European Federation of Pharmaceutical Industries and Associations

Good Practices in Model-Informed Drug Discovery and Development (MID3): Practice, Application, and Documentation



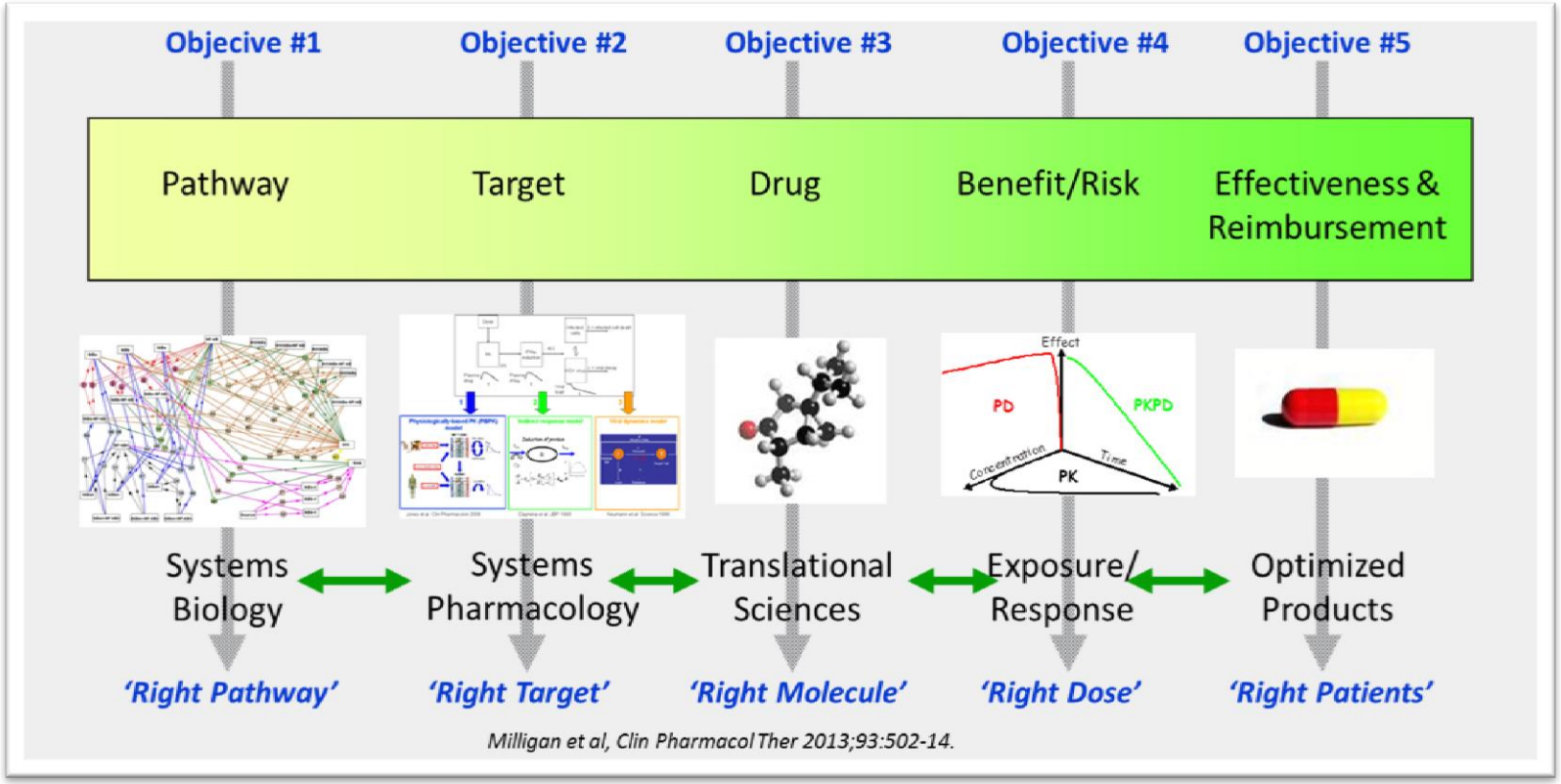


Scott Marshall

on behalf of the EFPIA MID3 Working Group

EFSPI Modelling and Simulation Webinar Oct 4th 2016

Constructing the Reproducible Quantitative Framework across R&D



Model-Informed Drug Discovery & Development - **MID3**:
"A quantitative framework for **prediction** and **extrapolation** centered on **knowledge** and **inference** generated from integrated models of **compound**, **mechanism** and **disease level data** aimed at improving the quality, efficiency and cost effectiveness of decision making"

