Integrating the New EMA Requirements on Public Disclosure in the Study Conduct Process

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EMA Objectives of Transparency

Objectives of transparency

EUROPEAN MEDICINES AGENCY

12

Source: EMA Update, Sweeney & Alteri, CDISC European Interchange, Vienna, 27 April 2016

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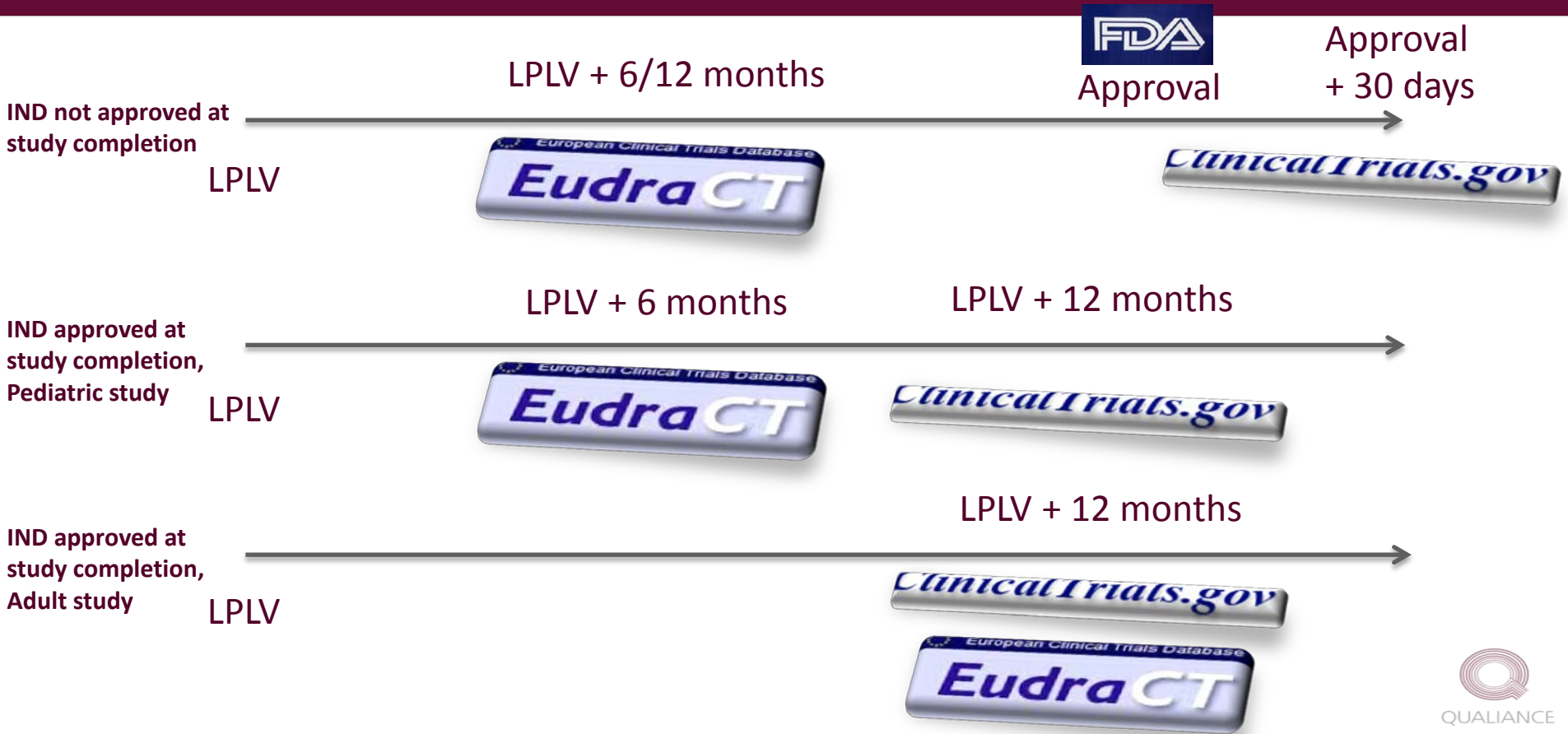
Agenda

- Study Results Public Discolsure Overview
- EudraCT and ClinicalTrials.gov Processes
- Policy 0070 Anonymization Guidance Overview
- Conclusions

