Best Practice for Modelling and Simulation: EFSPI Special Interest Group proposal

Michael O'Kelly, member SIG for Modelling and Simulation.

Acknowledgements

- SIG members and PSI members who reviewed draft Best Practice proposal.
- SIG Chair Chris Campbell and Professor Chris Jennison provided the 2015 “Hackathon” that tested the Best Practice proposal
  - and the participants in the “Hackathon”, who provided fruitful input on the SIG Best Practice proposal, resulting in many improvements to the Best Practice document.
- Co-authors of Best Practice document Vlad Anisimov, Chris Campbell, Sinéad Hamilton.

O’Kelly M, Anisimov V, Campbell C, Hamilton S. Proposed Best Practice for Projects that Involve Modelling and Simulation. *Pharmaceutical Statistics* (accepted).

Best Practice, background

- November, 2011: European Federation of Pharmaceutical Industry Associations (EFPIA) and European Medicines Agency (EMA) organized workshop on Modelling and Simulation (M&S).
  - FDA attendee.
- Rob Hemmings of EMA called for a Best Practice document.
- EMA stressed that levels of pre-specification and justification of assumptions etc. for modelling and simulation would and should vary depending on “importance” of the project and its outcome in the process of approval.

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EMA: “Best practice” depends on importance of project

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA-EFPIA Modelling and Simulation Workshop

Good practices and next steps

Robert Hemmings, EMA

M&S good practices

- Different standards for different exercises (L,M,H)
- Standard should be high!
  - Assumptions (not only mathematical)
  - Model building rationale
  - Model testing
  - Inference
  - Sensitivity analyses / Challenge assumptions
  - Reporting
- Detail of regulatory response might be vary according to impact

QUINTILES

Hemmings R. M&S good practices and next steps. EMA-EFPIA Modelling and Simulation Workshop, 30 Nov – 1 Dec 2011, London. Available at https://www.youtube.com/watch?v=BSsaUmMuUAE&index=12&list=PL7K5dNgKnawY96v4FlgjTwUFAgUCXrRmw. Accessed 31 March 2016.

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PSI early discussions with EMA on Best Practice

- EMA suggestion: should cover
  1. Pre-specification
  2. Analysis
  3. Check of assumptions
  4. Presentation of results
  5. Sensitivity analysis
- Conclusions of simulations should be robust to missing data

EFSPI proposed Best Practice document

- EFSPI SIG Best Practice document
  - Authored by volunteers from the SIG
    - SIG members from variety of pharmaceutical companies.
    - All authors of the Best Practice document were from contract research organizations.
    - Agreed to be adopted by Board of PSI.

EFSPI Modelling and simulation SIG Best Practice document

- Defines modelling and simulation.
  - Tricky – e.g., what's the difference between prediction and simulation?
- Declares its scope to be ***all*** uses of modelling and simulation.
  - Controversial: can same Best Practice cover use of modelling and simulation in pharmacometrics and in simulating the running of a clinical trial?
- When should we use modelling and simulation (vs., say, employing a closed-form solution)?
- Heart of Best Practice: the specification of the project.
  - EFSPI proposal names key elements of a specification.
  - Important: allows flexibility in what elements may be included and in level of detail provided.
  - Best Practice requires the plan to justify omission of elements, justify level of detail.
- Quality control.
- Changes to the modelling and simulation plan.

Introduction: role of the specification in Best Practice

- Specification enables
  - › users to answer in advance the question “will this modelling and simulation project answer my research question”?
  - › team members to act consistently to achieve the planned outputs;
  - › sponsor to assess whether the project achieved its goals.
- SIG document allows the flexibility necessary for Best Practice in this area where the regulatory and scientific importance of the projects varies widely.

Example best-practice specification for low-impact work

Planning and Reporting for Projects that Involve Modelling and Simulation
Best Practice Document

Appendix B: example specification with a low level of detail

Using simulated data to verify an estimate of probability of success

Specification of simulations

B.1 Introduction
Given five treatment development programs with known probability of success, it is desired to know the probability of zero successes and of four and five successes. These probabilities have been calculated analytically. It is requested that a simulation be run to verify that the analysis is correct.

Since this is a one-off query on whose evidence alone no decision will be made, this is judged a project of low importance. Therefore the clinical background is not described; nor are metrics and criteria for decisions appropriate.