EMA/EFPIA M&S WORKSHOP (Dec 2011)

Objectives

- Discuss the role and scope of M&S in drug-development from both the developer's and the regulator's perspectives.
- An opportunity for industry, academia and regulators:
  - To learn from each other
  - Create greater awareness
  - Share experiences
  - Identify gaps and future opportunities

Outputs

EDITORIAL

Regulatory Modeling and Simulation Moves Into the Next Gear in Europe

CPT: Pharmacometrics & Systems Pharmacology (2013) **2**, e32; doi:10.1038/psp.2013.8; advance online publication 27 February 2013

PERSPECTIVE

The Role of Modeling and Simulation in Development and Registration of Medicinal Products: Output From the EFPIA/EMA Modeling and Simulation Workshop

E Manolis[1], S Rohou[2], R Hemmings[1,3], T Salmonson[1,4], M Karlsson[5] and PA Milligan[6]

PERSPECTIVE

Modeling and Simulation at the Interface of Nonclinical and Early Clinical Drug Development

SAG Visser[1,2], E Manolis[3], M Danhof[4] and T Kerbusch[5]

BOS 1

PERSPECTIVE

Modeling and Simulation in Clinical Pharmacology and Dose Finding

A Staab[1], E Rook[2,3], M Maliepaard[2,3], L Aarons[4] and C Benson[5]

BOS 2

PERSPECTIVE

Modeling and Simulation as a Tool to Bridge Efficacy and Safety Data in Special Populations

L Harnisch[1], T Shepard[2,3], G Pons[3,4] and O Della Pasqua[5]

BOS 3

PERSPECTIVE

Modeling and Simulation to Optimize the Design and Analysis of Confirmatory Trials, Characterize Risk–Benefit, and Support Label Claims

SF Marshall[1], R Hemmings[2,3], F Josephson[2,4], MO Karlsson[5], M Posch[2,7] and J-L Steimer[6]

BOS 4

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Opportunities identified (Dec 2011) and progress (Sept 2016)

Completed, Progress

Opportunities	Key Challenges	Actions	Progress
Robust informed R&D decision making - Improve R&D efficiency	• MID3 - underutilized & undervalued by Pharma • Communication gap between modellers & non-modellers	• Develop **Common understanding** in terms of the practice, application and **value** of MID3	• **Good Practices in MID3 White Paper: Why, What & Challenges /Opportunities for Pharma Sections**
Robust informed R&D regulatory assessment • Inform Risk Benefit assessment • Greater acceptance in extrapolation and other medium & high impact Regulatory Decisions	• Heterogeneity of MID3 reporting in submissions	• EFPIA to **agree basic documentation standards** for submissions	• **Good Practices in MID3 White Paper: How (Documentation)**
	• Variable readiness of EMA & other agencies to evaluate MID3: staff & lack of guidelines	• EMA to **form and evolve MSWG** • Develop guidelines	• **MSWG Formed 2013** • **Activity reports 2013, 2014**, 2015 • **Development of MID3 regulatory guideline planned?**
	• Mis-perception that dose response is only company risk	• Host workshop and **evolve Dose Response practice & Review**	• **Workshop held Dec 2014-** Report, papers • **Review templates to be updated** • **Formation of expert group to drive output**
	• Communication gap between modellers & non-modellers	• Host **workshops involving multifunctional group**	• **Extrapolation Workshop** (EMA Sept 2015, EMA/EFPIA May 2016) • **PBPK workshop** (TBC) • **Qualification Procedures x3 with Key M&S component**
	• Data Sharing	• Strengthen **data sharing** initiatives	• **DDMoRe (2016) / Access to Clinical Trial Data**

Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 00, 00; doi:10.1002/psp4.12049

WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup: SF Marshall[1*], R Burghaus[2], V Cosson[3], SYA Cheung[4], M Chenel[5], O DellaPasqua[6], N Frey[3], B Hamrén[7], L Harnisch[1], F Ivanow[8], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

Objectives:

- To promote "Good Practices" with regards to the planning conduct & documentation
- To include illustrative examples to demonstrate their use, impact & value
- To promote Model Informed Drug Discovery & Development (MID3)

Acknowledgements :

- Efthymios Manolis (EMA/MSWG)
- Terry Shepard (MHRA/MSWG))

Abstract:
http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/abstract
Paper:
http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/pdf
Supplemental info:
http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/suppinfo
Podcast:
http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2163-8306/homepage/podcasts.htm