Study Results Public Disclosure Overview

US Public Disclosure Database	EU Public Disclosure Database	Policy 0070	
		Part A	Part B
Study Results Effective SEP2008	Study Results Effective 20JUL14	CSR Effective 01JAN15	IPD Effective ???
Any Study part of an approved IND application	Any Study with sites in Europe (EEA) & Studies in Children conducted outside EU but part of a PIP	Any Study part of a Centralized Marketing Authorization application	???
Inform public and trial participants on core Results	Inform public and trial participants on core Results	Understand conclusions	Conduct secondary-purpose analyses, review data or verify results

EudraCT and ClinicalTrials.gov Timelines



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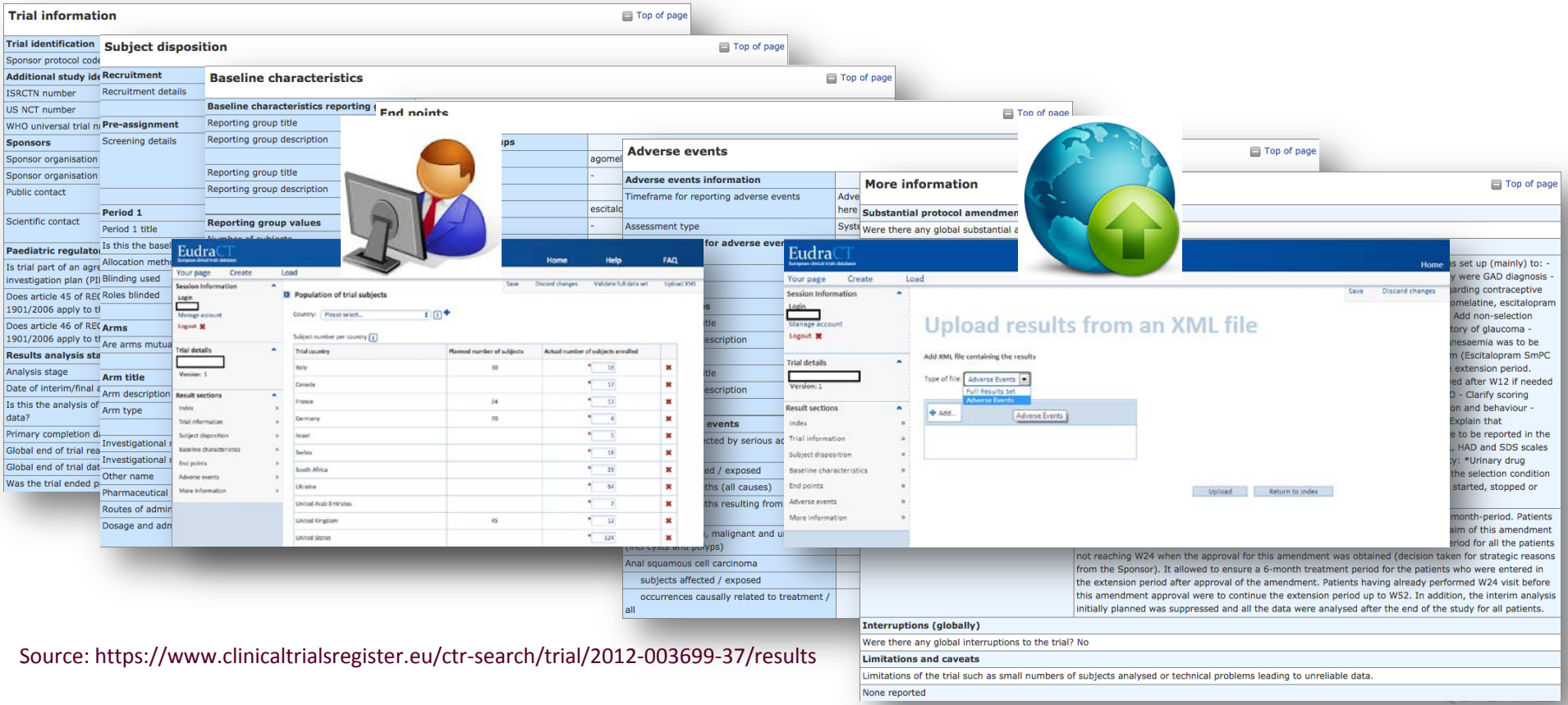
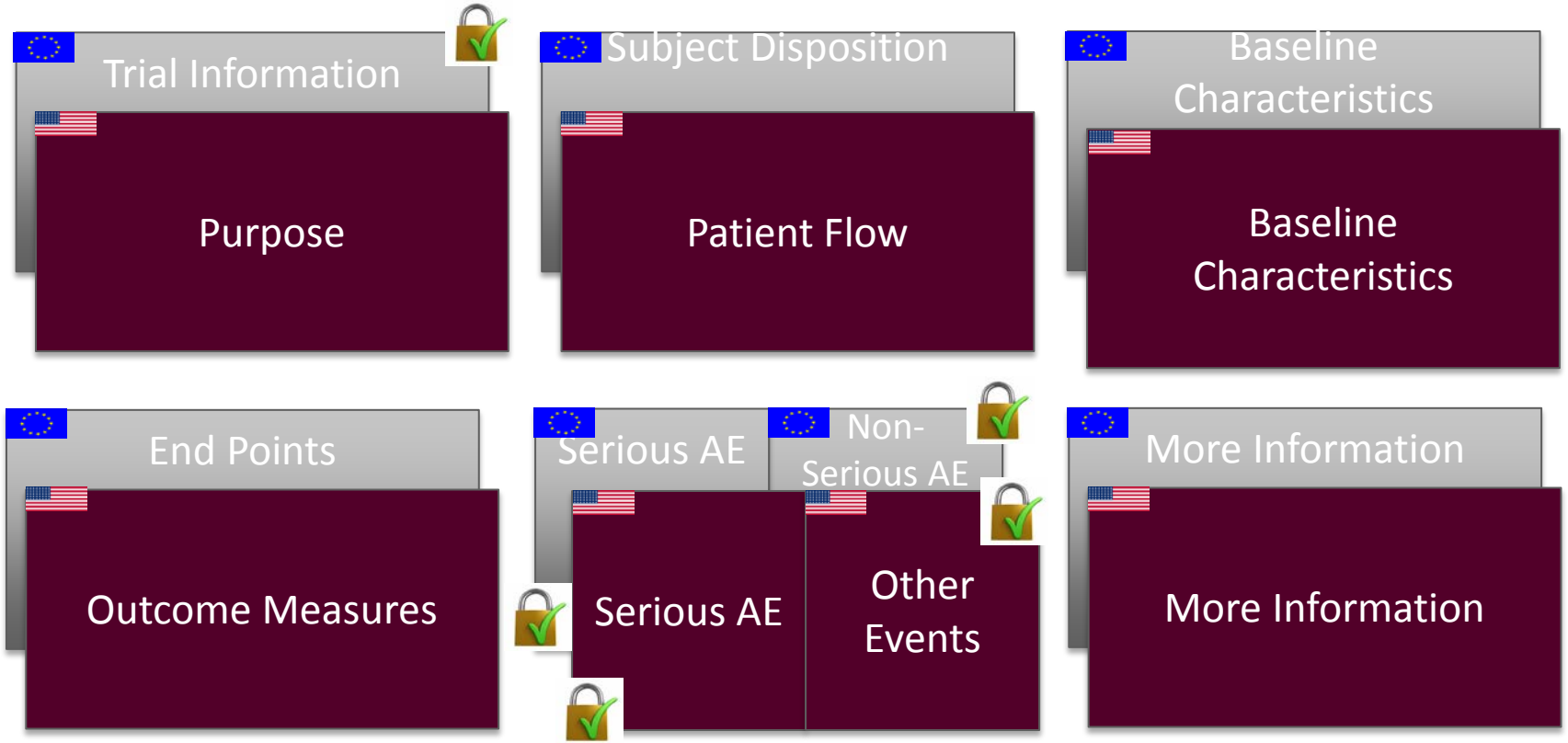
EudraCT data on EU Clinical Data Register



