European Medicines Agency Policy 0070: An exploratory review of data utility in Clinical Study Reports for academic research

Clinical Trial Data Transparency Forum
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Disclosure statement

- JMF: I have worked for various Pharmaceutical companies as a consultant since January 2010 on compound specific clinical projects or cross-compound system-related projects. I have also entered a strategic alliance in January 2017 with d-Wise Inc. (North Carolina) where I contribute as an SME to the design and development of their data de-identification products. I am an appointed member of the European Medicines Agency Technical Anonymisation Group and Health Canada Stakeholder Reference Group on Public Release of Clinical Information. The views expressed within this research are my own.
- SN: I have no known conflicts of interest. I am an appointed member of the European Medicines Agency Technical Anonymisation Group. The views expressed within this research are my own.

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Data Utility & Policy 0070

- Since January 2015: EMA Policy 0070 (Phase 1) on the publication of clinical data for medicinal products for human use, allowing global access to regulatory documents (including clinical study reports) for non-commercial purposes

- <u>Policy 0070 "Phase 1" Guidance:</u>
  - Data Controller must demonstrate that data utility has been considered and optimized
  - Data Utility is absent from section "3. Definitions"
  - Only reference to preserving results and conclusions

Data Utility & Policy 0070

Data Utility: a definition from the OECD*:

"A summary term describing the value of a given data release as an analytical resource. This comprises the **data's analytical completeness and its analytical validity**. Disclosure control methods usually have an adverse effect on data utility. Ideally, the goal of any disclosure control regime should be to maximise data utility whilst minimizing disclosure risk. **In practice disclosure control decisions are a trade-off between utility and disclosure risk**."

Source: Organization for Economic Co-operation and Development (OECD) Data Utility Definition: https://stats.oecd.org/glossary/detail.asp?ID=6905

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Data Utility & Policy 0070

Data Utility: a definition from the OECD*:

"…**data's analytical completeness and its analytical validity.**"

Completeness and validity depends on

- **Who** is using the data?
- **How** they are using the data?
- **Why** they are using the data?

Source: Organization for Economic Co-operation and Development (OECD) Data Utility Definition: https://stats.oecd.org/glossary/detail.asp?ID=6905

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Who will use EMA Policy 0070 data? Researchers?

Survey conducted among authors of Cochrane Reviews between June and September 2016 on the theme "How is academia using regulatory data?"

156 Respondents (out of over 3000 registered Cochrane authors)

- **Only 10% (i.e. 16 people) have used or requested regulatory data**
  - **80% of these respondents believe regulatory data must be part of a Cochrane review**
- 5% considered using regulatory data
  - **32% of these respondents believe regulatory data must be part of a Cochrane review**
- 85% have not considered using regulatory data
  - **38% of these respondents believe regulatory data must be part of a Cochrane review**

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Who will use EMA Policy 0070 data? Researchers?

Survey conducted among authors of Cochrane Reviews between June and September 2016 on the theme "How is academia using regulatory data?"

156 Respondents (out of over 3000 registered Cochrane authors)

- **32% of respondents had no understanding of the regulatory process**
- **12% of authors knew where to access regulatory data**
- **67% of respondents who accessed and included data in their reviews mentioned barriers** when using data:
  - Restricted and limited data
  - Time constraints
  - Lack of experience

