world .
- Overall safety evaluations with specific highlighting.
- Cumulative data is analyzed for assessing benefit risk balance.

- Approved by US FDA
- Adverse events occurring in the U.S. (especially 15 day report).
- Non-Serious Adverse Events can be exempted.
- Specific periodic data is analyzed for assessing benefit risk balance.

PADER-Periodic Adverse Drug Experience Report

Periodic Benefit Risk Evaluation Report (PBRER)

- Periodic Benefit Risk Evaluation Report (PBRER) is an analysis of the safety, efficacy, and efficiency of a drug, once it is already in the market.

- The PBRER submission is intended to present a periodic, comprehensive, brief and critical evaluation of new or emerging information on the risks of the health product and the product's overall benefit-risk profile.

PBRER

- The authorities like the Food and Drug Administration (FDA), and European Medicines Agency (EMA) hold great prominence in terms of compliance with the periodic safety reporting.
- In simple terms, PBRER means submitting safety information to Regulatory authorities periodically. But in practice the Regulatory requirements make the process much more complex.

Timelines for PBRER

- A Market Authorization Holder (MAH) is required to make the PBRER submission:
  - every 6 months for the first 2 years after the product is marketed
  - once a year for the following 2 years

What is the summary of product characteristics (SmPC)?

- The SmPC is a legal document approved as part of the marketing authorisation of each medicine
- The SmPC is the basis of information for healthcare professional on how to use the medicine
- Its information is updated throughout the life-cycle of the product as new data emerge

Which information can be found in the SmPC?

- Essential information for the use of a medicine
- Qualitative and quantitative information on the benefits and the risks
- Information for individualised care
  - Paediatric and elderly population
  - Organ impairment, concomitant disease
  - Interaction with other medicines
  - Genomic factors
  - Pregnancy, lactation and fertility
  - Composition of the medicine: prevention of hypersensitivity and excipients with known effects
  - Information on specific situations
- Pharmaceutical information

What is not included in the SmPC?

- Detailed information on the scientific development which is available in the public assessment report
- Information in non-approved indication
  - Because the MAH has not claimed the indication
  - An indication has been claimed but data did not demonstrate a positive benefit risk of the medicine; withdrawal or refusal AR provide available data.
  - Exception in the paediatric group; the Paediatric Regulation aims to improve the information regarding this subgroup by providing all information on clinically relevant trials
- Specific issue for which data is lacking
- General advice on the treatment of particular medical conditions