Best Practice in Modelling and Simulation

Example: Modelling a Phase 3 trial with treatment selection

Chris Jennison

EFPSI Webinar

4 October, 2016

A Phase 3 Clinical Trial

Proposed Design

- 2 versions of a new treatment are to be compared against a control treatment.
- Initially, patients will be randomised between all 3 treatments.
- At an interim analysis, one version of the new treatment will be selected.
- After this analysis, patients will be randomised between the selected version of the new treatment and the control.
- All the data will be used in the final analysis.

A Phase 3 Clinical Trial

Proposed Analysis

- There are two null hypotheses,

  H_{01}: New treatment 1 is no better than control,

  H_{02}: New treatment 2 is no better than control.

- A *closed testing procedure* will be used in order to control the *family-wise type I error rate* at level α.

  This requires level α tests of H_{01}, of H_{02} ,and of the intersection hypothesis $H_{01} \cap H_{02}$.

A Phase 3 Clinical Trial

Proposed Analysis

- The closed testing procedure can reject H_{01} overall if both level α tests reject H_{01} and $H_{01} \cap H_{02}$ (and similarly for H_{02}).
- Each of the three level α hypothesis tests will apply a *combination test* to the two sets of data from before and after the interim analysis.
- You are provided with a document giving further explanation of closed testing procedures and combination tests.

You are asked to:

- Understand the design and be prepared to **explain** it to various parties − you may wish to use simulations when doing this.
- Demonstrate that the proposed design is **valid**, in particular, that it protects the family-wise type I error rate.
- Demonstrate that the proposed design is **worthwhile**.
- Make choices within the definitions of closed testing procedure and combination test to **optimise the design**.
- **Provide software** to be used when the Statistical Analysis Plan is implemented.

Your audiences include:

- The trial team,
- The internal governance team and independent Data Monitoring Committee,
- Regulators,
- Readers of the methodology paper that you will write.

What are the important points to address in order for you to achieve *Best Practice* in this project?