Source: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-003699-37/results

EudraCT vs. ClinicalTrials.gov



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Serious Adverse Event Data Elements


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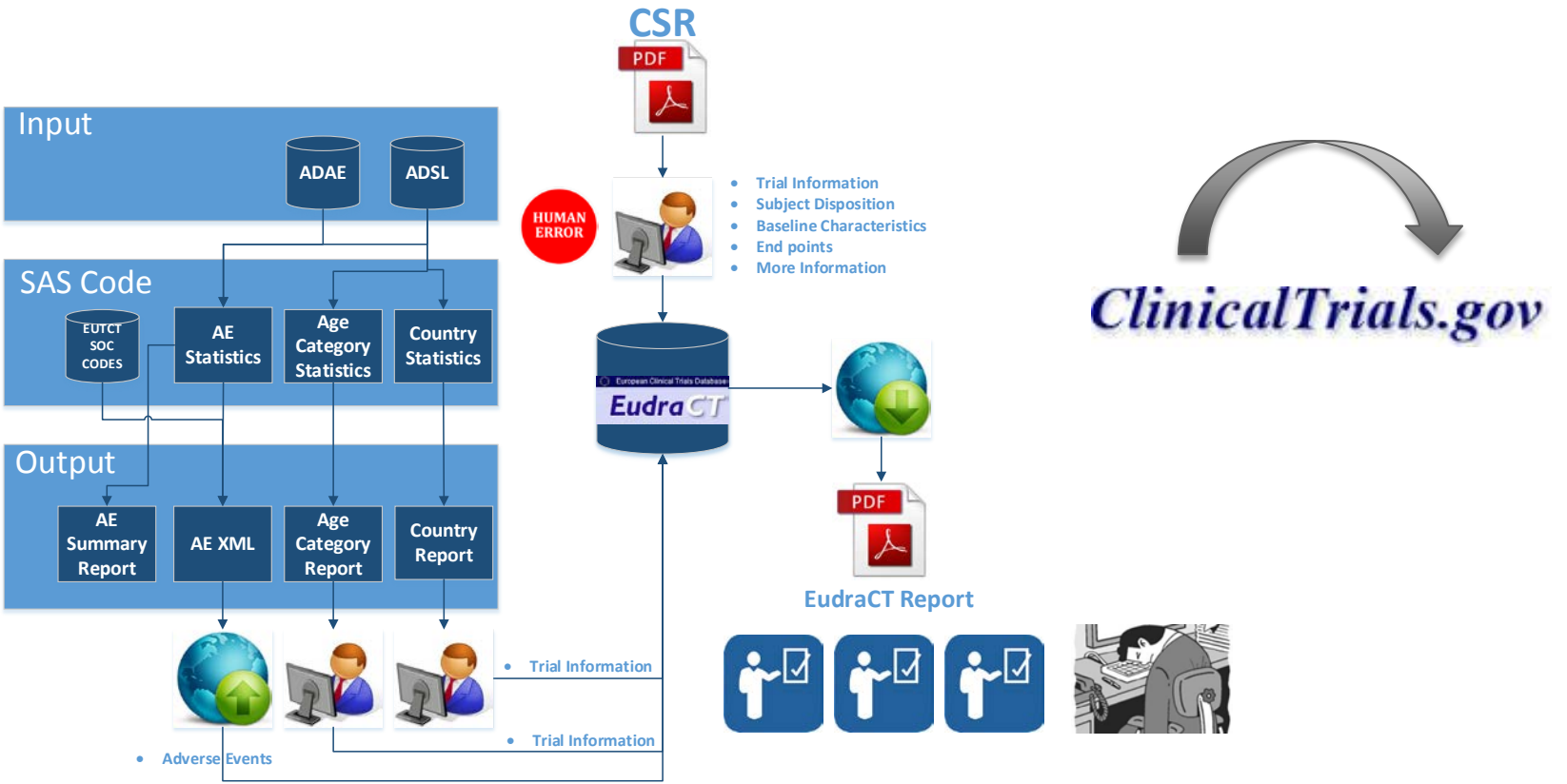
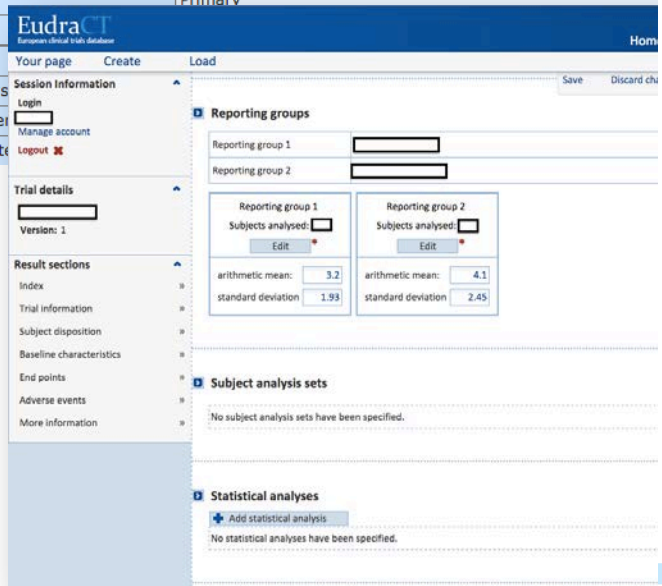
Current Public Disclosure Process



