Hot Topics In Pharmaceutical Statistics

Comments/observations from PSI and DIA

Annie Solterbeck

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DIA Session

- What are the most pressing problems facing statisticians in drug development today?
  - Steve Ruberg, Eli Lilly
  - Laura Meyerson, Biogen Idec
  - Andrew Garrett, Quintiles
  - Gary Koch, UNC

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The DIA Session

- ***Steve Ruberg***
  - **Tailoring therapeutics – subgroup identification**
  - **Bayesian statistics**
  - **Non-inferiority**
- ***Laura Meyeson***
  - **Missing data**
  - Benefit risk assessment
  - Use of biomarkers and surrogate markers
- ***Andrew Garrett***
  - Subgroup analysis
    - Within patient variability
  - Non-inferiority
  - **Accessing data during the course of the study**

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PSI Session

- Steven Julious
  - Non-inferiority margins
- Fabrice Bancken
  - Benefit risk analysis
- Boessen Ruud
  - Optimizing trial design in pharmacogenetics research
- Plenary – James Matcham
  - Best practice guidelines for industry statisticians

Topics for Today

- Subgroups
- Bayesian/Non-inferiority
- Risk benefit assessment
- Access to data during trial
- Best practice guidelines

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Subgroups

Subgroups

- Tailoring therapeutics – subgroup identification
- All drugs approved has a type I error
- Propose subgroup identification
- “Disciplined subgroup search”
- Merge of data mining with disciplined type I error control
- Type I error control and honest estimation of treatment effect
- Pre-specification of variables of interest, declaring biological plausibility *a priori*

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Why do Subgroup Analyses?

- Pre-planned
- Check internal consistency ie assuming treatment effect is homogeneous
  - Risk of false negative/positive
- Post-hoc
  - Improve risk benefit
  - Rescue a failed trial
- Interaction tests
- For BR look for consistency – forest plot
- Need pharmacological justification

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Bayesian Statistics and Non-inferiority

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Bayesian Statistics

- How and where can we use Bayesian?
- Steve suggest we start with non-inferiority
- Here we are trying to do 2 comparisons:
  - Non-inferiority active vs control
  - Indirect comparison of active vs control from NI with control effect from a MA of historical trials
- Use a Bayesian Network meta-analysis or indirect comparison methods?
- I.e. put in one analysis
- Rather than MA of historical then arbitrary setting of NI margin and second stage analysis of NI trial

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Benefit Risk Assessment

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Benefit Risk

- How to assess benefit risk?
- Effective drug with rare but potentially fatal adverse effect – how do you quantify benefit-risk in this scenario
- E.g. Drug for MS which enables patients to walk, BUT risk of seizure
- PSI meeting Richard Nixon PhRMA framework BRAT – illustrate with Tysabri
  - Structured transparent framework and methodology for benefit-risk assessment
- DIA had a complete session on BR – illustrate with triptans

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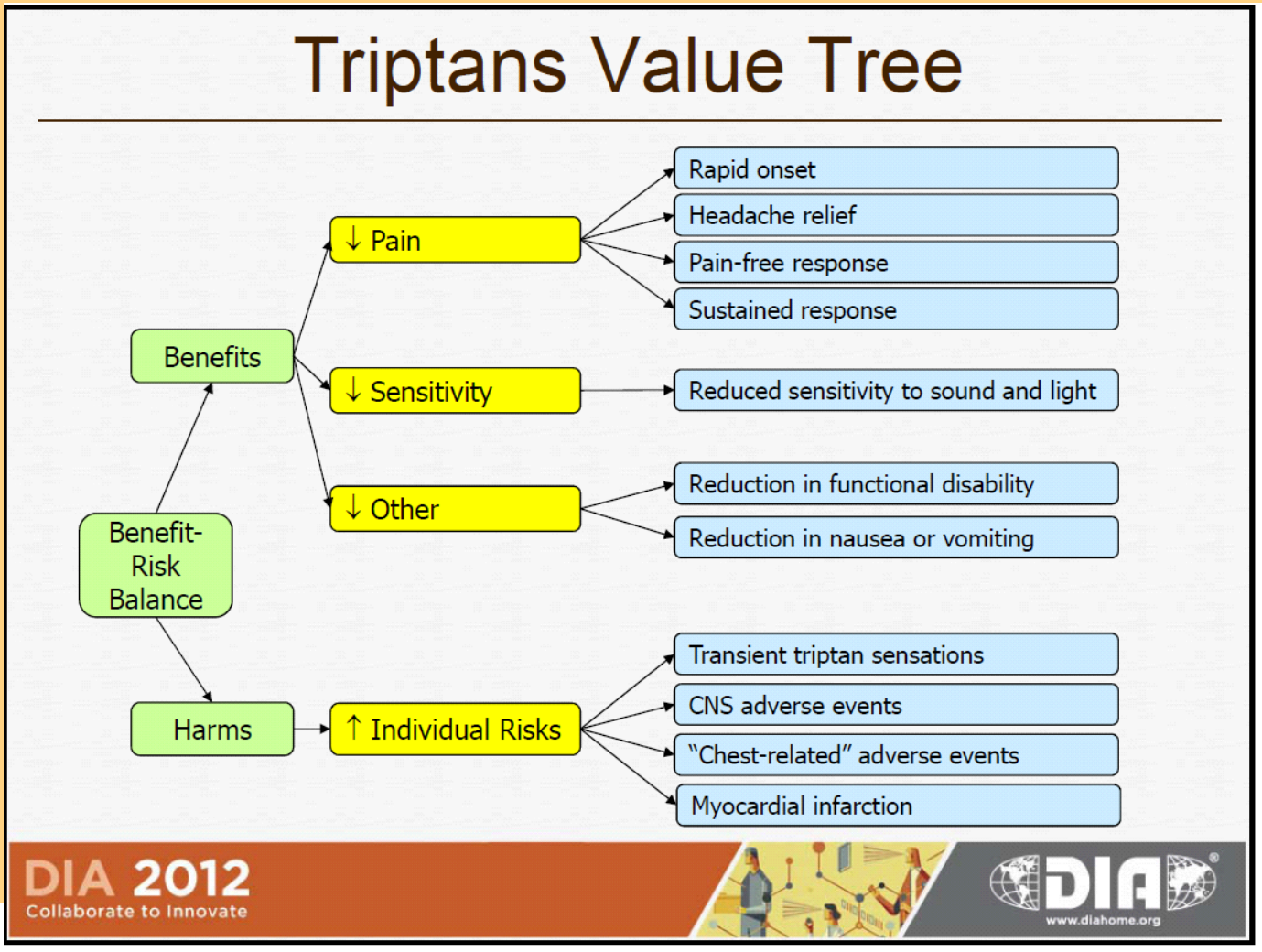
Benefit Risk

- Area of intense work
- Several working groups and guidelines
- Integration of:
  - What can happen – outcomes
    - Positive and negative
  - How often - rates and uncertainty
  - Consequences - weights

BRAD Framework

- Step 1 – define the question
  - What drug
  - What comparator
  - Who is making the decision
  - Decide the timeframe
- Triptans for acute migraine
- Low risk of CV events including MI
- NSAID or placebo as comparator

Step 2 Draw a Value Tree



What Next?

- Step 3 – extract the data
- Step 4 – fine tune the tree
- Step 5 – assess outcome importance and apply a weighting system
  - In many cases not formal
  - Some decisions difficult so need a weighting scheme
    - MCDA, Conjoint
- Step 6 – display results e.g. a waterfall plot

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