Good Practices in MID3 White Paper: Highlights

"Why" MID3 is important for decision makers

- Summary of the collated business value to-date based on available literature
- Compare and contrast different MID3 Modelling approaches
- Categorized review of 100 published case studies across Drug Discovery, Development and Life Cycle Management

"What" MID3 means for practitioners

- Premise of MID3 & Implementation strategy
- Challenges and opportunities at Pharma, Organization & Asset Levels
- EFPIA classification of MID3 Internal impact

"How" MID3 should be documented

- Basic standards in planning & reporting
- Risk Based QC/verification
- Documentation of assumptions, evaluation & impact assessment

Planning, Conduct and Documentation of MID3 analyses

Components of Good practice Plans: “Fit for Purpose”

Good Practice

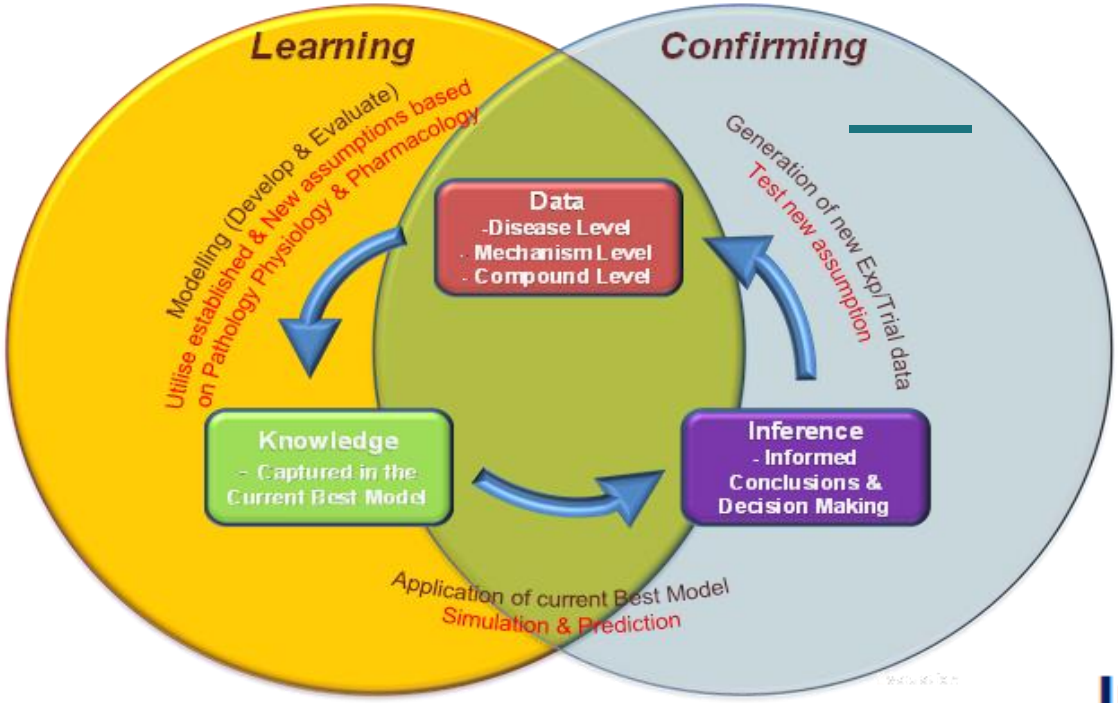
- Clarity on the key questions & Objectives
- Transparency of Assumptions & their Evaluation
- Simulations to Integrate the necessary Levels of Uncertainty
- Reproducible Research - Utilize QA/QC Risk Based Guideline:
  - QA - Audit Trail
  - Scientific Review
  - Risk assessment to determine the extent of the QC required
- Sufficient Information to judge the model
- Documentation orientated to satisfy all end-users
- “Fit for Purpose” Use Adequate Graphical and/or Tabulated display of Key Data features, Model and Simulation Results.
- Good practice proposal on Inclusion of MID3 Analyses and Conclusions in CTD

Table 4 The common general structure of documents describing MID3 analyses

Analysis plan	Simulation plan	Report
• Introduction	• Introduction	• Synopsis
• Objectives	• Objectives	• Introduction
• Data plan	• Additional information	• Objectives
• Data exploration	• Methods	• Data
• Methods	• Assumptions	• Methods
• Assumptions		• Assumptions
		• Results
		• Applications (prediction/simulation)
		• Discussion
		• Conclusions
		• Appendix