Endpoint Summary

Primary: Proportion of Patients With Complete Response — Top of page

End point title	Proportion of Patients With Complete Response
End point description	Complete Response was defined as no vomiting, no retching, and no use of antiemetic rescue medication during the first 24 hours postoperatively, starting at T0. Time patient wakes up and is able to show any active reaction pos included all randomized patients who received the active stu (evaluable patients). Following the intent-to-treat principle, arm according to their randomized treatment.
End point type	Primary
End point timeframe	
End point values	
Number of subjects analys	
Units: percentage of patie	
number (confidence inte	

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Endpoint Statistical Analysis

Statistical analysis title	Comparison of Proportion of Patients With Complete
Statistical analysis description	The null hypothesis (H0) was stated as: • H0 : CR 0-24 hr palonosetron - CR 0-24 hr ondansetron <-10% The alternative hypothesis (H1) was stated as: • H1 : CR 0-24 hr palonosetron - CR 0-24 hr ondansetron >-10% A power of 80% was used for sample size computation.
Comparison groups	Palonosetron and Placebo to Ondansetron v Ondansetron and Placebo to Palonosetron
Number of subjects included in analysis	661
Analysis specification	Pre-specified
Analysis type	non-inferiority [1]
Method	
Parameter type	Risk difference (RD)
Point estimate	-4.4
Confidence interval	
level	95%
sides	2-sided
lower limit	-10.5
upper limit	1.7

