Considerations for analysis plans for data sharing requests

Joint BBS-EFSPI Seminar on
Data Sharing in Clinical Development
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The views and opinions expressed herein are the presenter's own, and cannot and should not necessarily be construed to represent those of her employers or affiliates.

Pharmaceutical industry has responded to calls for data transparency

Principles for Responsible Clinical Trial Data Sharing

Our Commitment to Patients and Researchers

Biopharmaceutical companies are committed to enhancing public health through responsible sharing of clinical trial data in a manner that is consistent with the following Principles:

- **Safeguarding the privacy of patients**
- **Respecting the integrity of national regulatory systems**
- **Maintaining incentives for investment in biomedical research**

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Will the outcome also be viewed positively?

Differences in Reporting of Analyses in Internal Company Documents Versus Published Trial Reports:

PLoS Med 10(1): e1001378. doi:10.1371/journal.pmed.1001378

What Do These Findings Mean? These findings from a sample of industry-sponsored trials on the off-label use of gabapentin suggest that when compared to the internal research reports, the trial publications did not always accurately reflect what was actually done in the trial. Therefore, the trial publication could not be considered to be an accurate and transparent record of the numbers of participants randomized and analyzed for efficacy.

Further guidance is also needed to ensure consistent terminology for types of analysis. Of course, these revisions will improve reporting only if authors and journals adhere to them. These findings also highlight the need for all individual patient data to be made accessible to readers of the published article.

Reanalyses of Randomized Clinical Trial Data

CONCLUSIONS AND RELEVANCE A small number of reanalyses of RCTs have been published to date. Only a few were conducted by entirely independent authors. Thirty-five percent of published reanalyses led to changes in findings that implied conclusions different from those of the original article about the types and number of patients who should be treated.

JAMA. 2014;312(10):1024-1032. doi:10.1001/jama.2014.9646

Key considerations

- We have an opportunity to influence the planning, conduct, and interpretation of analysis on shared data
- Work in progress!
  Suggested additions and improvements are welcome

EFSPI / PSI Data Sharing Sub-group on best analysis practice

- Minimal best practice will differ according to the kind of analysis being performed; recommendations for analyses performed on shared data sharing may require additional guidelines
- The sub-group‘s report will focus on recommendations for key features to be included in analysis plans, including references to further sources of existing guidance
- Limitations in interpreting the results of research using shared data will also be considered

Types of analysis

- **Requests to AstraZeneca since December 2013**
  - ~40 centrally recorded requests from external researchers
  - ~50% were requests for data for meta-analysis
  - ~25% involved methodological research
  - ~20% involved prediction of outcome
  - ~10% (including some of the meta-analyses) involved prediction of response to treatment
- **Other sponsors' experience**
  - 23 published research proposals on cross-sponsor sharing site show a similar profile
  - 1 proposal to re-analyse the data from a study due to concerns about the way in which the study was analysed and reported.

Classification of types of analysis

- **Analyses related to risk-benefit of the product**
  - Checking that the analysis performed by the Sponsor was correct according to their analysis plan
  - Further analyses based on the randomised comparison, eg new endpoints, new sub-groups, new statistical methods
  - Meta-analysis using IPD
- **Additional analyses indpendent of the risk-benefit assessment of the product**
  - Prediction of outcome, development of new assessment methods, ...

Classification of types of analysis

- **Analyses related to risk-benefit of the product**
  - Hypothesis generating as all alpha used up?
  - **Randomisation based analyses**
  - Interpretation should be in relation to the original interpretation
- **Additional analyses indpendent of the risk-benefit assessment of the product**
  - Completely new hypotheses
  - **Analyses not based on the randomised comparison**
  - Observational research
  - Interpretation is independent of the original

Reanalysis

- Recent debate about the place of analyses attempting to replicate the sponsor's findings
  - *"open science and replication should become the standard for all trials"* Krumholz & Peterson
  - *"data sharing for the purposes of reanalysis, ..., does not necessarily serve the public good and maybe counterproductive"* Christakis and Zimmerman
  - Core Principles of Study Reanalysis are proposed by Christakis and Zimmerman

Ebrahim S, Sohani ZN, Montoya L, et al. Reanalyses of randomized clinical trial data. JAMA. 2014;312(10):1024-1032.
Christakis DA, Zimmerman FJ. Rethinking reanalysis. JAMA. 2013;310(23):2499-2500.
Krumholz HM, Peterson ED. Open Access to Clinical Data. JAMA. 2014;312(10):1002-1003.

Further analyses related to risk-benefit of the product

- Further analyses based on the randomised comparison, eg new endpoints, new sub-groups, new statistical methods
  - Could generally be viewed as sensitivity analyses?
  - Guidance available on planning and reporting of sensitivity analyses, but interpretation is often subjective?
  - Which analyses go beyond sensitivity analyses?
- Meta-analysis using IPD
  - Chapter 18 of the Cochrane Handbook
  - Lack of guidance on combining aggregate and individual patient data?

Thabane et al. A tutorial on sensitivity analyses in clinical trials. BMC Medical Research Methodology 2013, 13:92
Morris et al. Choosing sensitivity analyses for randomised trials: principles. BMC Medical Research Methodology 2014, 14:11

Additional analyses indpendent of the risk-benefit assessment

- Prediction of outcome, development of new assessment methods, ...
  - Types of information to be included in an analysis plan can be described in broad terms, but key considerations will depend of the specific research question
  - Some relevant guidelines available
    - Eg pharmacoepidemiology guidelines such as EnCEPP etc
    - More guidance needed? E.g. strengthening analytical thinking for observational studies (STRATOS) initiative, to provide accessible and accurate guidance in the design and analysis of observational studies

Sauerbrei et al 2014. The STRATOS initiative. Statistics in Medicine, 2014.
The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). http://www.encepp.eu/standards_and_guidances

Many recommendations apply to all types of analysis

Planning

- Pre-specification allows transparent reporting of planned analyses and additional findings
- Research proposal should be submitted with request for data
  - Hypothesis, analysis details ...
- Interactions with the data owner may be needed to ensure that the analysis can be done as specified
  - Protocol provided prior to finalisation of request?

Conduct

- Good practice to replicate previous analyses prior to conducting new analyses?
  - Data redaction may prevent replication
    Data owners could consider providing results of their pre-specified analyses re-run on the redacted data?
- Should researchers aspire to emulate the pre-specification in our initial analyses?
  - E.g. for electronic health record studies sometimes a sample of records is used to finalise code prior to final run on full dataset

Interpretation

- Could the basis for interpretation be pre-agreed with the data owner?
  - Anticipated limitations – eg those that would be acknowledged in the discussion of a publication
  - Hypothesis generating or confirmatory?

What depends on type of analysis?

	Related to risk-benefit of the product?	
	Yes	**No**
Planning	Pre-specification important, but results may still be hypothesis generating? What about meta-analysis?	Pre-specification provides an opportunity to robustly test new hypotheses
Conduct	Same key considerations apply?	
Interpretation	Data owner should have opportunity to comment prior to publication?	Data owner may not need to comment?
Reporting	Transparency about the extent of pre-specification and limitations of the research	

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- **Any questions or comments?**