DH04
EMA Policy 0070:
Data Utility in Anonymised Clinical Study Reports (CSRs)

PhUSE 2017, Edinburgh
Jean-Marc Ferran (Qualiance) &
Sarah Nevitt (University of Liverpool)
Acknowledgement

• Thanks to the Researchers, Patient Organizations, Doctor Associations, Industry Representatives and Regulators, who engaged with us, for their time and invaluable input...
Heard here and there...

• “Only Pharmas access Policy 0070 documents to check what others are doing in terms of anonymization...”

• “Privacy is a secondary concern for Patients participating in Clinical Studies...”

• “Data must be available to ensure transparency of the information flow regardless of whether patients actually access the data themselves...”

• “Rare disease patients are concerned about Privacy as disease genetic roots may also affect their relatives...”

• “All data in CSR must be available in order to conduct efficient reviews”

• “Policy 0070 is not adapted for rare diseases”

• “It is more about transparency than utility...the submission documents are available to the public...”

• “What is Policy 0070, I cannot remember, we sent comments...”
Agenda

• Approach & Methodology
• Insights from Policy 0043
• Data Consumer Scenarios
• Data Consumer Needs of
  – Researchers
  – Patients & Patient/Consumer Organizations
• Limitations & Conclusions
• **Policy 0070 “Phase 1” Guidance:**
  – 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

• **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.”

***: OECD: Organization for Economic Co-operation and Development
Questions:
- “Who are/will be the Data Consumers of Policy 0070 CSRs?”
- “How can anonymized CSRs be used by legitimate Data Consumers?”
- “What data entities are at stake and must be preserved in priority?”
- “Is there a group of Data Consumers whose needs should be prioritized?”

Methodology:
- Review of academic literature based on industry CSRs
- Review of Policy 0070 comments received during 2013 public consultation [1]
  - NOTE: “Publication and access to clinical-trial data” of 24. June 2013 has both CSRs and IPD in scope
- Conduct of interviews across selected potential data consumers
- Input from PhUSE Data Transparency WG

Out-of-Scope:
- Analysis of “non-legitimate” Data Consumers or “Plausible Attackers”
  - DH09 – “Plausible Adversaries in Re-Identification Risk Assessment” by Lukasz Kniola – explores this topic – Wednesday 11. October, 10:30-11:00 – [2]
### Insights from Policy 0043

**Affiliation (per initial requests and appeals in 2016)**

<table>
<thead>
<tr>
<th>Affiliation</th>
<th>Number of requests received</th>
<th>In %</th>
<th>Number of pages released</th>
<th>In %</th>
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<tr>
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<td>0.12</td>
<td>139</td>
<td>0.04</td>
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<td>Regulator outside EU</td>
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<td>0.24</td>
<td>0</td>
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<td>EU NCA</td>
<td>4</td>
<td>0.49</td>
<td>103</td>
<td>0.03</td>
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<tr>
<td>Patients or Consumer</td>
<td>55</td>
<td>6.68</td>
<td>36388</td>
<td>9.55</td>
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<td>Healthcare professional</td>
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<td>2.92</td>
<td>16294</td>
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<td>Academia/Research institute</td>
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<td>Legal</td>
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<td>Media</td>
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<td>Pharmaceutical industry</td>
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<td>54.56</td>
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<td>Consultant</td>
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<td>10.45</td>
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<td>3.42</td>
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<tr>
<td>Other</td>
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<td>0.00</td>
<td>1542</td>
<td>0.40</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>823</strong></td>
<td><strong>100</strong></td>
<td><strong>380,911</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Source: Annexes to the annual report of the European Medicines Agency 2016 [3]
Data Consumers – Scenario 1
Simplified “Skill-based” Scenario

Anonymized CSR

Education & Standards
Other Pharma
Researchers

Input to Clinical Trials & Programs

Clinical Practitioners
Regulators
Patient Organizations

Drug Repurposing
Early Termination
Other...