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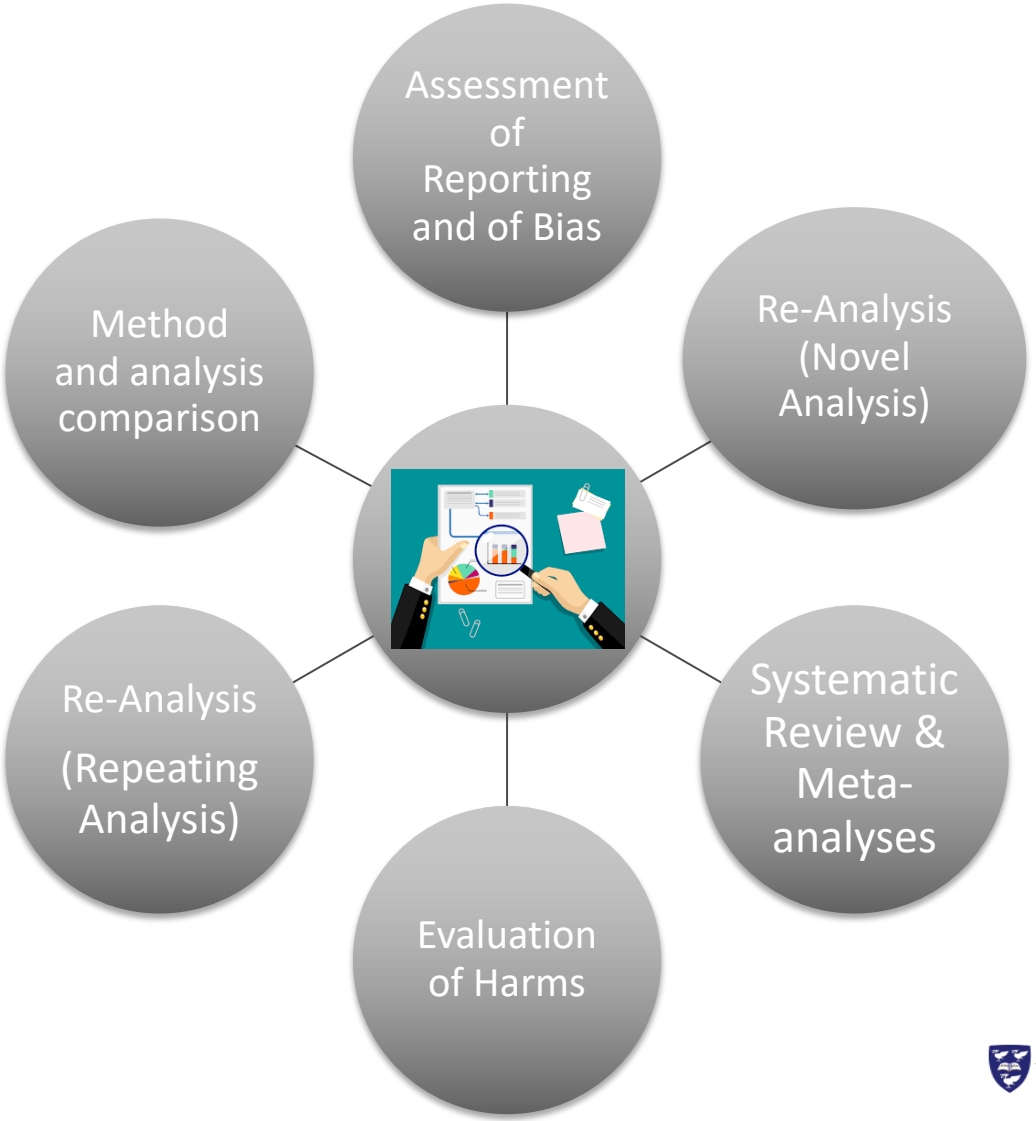
Who will use EMA Policy 0070 data? Researchers?

- We reviewed 13 academic research reports unpublished data from CSRs (prior to EMA Policy 0070)
  - Objectives
  - Methods
  - Findings
- We conducted interviews with eight researchers who have published academic work using CSRs and regulatory data to further explore:
  - Rationale and methods used
  - (Hypothetical) Potential impact of Policy 0070 on data utility

Ferran JM, Nevitt S. European Medicines Agency Policy 0070: an exploratory review of data utility in Clinical Study Reports for academic research (submitted, review comments addressed). Draft available from: http://www.phusewiki.org/docs/Conference%202017%20DH%20Papers/DH04%20Paper%20NEW.pdf

What are researchers doing with CSR data?