B.2 Simulation and analysis/design
As noted, this project is of low importance and no decision will be made by it alone. Therefore the description of the elements of the simulation and analysis will not be detailed and some elements are not applicable.

B.2.1 Scenarios assumed and assumptions made
Probabilities of 0.1, 0.2, 0.2, 0.05 and 0.4 were given for programs 1-5, respectively. Since the objective was simple verification of an existing calculation, no justification is given here of these probabilities. Since the question answered is theoretical, just one given scenario is used.

B.2.1.1 Sensitivity analyses
This project is not required to assess assumptions, so sensitivity to assumptions is not planned to be analysed via sensitivity analyses

B.2.2 Data sets generated
Temporary sets of binary outcomes will be generated. Data will not be bootstrapped because a simple verification is sufficient. Three million binary outcomes are simulated for each program.

B.2.3 Statistical analysis
The number of instances of zero, four and five successes was calculated for each of the 3 million simulations, and the probability of zero, four and five successes in a simulated instance was calculated and plotted.

B.2.4 Operating characteristics
Given that this modelling and simulation task is to be a sanity check, the number of simulations required to achieve a given accuracy with 5% confidence will be approximated. The probability of five successes is small (<1/100) so a precision of 0.001 is desired. Using the formula of Burton *et al.* (2006), with alpha=0.05, and approximating the variance of the probabilities as 5*p(1-p) where p==0.2, 3 million simulations will provide precision of approximately 0.001.

B.2.5 Logistics
The R language package mvtBinaryEP will be used to simulate the binary outcomes. The package allows for correlations between the outcomes, but this was not required for the primary objective. R version 3.0.1 will be used. See Appendix for the R code used. The seed used was 1.

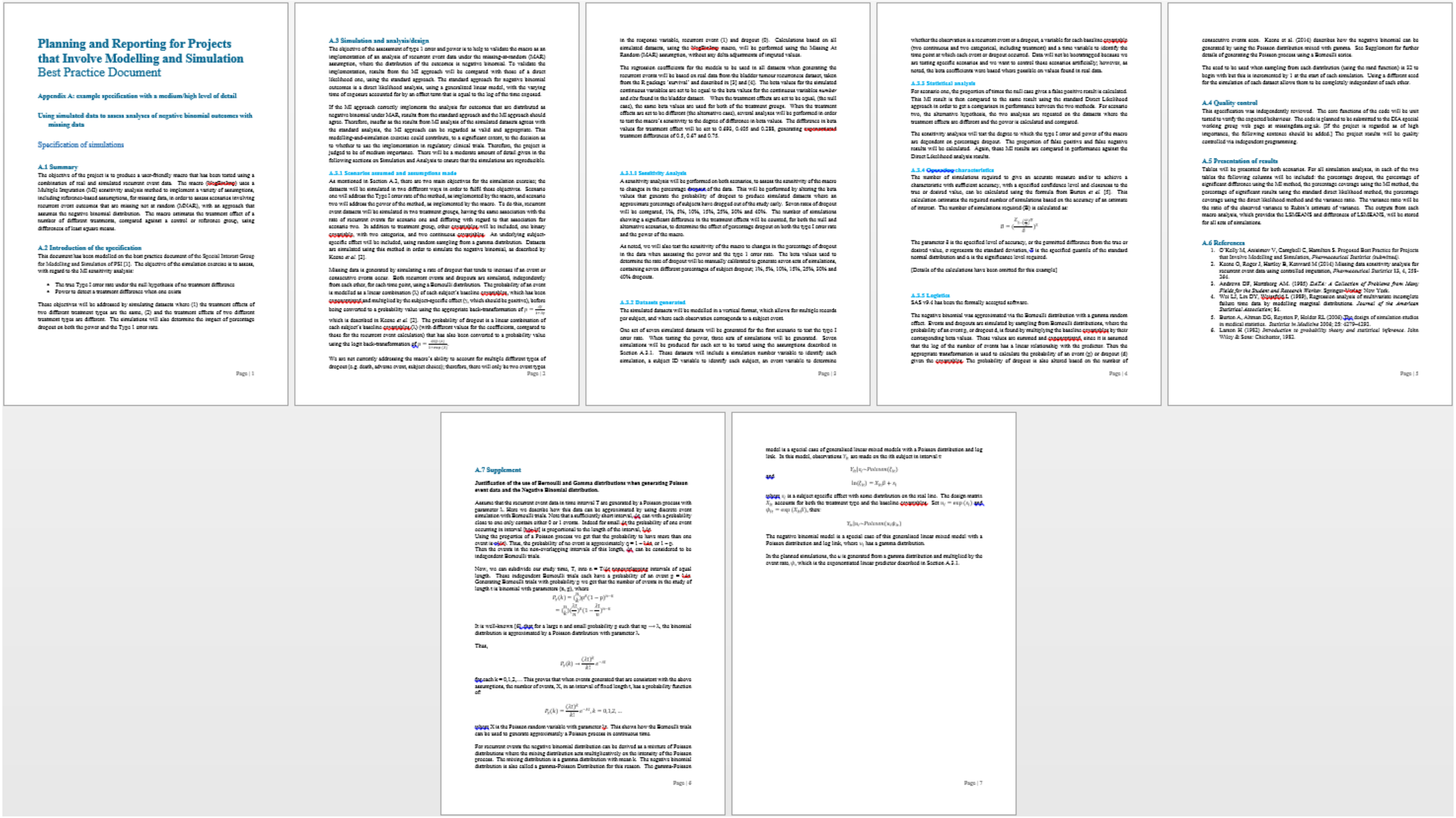
B.3 Quality control
Given that this modelling and simulation task is of low importance and will not of itself lead to a decision, the specification will be submitted to the requestor of the calculation, but no further QC of the production of results is planned. The output will be checked against the requestor's calculations.