Need to satisfy specific Guidelines, e.g. PIP

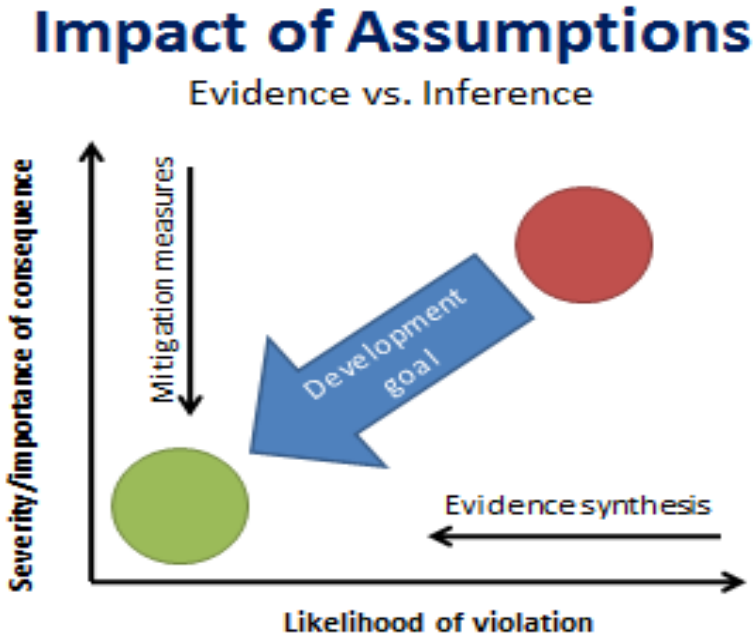
Assumption table to capture assumptions



Coloured Boxes represent key Steps in the "Learn and Confirm Cycle".

Arrows represent processes that link these key steps

Type of Assumptions
Pharmacological
Physiological
Disease
Data
Mathematical and statistical



Assumption setting, evaluation, impact assessment: examples

Important assumptions	Justification	New/ established	Testable/ not-testable	Test/approach to assess impact	Evaluation
Pharmacological assumption Emax model fixed to 100% is a more physiological description of the data compared to a linear model.	Emax model is not better than linear model; however, for this drug class, Emax of 100% is more realistic	New	Testable with a wider range of concentrations (external/ future study).	Comparison of simulated metrics of interest between the two competing models.	To achieve a 90% response (assumed to be clinically meaningful) requires a twofold higher dose using the Emax model compared to the linear model. ➔ Test doses suggested by Emax model in Phase 2.
Physiological assumption No difference in clearance between healthy subjects and patients.	Patients with major depression disorders are considered as healthy subjects (in regard of ADME/PK features) once age and weight are taken into account.	Established	Testable by pooling healthy subjects and patient data, assuming that all other qualities across the pooled trials are exchangeable.	Combined analysis with healthy subjects and patients.	Combined analysis found only a 10% lower clearance in patients. ➔ No dose adjustment necessary for PK reasons
Disease assumption: Linear progression of disease with a slope of X/year	Cannot be estimated directly from the dataset, but supported by literature review	Established	Not testable with the present dataset	Sensitivity analysis changing the value of the slope for disease progression from X to Y	Varying the slope by X and Y will not change the selected dose for P3 ➔ Selected dose for P3 can be implemented Varying the slope by X and Y will change the selected dose for P3 drastically ➔ Three different doses should be tested
Data assumption: Data below limit of quantification (BLQ) have no impact on analysis results	There are <20% BLQ concentrations after treatment	New	Testable	Run final model with BLQ using M3 method (Beal 2001[82]) and compare to model without BLQ	Negligible changes in parameter estimates ➔ Final model excluding BLQ observations selected
Mathematical and/or statistical assumption Similar variability in clearance between adults and children	Physiological and PK knowledge	New	Not testable at the stage of predictions but can be evaluated with data from children	Sensitivity analysis on the variance value of clearance	If variance is 2-fold, children would be still with the highest dose in the safety range established for adults? ➔ Suggested dosing can be used in Children

See Table 5 in white paper: http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/pdf

EFPIA Classification of MID3 Internal Impact

Impact on Internal decision

HIGH CATEGORY IMPACT
REPLACE - MID3 approach provides inference which informs internal decisions without requiring additional experimental or trial data to be generated

MEDIUM CATEGORY IMPACT
INFORM - MID3 approach provides inference which informs internal decisions

LOW CATEGORY IMPACT –
DESCRIBE - MID3 approach provides inference which has limited impact on internal decisions

The aim is:

- to provide a starting point for the discussion on impact on internal decision making
- to enable greater clarity in the level of impact of existing literature examples

*Low impact doesn't mean low value!