Purpose
Check for publication bias
Check for reporting bias
Systematic reviews
Novel analysis



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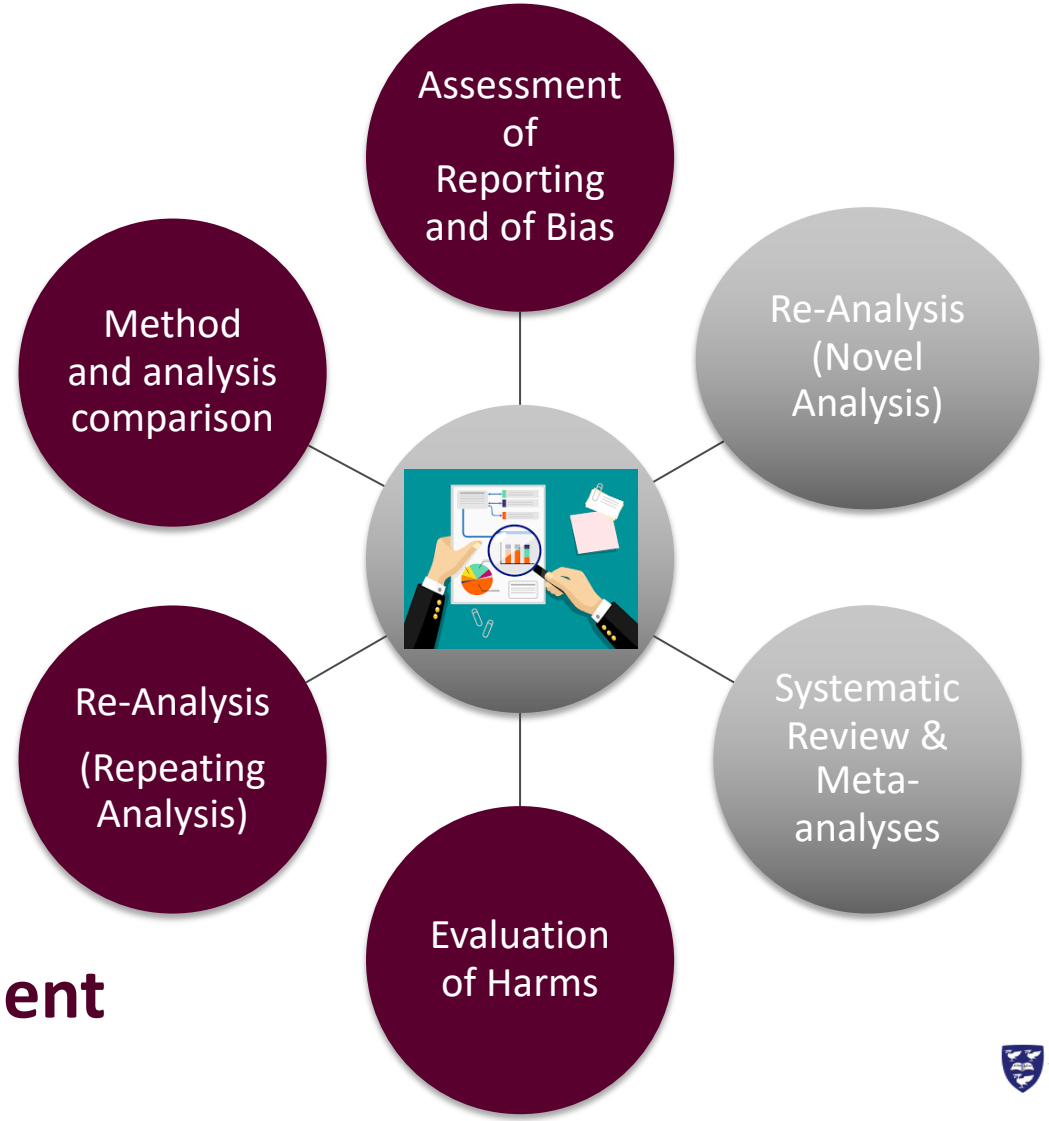
What are researchers doing with CSR data?