Reviews & Publications

Patients

Drug Repurposing
Early Termination
Other...
Data Consumers - Scenario 2
Versatile use across Data Consumers

Researchers
Other Pharma
Clinical Practitioners
Patient Organizations
“Expert” Patients

Anonymized CSR

Better Understanding of Disease
Reviews & Publications
Better Understanding of Treatments
Clinical Trial Participation
Input to Clinical Trials & Program
Input to HTA Work

“Non-Expert” Patients
“Clinical Trial” Patients
“Expert” Patients
Data Consumer Needs - Researchers
Awareness & Barriers

• **Survey Conducted among Cochrane authors** between June and September 2016 on the theme “How is academia using the 0043/0070 data?” [3]
  
  – **156 Respondents**
    • Only 10% have used or requested regulatory data
      – 80% of these respondents believe regulatory data must be part of a review
    • 5% considered using regulatory data
      – 32% of these respondents believe regulatory data must be part of a review
    • 85% have not considered using regulatory data
      – 38% of these respondents believe regulatory data must be part of a review
  
  – 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
• An “Interim guidance on the inclusion of Clinical Study Reports and other regulatory documents in Cochrane Reviews” is being developed.

• We conducted interviews with researchers who have published academic work using CSRs.

• All experience and published research we could collect feedback on at this stage is based on “non-Policy 0070” CSRs where little anonymization was applied.
Data Consumer Needs - Researchers
How to get data prior to Policy 0070?

Documents
- Policy 0043 Requests
- Requests directly to Sponsors
- Journal Articles

Registries
- Public Registries
- Sponsors’ Online Registries

IPD
- Research Requests to Sponsors providing access to IPD through portals or other
<table>
<thead>
<tr>
<th>Article</th>
<th>Data Source</th>
<th>Methods</th>
<th>Article Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine - Maund 2014</td>
<td>9 CSRs inc. protocols as appendices obtained from the EMA. Journal articles Clinicaltrials.gov and Eli Lilly's online clinical trial registry were searched for trial results.</td>
<td>Data extraction, Data comparison, AE counts, Method comparison</td>
<td>“Clinical study reports contained extensive data on major harms that were unavailable in journal articles and in trial registry reports. There were inconsistencies between protocols and clinical study reports and within clinical study reports.”</td>
</tr>
<tr>
<td>Gabapentin - Vedula 2009</td>
<td>20 CSRs available from Pfizer of which 12 were published in journals</td>
<td>Data extraction, Data comparison, Method comparison</td>
<td>“Selective outcome reporting for trials of off-label use of gabapentin. This practice threatens the validity of evidence for the effectiveness of off-label interventions.”</td>
</tr>
<tr>
<td>Reboxetine - Eyding 2010</td>
<td>Bibliographic databases, clinical trial registries, trial results databases, and regulatory authority websites up until February 2009, as well as unpublished data from the manufacturer of reboxetine (Pfizer)</td>
<td>Data extraction, Data comparison, Meta-analysis, Method comparison</td>
<td>“Reboxetine is, overall, an ineffective and potentially harmful antidepressant. Published evidence is affected by publication bias.”</td>
</tr>
<tr>
<td>Lamotrigine versus carbamazepine – Nolan, 2016</td>
<td>We included 13 studies in this review. Individual participant data were available for 2572 participants out of 3394 eligible individuals from nine out of 13 trials: 78% of the potential data.</td>
<td>Meta-analysis</td>
<td>“Lamotrigine was significantly less likely to be withdrawn than carbamazepine but the results for time to first seizure suggested that carbamazepine may be superior in terms of seizure control. A choice between these first-line treatments must be made with careful consideration. We recommend that future trials should be designed to the highest quality possible with consideration of masking, choice of population, classification of seizure type, duration of follow-up, choice of outcomes and analysis, and presentation of results.”</td>
</tr>
<tr>
<td>Tamiflu - Jefferson 2014</td>
<td>89 Clinical study reports from EMA and Roche (23 were used), trial registries, electronic databases, regulatory archives, and correspondence with manufacturers.</td>
<td>Data extraction, AE recoding, Meta-analysis, Method comparison</td>
<td>“The trade-off between benefits and harms should be born in mind when making decisions to use oseltamivir for treatment, prophylaxis, or stockpiling.”</td>
</tr>
<tr>
<td>Paroxetine and Imipramine - Le Noury 2015</td>
<td>Reanalyse SmithKline Beecham’s Study 329 using CSR publically available on the GSK’s website and IPD on SAS CTDT including de-identified CRFs.</td>
<td>AE recoding, Re-analysis using IPD</td>
<td>“Neither paroxetine nor high dose imipramine showed efficacy for major depression in adolescents, and there was an increase in harms with both drugs.”</td>
</tr>
<tr>
<td>Orlistat - Schroll 2016</td>
<td>7 Publications and corresponding study CSRs provided by EMA</td>
<td>Data extraction, Data Comparison, AE counts</td>
<td>“We identified important disparities in the reporting of adverse events between protocols, clinical study reports, and published papers. Reports of these trials seemed to have systematically understated adverse events.”</td>
</tr>
</tbody>
</table>
In summary, all of the authors stated that their analyses would not have been possible without access to CSRs.

