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

DH04

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EMA Objectives of Transparency

Objectives of transparency

Have all clinical trials been publicly registered?

Has the trial we are designing already been conducted? Were there problems with similar trials?

Is there a trial in which I could participate?

Can we review the data used to support the marketing authorisation?

What was the outcome of the trial I did participate in?

What is known about the medicine I am taking/prescribing?

What trials were the basis of the marketing authorisation, what were their results?

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

• Study Results Public Disclosure Overview

• EudraCT and ClinicalTrials.gov Processes

• Policy 0070 Anonymization Guidance Overview

• Conclusions
## Study Results Public Disclosure Overview

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Results</strong>&lt;br&gt;Effective SEP2008</td>
<td><strong>Study Results</strong>&lt;br&gt;Effective 20JUL14</td>
<td><strong>CSR</strong>&lt;br&gt;Effective 01JAN15</td>
<td><strong>IPD</strong>&lt;br&gt;Effective ???</td>
</tr>
<tr>
<td>Any Study part of an approved IND application</td>
<td>Any Study with sites in Europe (EEA) &amp; Studies in Children conducted outside EU but part of a PIP</td>
<td>Any Study part of a Centralized Marketing Authorization application</td>
<td></td>
</tr>
<tr>
<td>Inform public and trial participants on core Results</td>
<td>Inform public and trial participants on core Results</td>
<td>Understand conclusions</td>
<td>Conduct secondary-purpose analyses, review data or verify results</td>
</tr>
</tbody>
</table>
EudraCT and ClinicalTrials.gov Timelines

- **IND not approved at study completion**
  - LPLV
  - LPLV + 6/12 months
  - Approval + 30 days

- **IND approved at study completion, Pediatric study**
  - LPLV
  - LPLV + 6 months
  - LPLV + 12 months

- **IND approved at study completion, Adult study**
  - LPLV
  - LPLV + 6 months
  - LPLV + 12 months
EudraCT data on EU Clinical Data Register

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

- Trial Information
  - Purpose
- Subject Disposition
  - Patient Flow
- Baseline Characteristics
  - Baseline Characteristics
- End Points
  - Outcome Measures
- Serious AE
- Non-Serious AE
  - Other Events
- Serious AE
- Other Events
- More Information
- More Information
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Endpoint Summary

Primary: Proportion of Patients With Complete Response

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. Times to patient wakes up and is able to show any active reaction pos included all randomized patients who received the active study (evaluable patients). Following the intent-to-treat principle, arm according to their randomized treatment.

End point type: Primary

Number of subjects analyzed:
Units: percentage of patients

Reporting groups:
- Reporting group 1
  - Subjects analyzed: 132
  - Arithmetic mean: 3.2
  - Standard deviation: 1.83
- Reporting group 2
  - Subjects analyzed: 102
  - Arithmetic mean: 4.1
  - Standard deviation: 2.45

Subjects analysis sets:
No subject analysis sets have been specified.

Statistical analyses:
No statistical analyses have been specified.

Arm Reporting Groups:
ArmId="Arm-29136" id="EndPointArmReportingGroup-148954"
- Countable Values:
- Tendency Values:
  - Value: 72.2
- Dispersion Values:
  - Value: 73.3
  - HighRange Value: 80.5