Purpose 1: "Checking"

Appraisal

Purpose
Check for publication bias
Check for reporting bias
Systematic reviews
Novel analysis



- Cochrane Reviews
- Health Technology Assessment

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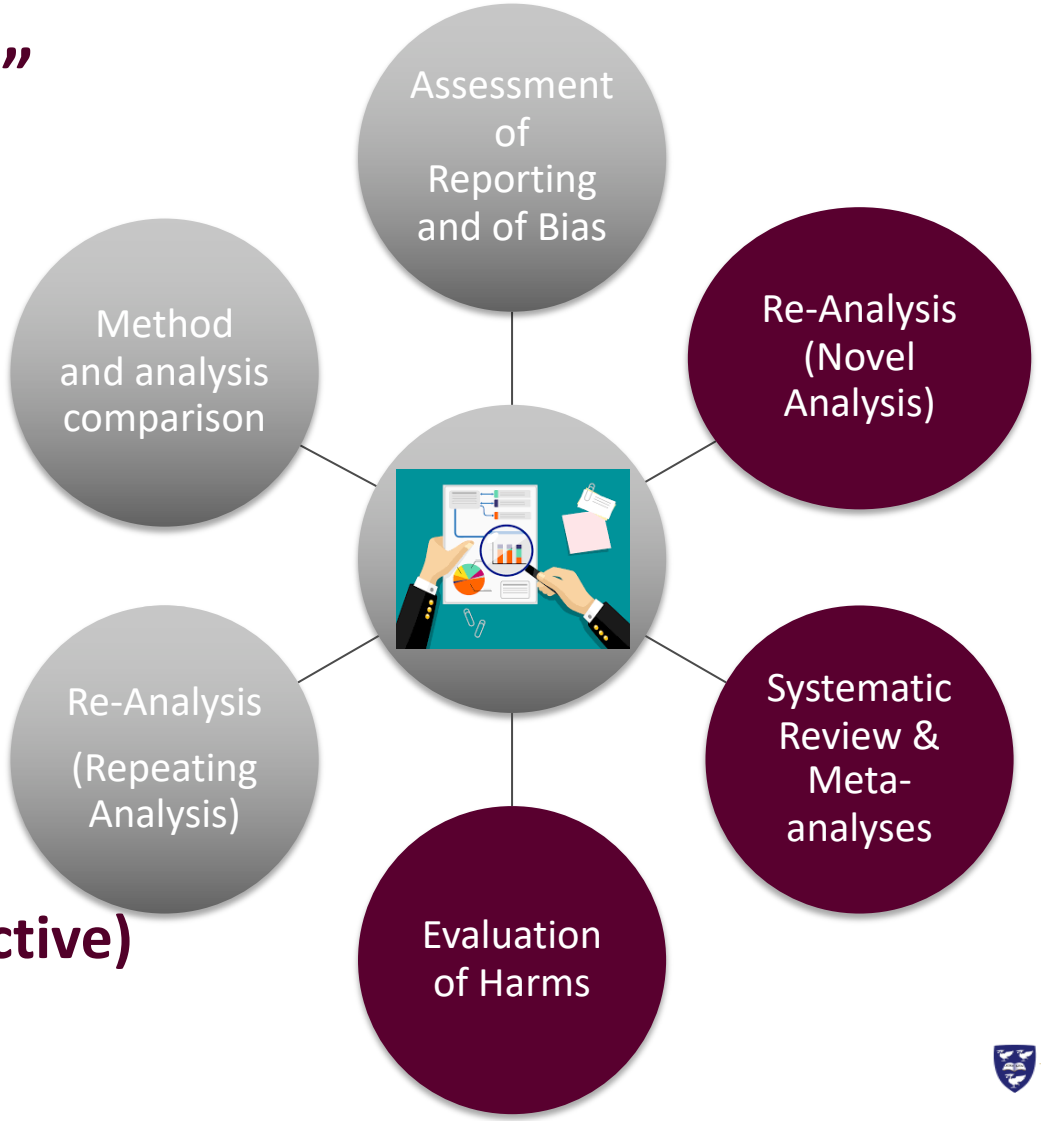
What are researchers doing with CSR data?

