Data Transparency: Crystal Clear to Everyone?

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What I and will not cover today...

• No
  ▪ Industry can do better
  ▪ Securing greater public trust in industry and the EU regulatory process is necessary
  ▪ EMA data transparency policy will go live 1\textsuperscript{st} Jan 2014
  ▪ Critical data protection, IC and CCI issues

• Yes
  ▪ Statistical, scientific standards in the evaluation of trial data pre- and post- licensure
  ▪ How best to improve the transparency of EMAs regulatory decision making
Content

• Background
  ▪ FDA, EMA and Industry positions
• Statistical standards in the analysis of CT data
  ▪ Pre-licensure and post data release
• Transparency of the regulatory review process
• A couple of proposals
• Summary
FDA Request For Comments, June 2013

• Propose to make available de-identified and masked data
• Access to data that have ‘research value’
  ▪ Safeguard the privacy interests of patients
  ▪ Protect the commercial investments of sponsors
• Not CSRs and will not make available business-related confidential commercial information
EMA’s Position, June 2013

- **Enabling public scrutiny and secondary analysis of CTs**
  - Access to CT data in an analysable format **will:**
    - benefit public health
    - make drug development more efficient
    - enable the wider scientific community to make use of high-quality CT data to develop new knowledge in the interest of public health
  - Independent replication of CT data analysis is a legitimate scientific and societal goal.
    - Access to CT data will enable third parties to verify the regulatory authority's position and challenge where appropriate
Industry Position, July 2013

• Data release via research proposal submitted to an independent review board to vet scientific validity, protect patient confidentiality and CCI
  ▪ Proposal = data requested, hypothesis to be tested, rationale, analysis plan, publication plan, qualifications of requester, statement of conflict of interest, source of funding

• Continued commitment to publish CT data and make CSR synopses available
  ▪ Full CSRs by process above
Little debate that access to CT data offers potential to provide new and important insights into patient health

- Identification and validation of new endpoints to better assess the utility of medical interventions
- Identification of patient phenotypes more likely to benefit from treatment
- Replication of critical trial results
  - E.g. ‘statistical jujitsu’¹, Scheen et al DPP4 non-inferiority²
- Examination of potential safety issues and possible class effects
- Characterisation of the natural history of disease
- Characterisation of rare events

- However raw data ≠ insight or learning
- This comes from the process of valid, unbiased data analysis and interpretation

In support of licensure, EMA (& FDA) require the application of high statistical standards and rigor

- Data analysis by professional statisticians
- *a priori* provision of a statistical analysis plan detailing, objectives, hypotheses, endpoints, analyses and methodology for inference
- Multiple scientific regulatory guidance pertaining to trial design and analyses
  - ICH, PtC, Reflection Papers, Guidance to Industry
- Drug developers held (rightly) to these high standards
- Efficacy claims based on post-hoc data, driven analyses or subset analyses of failed trials very seldom, if ever, accepted
  - Legitimate concerns regarding bias and Type I error inflation
EMA Policy: ‘controlled access’ to data where there are data protection concerns

- Requester must agree to a legally binding data-sharing agreement
  - Conduct analyses only in interest of public health
  - Submit an ‘exhaustive and detailed list’ of aims ‘though not necessarily a statistical analysis plan’
EMA Policy: ‘controlled access’ to data where there are data protection concerns

• Before access the requester will be:
  ▪ Made aware the Agency’s expectations relating to good analysis and transparency
    • requesters are advised to read the document, but no legal obligation resulting from it
  ▪ Given the opportunity to upload a statistical analysis plan (SAP)
    • the Agency considers preparation and uploading of a detailed protocol/statistical analysis plan before data access of utmost importance, to ensure the credibility of subsequent results;
  ▪ However, the requester may decline to upload a SAP
  ▪ Granting of data access is not influenced by the requester's choice to upload or not
EMA Policy: ‘controlled access’ to data where there are data protection concerns

- The Agency will NOT, at the time of allowing access:
  - Judge the requester's professional competence to conduct analyses
  - Judge the requester's statistical analysis plan (if uploaded)
EMA Policy: Addressing the consequences of inappropriate secondary data analysis

• “The Agency cannot guarantee that all secondary data analyses that are enabled by the policy will be conducted and reported to the highest possible scientific standard”
  ▪ Really?

• “However, the Agency will put in place measures to ensure the best-possible protection of public health (and regulatory decisions) against claims resulting from inappropriate analyses.”
  ▪ What measures?
If you torture the data, it will confess

• “Yes, the overall result was p=NS, but in the subgroup with the longest tongues, there was a benefit, p<0.05…”
Double Standard of Scientific Rigor?

• To protect public interest, should not the same high statistical and scientific standards apply to the analysis and evaluation of EMA released CT data both pre-licensure and post release?

• Do the EMA have a duty of care to put into place measures to protect the public from inappropriate post-hoc, data drive data analyses resulting from their own data release policy?
Flight Safety....