Notes
[1] - For the primary efficacy analysis, the confidence interval (CI) was built on the FAS using the stratum adjust
correction of continuity. The non-inferiority margin was -10%.

```
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      • H0 : CR 0-24 hr palonosetron - CR 0-24 hr ondansetron &lt;-10%&#xD;
      The alternative hypothesis (H1) was stated as:&#xD;
      • H1 : CR 0-24 hr palonosetron - CR 0-24 hr ondansetron &gt;-10%&#xD;
      A power of 80% was used for sample size computation.
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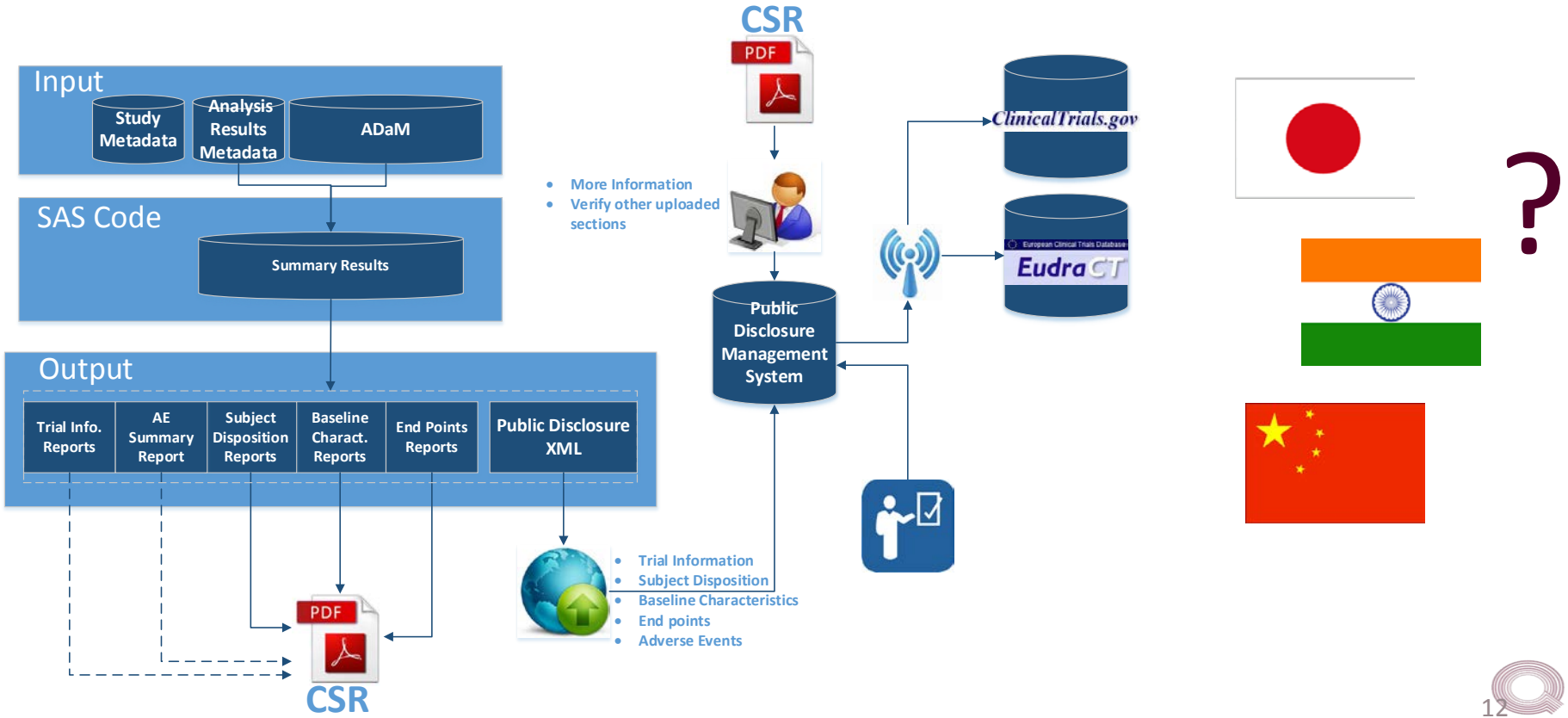
Future Public Disclosure Process



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Recent Initiatives on Harmonization

EU portal and database – Data standardisation

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WHO	WHO ICTRP standard will be fully met, and data provided to the ICTRP by the EU database
NIH (clinicaltrials.gov)	Collaboration and discussion on the anticipated changes to the data model (focusing on protocol / results) to ensure convergence and alignment where the same elements are used in both US and EU systems
CDISC	Collaboration on clinical trial registration including study design data model, and in due course on results model

Source: EMA Update, Sweeney & Alteri, CDISC European Interchange, Vienna, 27 April 2016

Industry Standards Being Developed

- **CDISC CTR-XML Specification, version 1.0 released on 28MAR2016**
  - Clinical Trial registry submissions to WHO, EudraCT registry and ClinicalTrials.GOV

CDISC PRIM

Protocol Representation Implementation Model

- Protocol schema that can be implemented in Software
- Harmonization with **TransCelerate protocol work**

CDISC CTR_2

Clinical Trial Registration & Results 2

- Summary results data elements
- Collaboration with the **PhUSE RDF Working Group**

Source: CTR Update, Paul Houston, CDISC European Interchange, Vienna, 28 April 2016

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Policy 0070 Part A & Part B, Data Transparency and more…

Sponsors Publications	Sponsors Data Transparency Initiatives	Policy 0070 Part A	Policy 0070 Part B
Based on Pseudomized IPD Forever…	Anonymized IPD Started in 2013 with GSK	Anonymized CSR Portal go-live SEP2016	Anonymized IPD *Effective ???*