Purpose 2: "Novel Analysis"

Purpose
Check for publication bias
Check for reporting bias
Systematic reviews
Novel analysis



- **Re-analysis (with a different perspective)**
- **Systematic reviews**
- **Meta-analysis**

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Example – Novel meta-analysis using CSR data

SJ Nevitt et al: Inhaled mannitol for cystic fibrosis. Cochrane Database of Systematic Reviews, 2018

- Regulatory objectives versus Cochrane objectives
  - Demonstration of efficacy (e.g. lung function) versus meaningful outcomes for patients (e.g. quality of life)
- Published sources focus on efficacy (lung function), very limited information about Quality of Life
- Manufacturer of Mannitol provided additional unpublished summary data to allow detailed analyses of Quality of Life
  - Improvement in Quality of Life but increase in Burden of Treatment
  - Manufacturer helped with interpreting data, made extensive comments on our final report
  - Level of information required would be available in CSRs

Example – Use of narratives in original research

Maund E et al. Coding of adverse events of suicidality in clinical study reports of duloxetine for the treatment of major depressive disorder: descriptive study. BMJ, 2014

- Comparing dictionary coded adverse events in summary tables to patient listings and narratives within CSRs
- Some re-coding and re-analysis (meta-analysis) of specific harms data
- Example: examination of CSRs of Duloxetine trials for events related to suicide
  - Coded events and narratives suggest different numbers of events
  - Coded events in summary tables may be misleading and not capture the true nature of the event
  - Different conclusions could be drawn
  - Authors suggest in this example, the narratives are more informative

Evaluation of Bias

Selective Outcome Reporting	Publication Bias	Safety Under-Reporting
Were planned analyses conducted as planned? • Comparison of Planned Analyses vs. Reported Analyses • Comparison of Planned Analyses vs. Published Analyses Complexity: Low	Publications in Journals based on study outcome? • Meta-analysis of primary/secondary endpoints results from published studies vs. Unpublished studies Complexity: Medium	Are all AEs/SAEs reported in CSR and subsequently in Registeries and Publications? • Re-count from narratives or patients listings and comparison with CSR's Safety Tables • Comparison with Publications and Registeries Complexity: Low (High Efforts though!)

Detailed Evaluation of Harm (1)

15-Criteria proposed by Hodkinson et al. (2016)

Table 1 Fifteen criteria (adapted from the CONSORT-harms extension) assessed to evaluate the completeness of reporting methods and results of harms

	Criteria	Criteria description	Description of complete reporting for criteria
Methods	1	List addressed adverse events with definitions	Listed AEs with definitions (with attention to the grading, when relevant)
	2	Mode for collecting data	Full description of questionnaires, interviews, or tests used to collect information on the harms. Detailed information on the questions asked
	3	Timing and time frame of surveillance	Description of the time frame of surveillance for AEs, with the stopping period detailed
	4	Attribution methods	Person responsible for making attribution disclosed and whether blinding was used
	5	Intensity of ascertainment	Specify clearly how the withdrawals are handled in the analyses
	6	Harms-related monitoring	Plans for monitoring and rules for stopping for the benefits and harms separately
	7	Coding of AEs	Reference to any coding system used and person responsible for the coding
	8	Handling of recurrent events	Specify how recurrent events are handled: detailed as separate events or as one
	9	Timing issues	Timing of events explained, if recurrent
	10	Plans to perform any statistical analyses and inferences	Described how pre-specified statistical analyses are separated from post hoc analyses, and any common problems addresses
Results	11	Withdrawals and discontinuations	Reasons for discontinuations and separated by arm. Flow diagrams used to display withdrawals
	12	Denominators for analyses on harms	Analyses and definitions used and clearly stated (i.e. intention to treat (ITT)), and all denominators for safety population are clearly detailed
	13	Specifying AE type	Results presented separately by System Organ Classification type
	14	Grading or scaling used	Each AE type should offer appropriate metrics of absolute risk
	15	Seriousness per arm	Reported separately for each type of event

FDA Considerations when Reviewing Safety

Issues Regarding Overall Submission Quality

FDA

Is applicant's approach to safety reasonable and appropriate?

- Is process for recording, coding, and categorizing adverse events (AEs) acceptable?
- Has applicant provided accurate definitions of AEs and serious adverse events (SAEs) in the protocol(s)?
- Has the applicant defined "treatment emergent" adverse events (TEAEs) and is the definition appropriate?
- Is the methodology and frequency of routine clinic testing adequate?