• Airline industry is heavily regulated (FAA, EASA)
• Extensive processes, procedures, guidance and inspection in the build of a new aircraft
• If, after certification of airworthiness and safety of a new aircraft, regulators were to allow planes to fly without the same on-going standard of rigor of oversight and re-validation of safety, would you be happy to fly...?
• ....And, further, what if the person flying the plane was not a qualified pilot?
Proton pump inhibitor use and risk of adverse cardiovascular events in aspirin treated patients with first time myocardial infarction: nationwide propensity score matched study

Table 2 | Association between treatment with proton pump inhibitors and risk of adverse cardiovascular outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events during follow-up</th>
<th>Propensity score matched Cox proportional hazards regression analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients not treated with PPIs</td>
<td>Patients treated with PPIs</td>
<td>1.61 (1.45 to 1.79)</td>
</tr>
<tr>
<td>Cardiovascular death, myocardial infarction, or stroke</td>
<td>2378 (15.2)</td>
<td>987 (22.9)</td>
<td></td>
</tr>
<tr>
<td>All cause death</td>
<td>1607 (10.3)</td>
<td>686 (15.9)</td>
<td>2.38 (2.12 to 2.67)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1328 (8.5)</td>
<td>540 (12.5)</td>
<td>2.19 (1.92 to 2.49)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1110 (7.1)</td>
<td>497 (11.5)</td>
<td>1.33 (1.13 to 1.56)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1207 (7.7)</td>
<td>338 (7.9)</td>
<td>1.20 (0.99 to 1.46)</td>
</tr>
</tbody>
</table>

PPIs = proton pump inhibitors.
Use of proton pump inhibitors was included as time to dependent covariate.

Fig 2 | Propensity score matched Kaplan-Meier analysis of risk of cardiovascular death, myocardial infarction, or stroke
• N=3873 randomised double blind trial of PPI vs placebo on the back of aspirin+clopidigrel (standard dual anti-platelet therapy).
• Primary safety endpoint CV death, MI, coronary revascularization, or ischemic stroke.
• Events adjudicated by independent committee of cardiologists blind to treatment assignment.
• Relative risk, PPI:placebo, 0.99 CI (0.68, 1.44) p = 0.96.
Perils of Comparative Effectiveness Research

“...exercise and many drug interventions are often potentially similar in terms of their mortality benefits in the secondary prevention of coronary heart disease, rehabilitation after stroke, treatment of heart failure, and prevention of diabetes”

Fig 2 Network of available comparisons between exercise and individual drug interventions in coronary heart disease, stroke, heart failure, and prediabetes. Size of node is proportional to number of trial participants, and thickness of line connecting nodes is proportional to number of participants randomised in trials directly comparing the two treatments. ACE=angiotensin converting enzyme
Perils of Comparative Effectiveness Research

• Indirect comparisons fraught with difficulties and inherent bias that cannot be fully addressed methodologically
• EMA have stated data transparency will enable (more) CER
• Yet multiple EMA (& FDA) guidelines govern the simple case of indirectly comparing A v C via randomised trials of A v B and B v C
  ▪ Constancy, assay sensitivity, temporal effects, similarity of populations and trial conditions, etc... = bias
• Why support a different standard for the more complex CER given the impact they can have on public health and health care utilisation decisions?
Cholesterol lowering agent

- Similar distributions
- $p=0.31$ by t-test
- Conclusion of no difference seems reasonable

courtesy of S. Senn
What I did not tell you

• This is *not* a randomised trial
• Patients given the intervention *if* they had high cholesterol at baseline, otherwise they received control

• Plotting outcome vs baseline...

• Analysis adjusting for baseline gives p<0.001
The Need for a Common Scientific Standard, Pre- and Post- Data Release

• Non-randomised comparisons are invariably prone to bias, no matter how sophisticated the statistical methodology employed
  ▪ Even worse for after-the-fact, data-driven, post-hoc analyses
  ▪ If such analyses are not suitable to support licensing decisions, then why are they acceptable post-licensure?

• Critical need for an upfront statistical thinking and analysis plan if public not to be flooded by confusing and inappropriate results
  ▪ EMA can help to increase scientific rigor by asking Requesters to adhere to the same standards EMA themselves set pre-licensure
EMA: “The Agency will put in place measures to ensure the best-possible protection of public health (and regulatory decisions) against claims resulting from inappropriate analyses”

A Statistical Proposal:

• The same professional standards should be applied by EMA for analyses performed post-release as was applied pre-release
• Requestors required to provide a Scientific rationale outlining intent of and hypothesis behind data request
• Requestors required to provide a pre-specified SAP
• Analyses performed by qualified personnel
• A governance process, including arbitration, in cases where attempt to replicate results gives rise to relevantly different conclusions from original analyses
• All post-release analyses should be published in context
EMA: “Access to CT data will enable third parties to verify the regulatory authority's positions and challenge them where appropriate”

- Is providing data to third parties the best way to verify the EMA’s decision making?
- Other examples where scientific judgements of paid public service professionals are validated by the community?

- A Second Statistical Proposal: Employ the US model
  - Employ professional statisticians within EMA to independently analyse CT data submitted in support of a license application
  - Engage a Panel of Academic Experts to review the trial data and hold Open Public Hearings where they can vote on licensure

- Arguably, this will bring greater public accountability and transparency to EMA’s decision making process than simply releasing CT data in fashion proposed by new policy
Summary

• Data transparency is here and offers real potential to enhance patient health

• Making trial data available is not, *per se*, the issue – but how, and to whom, is

• A critical feature of the new policy is the absence of a common standard for pre- and post-release analysis of CT data

• EMA have a duty to the public to ensure rigor throughout the process in order to avoid a surge in post-hoc analyses that serve not inform and enlighten, but rather to confuse and concern

• Anything less cannot be said with certainty to be in the public good

• As for the validity and transparency of EMAs decision making in the drug approval process, why not open this up to public scrutiny by introducing a US style Open Public Advisory Committee Process?