Sponsors' choice	Any Study related to a an approved application in EU & US	Any Study part of a Centralized Marketing Authorization application	*???*
No Anonymization	Safe-Harbor or Average Risk Metrics	Qualitative or Maximum Risk Metrics	Average or *Maximum Risk Metrics?*
Public Domain	May result in Publications available in Public Domain	Semi-Public Domain	*Public Domain or Controlled?* Publications available in Public Domain

Policy 0070 Part A
EMA CSR Anonymization Guidance

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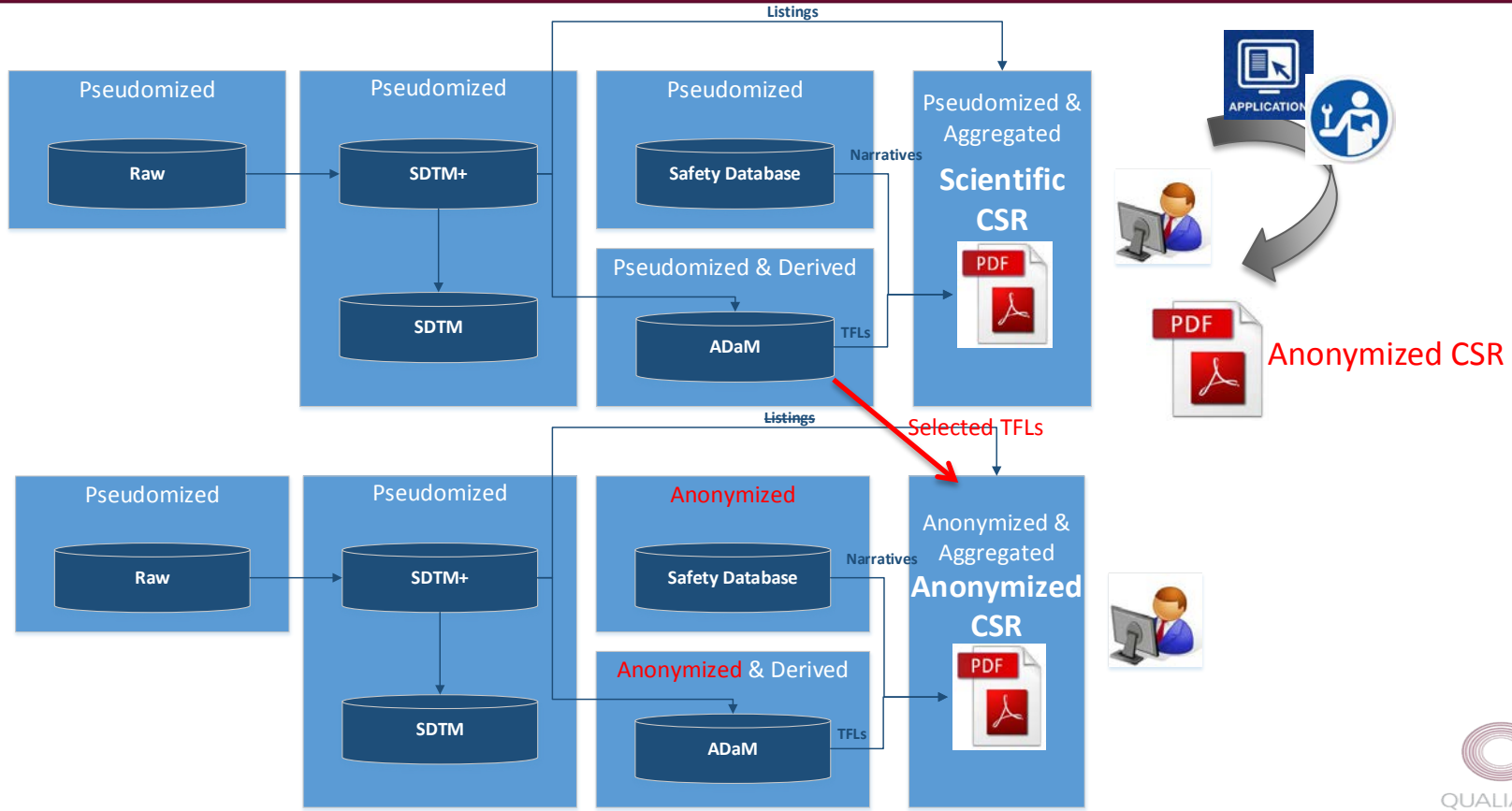
Current & Possible Future Process



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Can we wish for more alignment?

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FDAnews Drug Daily Bulletin
Pharmaceuticals / Regulatory Affairs

EU: Align U.S. and EU Requirements on Approval, Guidelines and GMP

June 3, 2016

The European Union wants to expand ongoing trade talks between the U.S. and EU to work toward regulatory harmonization for drug approvals, guidelines and GMP compliance.

The EU recommends the FDA and EMA accept one another's GMP compliance certificates for manufacturing facilities located in and outside of their respective jurisdictions and suggests U.S. and EU regulators eliminate duplicate clinical trial and GMP inspection requirements by synchronizing rules.

The proposal is being presented as a new annex on medicinal products to be discussed at the Transatlantic Trade and Investment Partnership talks.

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Conclusions

- Can we expect Regulatory Agencies to align or even integrate such requirements?
  - Probably not fully…but to some extent yes…
    - Different legal environments
    - Large difference in resources
- Global data models for protocol and results summary will be required to ensure interoperability and reuse
- EMA CSR Anonymization Guidance is still being interpreted by a number of industry groups and companies and a number of solutions should emerge in the coming year…

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Thanks!

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