# Practical Benefit Risk Assessment

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# Disclaimer

Note the views expressed in this presentation are my own and are not necessarily shared by my previous employer, the MHRA, or my new employer, AstraZeneca.

# Alternative titles

- Reflections on 16 years and 11 months of assessing licensing applications. How to decide whether or not to recommend a drug is licensed.
- Benefit risk assessment for decision making.
- Opportunities for statisticians to improve regulatory decision making.

# Statistical Assessment of Efficacy – historical perspective

- Initially assessment was largely focussed on the results of the pivotal trials and whether sufficient evidence of efficacy had been provided. If so, one of the 3 licensing hurdles of quality, safety and efficacy had been achieved.
- Later there were examples when a discussion of the trade-off between efficacy and safety was required. I will give an example of in this talk.

# Missing Data

- Revision of Missing Data guideline highlighted that some people thought statisticians in regulatory authorities should focus on statistical assessment of efficacy and not consider statistical assessment of benefit risk.
- As a regulator my main consideration was to protect public health. I could not do this by looking at efficacy alone and not taking into account safety.

# Example – Angiox (bivalirudin)

- Angiox is indicated as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.
- Angiox is also indicated for the treatment of adult patients with unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) planned for urgent or early intervention.
- Angiox should be administered with acetylsalicylic acid and clopidogrel.

# Angiox SmPC

| **Endpoint** | **Intent-to-treat** | | **Per-protocol** | |
|---|---|---|---|---|
| | **bivalirudin (N=2,994) %** | **heparin + GP IIb/IIIa inhibitor (N=3,008) %** | **bivalirudin (N=2,902) %** | **heparin + GP IIb/IIIa inhibitor (N=2,882) %** |
| Quadruple endpoint | 9.2 | 10.0 | 9.2 | 10.0 |
| Triple endpoint* | 7.6 | 7.1 | 7.8 | 7.1 |
| Components: | | | | |
| Death | 0.2 | 0.4 | 0.2 | 0.4 |
| Myocardial Infarction | 7.0 | 6.2 | 7.1 | 6.4 |
| Major bleeding** (based on non-TIMI criteria - see section 4.8) | 2.4 | 4.1 | 2.2 | 4.0 |
| Urgent revascularisation | 1.2 | 1.4 | 1.2 | 1.3 |

# Fairly simple example of benefit risk decision?

- But at CHMP still lots of discussion on this and other similar examples.
  - Comments such as – it is inappropriate to mix up efficacy and safety endpoints. So when a net clinical benefit endpoint was provided the usefulness of this endpoint was a contentious issue.

# Of course the situation is more complicated

- For example what part does time play in this example?
  - i.e. This treatment is given short term after an MI. So maybe the risk of stroke is increased slightly during treatment and then returns to background rate shortly after treatment stopped but rate of MI's is reduced for a longer period of time. Was the study long enough to fully capture the benefit of treatment? Or to evaluate when the benefit wore off.
- What about severity of event?
  - Some MI's are "silent" i.e. you would only know you have had it if it occurred in the clinical trial and appropriate measurements taken.
  - Some strokes are completely life changing, others can be less severe and sometimes subjects can make a full or near full recovery
- So some of the apparent benefits or risks in the table may be less relevant to a patient.

# Quantitative Benefit Risk at time of Licensing

- CHMP looked at this and does not at this time use it to make decisions.
- What needs to be done to make the decision making more quantitative?

# Estimands and Subgroups

- We heard alot about estimands yesterday.
- They can also play a role in Benefit Risk decision making
  - CHMP may decide to licence in only a subgroup or licence a treatment for short term use even though it was given long term in a study. In other words, they change the Estimand after evaluation of the dossier.
  - This also relates to the Subgroup guideline. This guideline is aiming at giving a more rigorous framework to aid regulatory decision making. More research is needed into this area to assist CHMP in deciding when it is appropriate to licence in a subgroup.

# Opportunities for Statisticians

- Enormous
  - We offer a unique skill to aid the interpretation of clinical data
  - Still under used in decision making
  - Currently 1 methodological expert on CHMP, it would be great to have another one who maybe specialised in Benefit Risk decision making

# Reflections on being a regulatory statistician

- Interesting and varied list of projects to work on
- Unique opportunity to see what Company's are proposing through scientific advice and later to assess data that comes from subsequent clinical trial programme