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Detailed Evaluation of Harm (2)

AE Collection	AE Coding Appraisal & Other Appraisals	Re-evaluation of Harm
Is the approach to AE collection and assessment appropriate?	Re-assessment of Dicotionary-coding of AEs, Re-assessment of Seriousness, Severity, Relationship to Study Drug, Masking effect of concomitant medication, etc.	Re-evaluation based on re-assessment
• Review of methods	• Detailed review of Narratives, In-text Listings and/or Patient Listings	• Re-Analysis • Meta-Analysis
Complexity: Low	Complexity: Medium (Requires advanced knowledge of the clinical area!)	Complexity: High

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Meta-analysis & Systematic Review

Meta-Analysis based on Results/Aggregate Data	Meta-Analysis based on Patient Listings
Various purposes ranging from evaluation of bias, evaluation of harm to novel analysis. • Pooling and re-analysis of aggregate data from several studies Complexity: Medium to High	Various purposes ranging from evaluation of bias, evaluation of harm to novel analysis. • Pooling and re-analysis of individual patient data from several studies Complexity: High

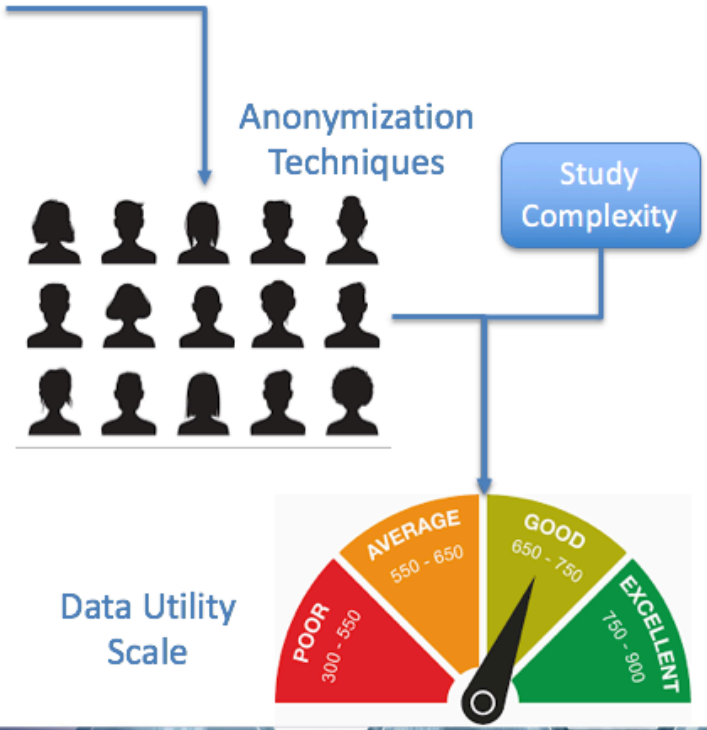
Re-Analysis

Re-Analysis (Repeating Original Analysis)	Re-Analysis (Novel Analysis)
Are the study results reproducible and consistent with planned methods and collected data? Complexity: High	Various purposes Complexity: High

PhUSE Data Transparency Working Group
Data Utility Scale Project (In Progress)

Data Utility Project Approach

Research Objectives	CSR Sections
Assessment of reporting and evaluation of bias	Methods, results (aggregate summary tables and text), narratives, participant listings
Comparison of methods and/or results (including adverse events) with data registries or manuscripts	Methods, results (aggregate summary tables and text)
Detailed evaluation of harms and adverse events	Results (aggregate summary tables and text), narratives, participant listings
Systematic review and meta-analysis (evidence synthesis)	Methods, results (aggregate summary tables and text), narratives
Re-analysis (repeating original analysis)	Methods, results (aggregate summary tables and text), narratives, participant listings
Re-analysis (different method or objective to the original analysis)	Methods, results (aggregate summary tables and text), narratives, participant listings



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Conclusions

- The use of Methods and Results can support a number of secondary-purpose analyses such as the evaluation of bias type of analysis and any meta-analyses using aggregate data.

- The use of In-text Listings and Narratives in an anonymized formats can also support some of the detailed evaluation of harms type of analysis but not all.

- Patient Listings and/or Individual Patient Data are ultimetly necessary to support the most advanced type of analysis.

- **SN & JMF:** We would encourage communication between Researchers and Sponsors prior to publication.

Thanks!

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