B.4 Presentation of results
A table will be presented of the probability of zero, four and five successes among the five programs, calculated as the proportion of instances of zero, four and five successes in 3 million simulations of the five programs. The number of instances will also be plotted in a histogram with one stack for each level of successes, a stack for zero successes, 1 success, ...and so on up to five successes. These outputs are judged sufficient to act as a check of the analytic estimates, which is the objective of this project.

The precision of the result (standard error) will be presented in a footnote to the plot. Given the inclusion of precision, no confidence intervals will be presented. Given the theoretical nature of the problem and the corresponding simplicity of the simulation, no bias is to be expected in the simulation-based estimates.

The results of the modelling and simulation will not be stored. The R code will be stored in [location]. A note of the contents of the table output will be included as a comment in the R code.

Example best-practice specification, high-impact work


Planning and Reporting for Projects that Involve Modelling and Simulation
Best Practice Document

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Best Practice for modelling and simulation, the work of the two groups, MID3 and EFSPI

- Agreement all aspects of the process
- Some differences in emphasis
- The two groups are working together to promote good practice
- The two groups are participating at session on Best Practice at 2016 annual American Statistical Association Biopharmaceutical Workshop with FDA speakers.

Informal survey of Best Practice: background.

- MID3 group
  - › MID3 paper on Good Practice, supplementary material
  - › Lists 103 publications describing projects involving modelling and simulation.
- These slides make use the MID3 supplementary material.
- These slides do not represent the views of the MID3 group or the authors of the MID3 paper.

Marshall S, Burghaus R, Cosson V, Cheung S, Chenel M, DellaPasqua O, Frey N, Hamren B, Harnisch L, Ivanow F, Kerbusch T, Lippert J, Milligan P, Rohou S, Staab A, Steimer J, Tornøe C, Visser S. (2016) Good Practices in Model-Informed Drug Discovery and Development (MID3): practice, application and documentation. *CPT: Pharmacometrics & Systems Pharmacology*; (2016) 5, 93–122, available at http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/epdf, accessed 22Apr2016

Survey

- Random sample of 48 of the 103 publications listed by the MID3 paper.
  - 12, 17 and 6 of low, medium and high regulatory importance.
    - Regulatory importance assessed by the authors.
  - Publications freely downloadable for 36.
  - Of these 36, 29 included an element of simulation.
  - Survey includes six slidesets, 23 journal papers.
- Limitations
  - Many journal papers are not written with regulatory requirements in mind.
  - Survey includes six slidesets - less space to describe elements of best practice.
    - Included only very slightly fewer of the elements of best practice surveyed.
  - Assessments in this survey not independently reviewed.
- Average “Best Practice” items present, out of a possible 21 items
  - 14.3, 12.3 & 8.3 for papers of low, medium and high regulatory importance, respectively.