Qualiance
# Endpoint Statistical Analysis

<table>
<thead>
<tr>
<th>Statistical analysis title</th>
<th>Comparison of Proportion of Patients With Complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical analysis description</td>
<td>The null hypothesis (H0) was stated as: $H_0: \text{CR 0-24 hr palonosetron} - \text{CR 0-24 hr ondansetron} &lt; -10%$</td>
</tr>
<tr>
<td></td>
<td>The alternative hypothesis (H1) was stated as: $H_1: \text{CR 0-24 hr palonosetron} - \text{CR 0-24 hr ondansetron} \geq -10%$</td>
</tr>
<tr>
<td></td>
<td>A power of 80% was used for sample size computation.</td>
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<tr>
<td>Comparison groups</td>
<td>Palonosetron and Placebo to Ondansetron v Ondansetron and Placebo to Palonosetron</td>
</tr>
<tr>
<td>Number of subjects included in analysis</td>
<td>661</td>
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<tr>
<td>Analysis specification</td>
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<tr>
<td>Analysis type</td>
<td>non-inferiority [1]</td>
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<tr>
<td>Method</td>
<td></td>
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<tr>
<td>Parameter type</td>
<td>Risk difference (RD)</td>
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<tr>
<td>Point estimate</td>
<td>-4.4</td>
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<tr>
<td>Confidence interval</td>
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<tr>
<td>level</td>
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<tr>
<td>sides</td>
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<tr>
<td>lower limit</td>
<td>-10.5</td>
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<tr>
<td>upper limit</td>
<td>1.7</td>
</tr>
</tbody>
</table>

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

---

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    The null hypothesis (H0) was stated as:
    $H_0: \text{CR 0-24 hr palonosetron} - \text{CR 0-24 hr ondansetron} \leq -10\%$
    The alternative hypothesis (H1) was stated as:
    $H_1: \text{CR 0-24 hr palonosetron} - \text{CR 0-24 hr ondansetron} \geq -10\%$
    A power of 80% was used for sample size computation.
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    For the primary efficacy analysis, the confidence interval (CI) was built on the FAS.
    The non-inferiority margin was -10%.
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  <variabilityEstimate/>
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Future Public Disclosure Process

- Input
  - Study Metadata
  - Analysis Results Metadata
  - ADaM

- SAS Code
  - Summary Results

- Output
  - Trial Info. Reports
  - AE Summary Report
  - Subject Disposition Reports
  - Baseline Character. Reports
  - End Points Reports
  - Public Disclosure XML

- CSR
  - More Information
  - Verify other uploaded sections

- ClinicalTrials.gov
- EudraCT

- Public Disclosure Management System

- More Information:
  - Trial Information
  - Subject Disposition
  - Baseline Characteristics
  - End points
  - Adverse Events

- Verification of other uploaded sections
Recent Initiatives on Harmonization

**EU portal and database – Data standardisation**

**WHO**

WHO ICTRP standard will be fully met, and data provided to the ICTRP by the EU database

**NIH**

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

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

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

Source: CTR Update, Paul Houston, CDISC European Interchange, Vienna, 28 April 2016
# Policy 0070 Part A & Part B, Data Transparency and more...

<table>
<thead>
<tr>
<th>Sponsors Publications</th>
<th>Sponsors Data Transparency Initiatives</th>
<th>Policy 0070 Part A</th>
<th>Policy 0070 Part B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on Pseudomized IPD Forever...</td>
<td>Anonymized IPD Started in 2013 with GSK</td>
<td>Anonymized CSR Portal go-live SEP2016</td>
<td>Anonymized IPD Effective ???</td>
</tr>
<tr>
<td>Sponsors’ choice</td>
<td>Any Study related to an approved application in EU &amp; US</td>
<td>Any Study part of a Centralized Marketing Authorization application</td>
<td>???</td>
</tr>
<tr>
<td>No Anonymization</td>
<td>Safe-Harbor or Average Risk Metrics</td>
<td>Qualitative or Maximum Risk Metrics</td>
<td>Average or Maximum Risk Metrics?</td>
</tr>
</tbody>
</table>
Guidance
2. March 2016

Narratives must be anonymized

Recall that the PhUSE DeID standard is recommended. Focus on Data Utility must be demonstrated, and Anonymization Report is made public.

Sponsor remains Data Controller. Available Public Data and Technology may evolve.

Conclusions must be similar.

Listings not in scope of Part A.
Where to Measure the Risk?

- Restricted
- Public Domain

(A anonymized) SDTM/ADaM

Risk!

(A anonymized) CSR

(A anonymized) Publication 1

(A anonymized) Publication 2
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...
Thanks!

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