None of the authors raised any specific concerns about anonymized or redacted CSRs (in line with EMA policy 0070).

All of the authors stated that some or all of their analyses or research would not have been possible if narratives and/or appendices (with participant listings) were removed from anonymised CSRs under EMA policy 0070.

One author stated that: “Anonymized CSRs are ok, but the current EMA policy redacts important information about when the adverse events appeared as well as what they were...”
Data Consumer Needs - Researchers
What Analyses & Tasks to carry out using CSRs?

<table>
<thead>
<tr>
<th>Purpose</th>
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<tbody>
<tr>
<td>Check for publication bias</td>
</tr>
<tr>
<td>Check for reporting bias</td>
</tr>
<tr>
<td>Systematic reviews</td>
</tr>
<tr>
<td>Novel analysis</td>
</tr>
</tbody>
</table>

- Data Extraction from documents & QC
- Method and analyses Comparison
- Data Comparison with Registries and Manuscripts
- Re-Analysis (If patients listings or IPD available)
- AE Counts & Coding Verification (or re-coding)
- Meta-analyses using any endpoints data
Main Findings from Policy 0070 2013 public consultation comments review [1]:

- The initiative is received very positively
- Concerns around current **Informed Consent** forms that patients signed
- Concerns around possibility of **wrong secondary analyses**
- They do not believe there are **CCI in clinical trials data**
- **Patients privacy is of utmost importance**
- ”**Expert Patients**” (in e.g. rare or chronic diseases) may be able to consume complex and dense data from CSRs.
What can Patients Organizations do with Regulatory Data?

- **Use in HTA work**
  CSR data can be used to build stronger cases in HTA work and provide stronger arguments towards investment and research.

- **Understand better disease, treatments and provide input to clinical trials**
  - **Placebo data** can be used to understand better the disease from this controlled and carefully monitored population.
  - CSR data can be used to support **Community Advisory Board** discussions.
    - Patient representatives interacting with sponsor on methods, ethics and logistics etc.

- **Drug Repurposing**
  - In the case of drug repurposing (from e.g. a frequent to a rare disease area), having access to all previous data is of the utmost importance and would speed up the process.
Limitations

• The work presented is not based on surveys across a significant population of data consumers and only represent tendencies to explore further.

• Certain data consumers such as “Other Pharmas”, “Generics” or “Regulators” should be investigated further.

• This field is “merely a new born” and more experience from use and findings based on Policy 0070 data should be reviewed in the future.
Conclusions

- **Further guidance and education are required** to ensure a larger number of Data Consumers including Researchers are aware of and can utilize Policy 0070 data.

- **Using CSRs require time and expertise.** The Researchers community are probably the main Data Consumer to consider.

- **Overviews and Summaries** may be more accessible to e.g. Patients and Clinical Practitioners.

- Data from Policy 0043 indicates that the **Pharmaceutical Industry could also be an important Data Consumers** of Policy 0070 data.

- There may be **different opinions and trends across patients** and therapeutic areas participating in clinical trials with regards to **privacy**.

- **More efforts on preserving Subject IDs and Dates in an anonymized format** should be considered to enable as a minimum to follow patients through the narratives and relationships as well as distances between events.

- **Reported terms (free-text)** are also used for checking medDRA coding and subsequent re-analysis and should be considered for anonymization in the future.

- **PhUSE Data Transparency Working Group** is developing a **Data Utility Qualitative Scale** to evaluate Data Utility in Anonymized CSR according to Data Consumers’ needs.
References

• [1]: Overview of comments from stakeholders received as part of public consultation on EMA Policy 0070 of June 2013

• [2]: Kniola, Plausible Adversaries in Re-Identification Risk Assessment, PhUSE 2017 - DH09
  – Soon online...

• [3]: Jefferson, « EMA’s policy 0070: opportunities, challenges and measuring success » - DIA 2017, Glasgow
  – Slides not publicly available on DIA website

• [4]: Annexes to the annual report of the European Medicines Agency 2016, Annex 19
Thanks!

Jean-Marc Ferran
Consultant & Owner, Qualiance

Sarah Nevitt
Research Assistant, University of Liverpool