Attributes assessed in survey – planning & presentation

- Statement of objective
- Clinical background
- Criteria for conclusion
- Input data described
- Assumptions for scenarios described
- Assumptions for scenarios justified
- Model assumptions stated
- Model assumptions justified
- Model assumptions checked
- Sensitivity analyses presented
- Any sensitivity results unfavourable to thesis?
- Limitations described
- Analysis described

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Attributes assessed in survey – planning & presentation

• Statement of objective	26 (90%)
• Clinical background	26 (90%)
• Criteria for conclusion	2 (7%)
• Input data described	26 (90%)
• Assumptions for scenarios described	18 (62%)
• Assumptions for scenarios justified	16 (55%)
• Model assumptions stated	26 (90%)
• Model assumptions justified	21 (72%)
• Model assumptions checked	21 (72%)
• Sensitivity analyses presented	8 (31%)
• Any sensitivity results unfavourable to thesis?	0 (0%)
• Limitations described	14 (48%)
• Analysis described	14 (48%)

More technical attributes assessed in survey

- Software stated
- Software version given
- Seed(s) stated
- Programming code available
- QC process described
- Measure of simulation uncertainty
- Results include confidence intervals (CIs)
- Any operating characteristics assessed
  - e.g. type I error, power, bias, coverage of CIs

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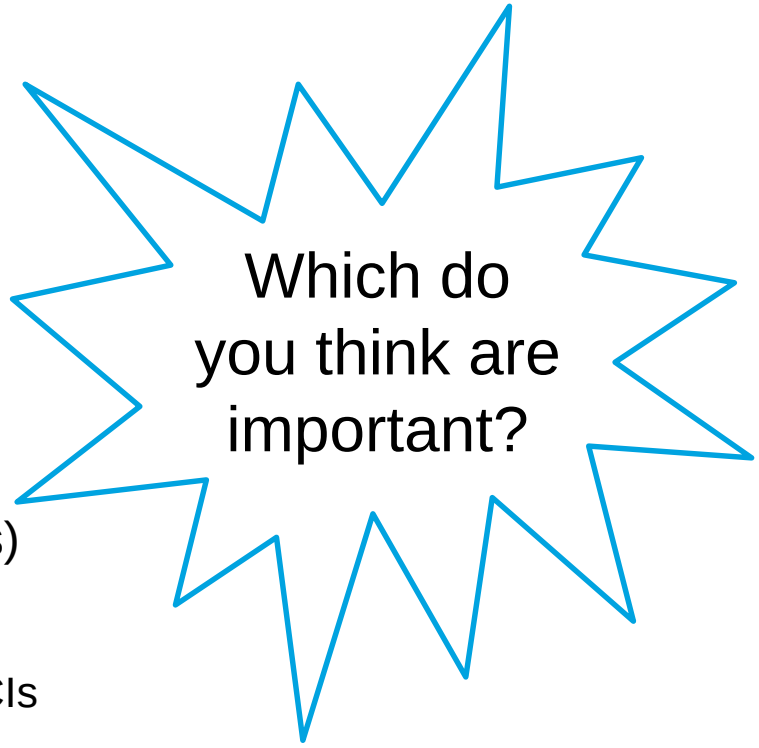

More technical attributes assessed in survey

- Software stated
- Software version given
- Seed(s) stated
- Programming code available
- QC process described
- Measure of simulation uncertainty
- Results include confidence intervals (CIs)*
- Any operating characteristics assessed
  - e.g. type I error, power, bias, coverage of CIs

* or quantiles other than medians

More technical attributes assessed in survey

• Software stated	18 (62%)
• Software version given	14 (48%)
• Seed(s) stated	2 (7%)
• Programming code available	4 (14%)
• QC process described	1 (3%)
• Measure of simulation uncertainty	5 (17%)
• Results include confidence intervals (CIs)*	17 (59%)
• Any operating characteristics assessed	11 (38%)

  › e.g. type I error, power, bias, coverage of CIs

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* or quantiles other than medians

Essential to a successful program simulation

- Integrate the quantitative experts, the clinical experts and the other decision-makers
- The whole team is needed, to decide on
  - > what aspects of development program to assess
  - > assumptions
  - > scenarios
  - > how to interpret results
  - > what new alternatives to assess

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