MID3 Good Practice White Paper
Next steps: Share, Implement & Evolve

- **Share**
  - PAGE & ACOP (2015),
  - DIA meeting (2015) , EMA Extrapolation workshop (2016), TOPRA (2016)
  - PSI/ EFSPI special interest group for M&S (2016), & ASA Best Practice in Modelling and Simulation (2016)
  - External communications in Japan & China in planning
  - Colleagues continue to create awareness within and across companies
- **Implement**
  - EMA (F2F & Extrapolation workshop) endorsement
  - OCP FDA (Guideline Development) June 2016 discussions
  - ICH (Paed E11 & standalone Guideline) ongoing discussions
  - Update to internal companies guidelines to meet good practice and aligned regulatory guidelines
- **Evolve**
  - Continue to discuss good practices, terminology and improve understanding across pharma & regulatory stakeholders
    - e.g. Decision Makers, Clinicians, Statisticians and Clin Pharmacologists
  - Continue to review ongoing MID3 practice with MSWG
  - Enhanced integration with DDMoRe via
    - "Products"- e.g. model repository, model review, standards, tools
    - "Sustainability" e.g. galvanise the broader user community to increase capabilities and capacities in delivery of MID3

“ Clinicians, modellers, statisticians; no one discipline should work alone in extrapolation”

Rob Hemmings MHRA, Paed Extrapolation WS May 2016

Statistics and Pharmacometrics

Learning from each other to facilitate better drug development

- *“Pharmacology and statistics are the two threads that run right through drug development. I hope that our two communities can increase our collaboration in the future, learn from each other, and help spread to others in drug development what we have learned.”*

- **Pharmaceutical statistics**
  - *“pragmatic in purpose, empirical in method, and skeptical and pessimistic in attitude. Its approach to modelling is biologically innocent and its view of causality is 'voluntary'.”*
- **Pharmacometrics**
  - *“explanatory in purpose, theory based, and optimistic in attitude. Its approach to modelling is biologically knowledgeable and its view of causality is mechanistic”.*

Senn (2010)

7 | EMA Extrapolation workshop | Bretz & Looby | Quantitative challenges of extrapolation

NOVARTIS

efpia

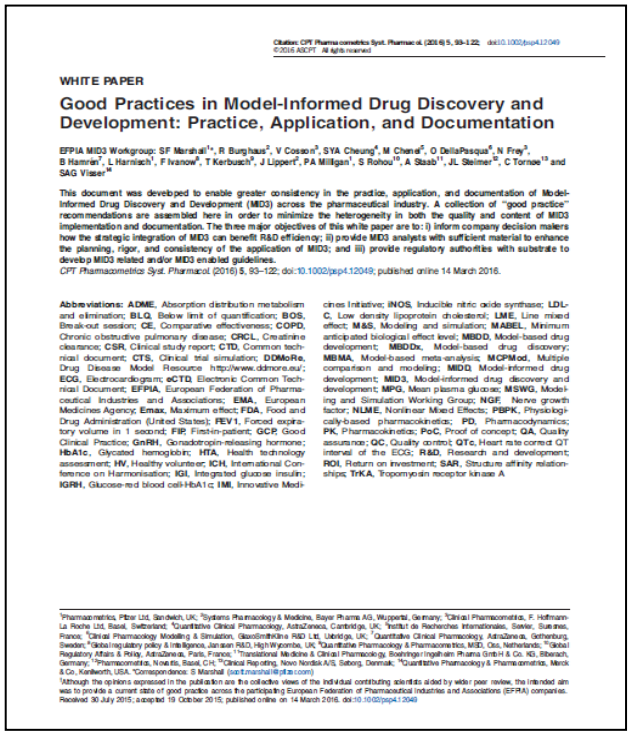
Mick Looby Paed Extrapolation WS May 2016

Share, Implement and Evolve

Proposed GP in MID3

Why …

What..



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WHITE PAPER

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This document was developed to enable greater consistency in the practice, application, and documentation of Model-Informed Drug Discovery and Development (MID3) across the pharmaceutical industry. A collection of "good practice" recommendations are assembled here in order to minimize the heterogeneity in both the quality and content of MID3 implementation and documentation. The three major objectives of this white paper are to: i) inform company decision makers how the strategic integration of MID3 can benefit R&D efficiency; ii) provide MID3 analysts with sufficient material to enhance the planning, rigor, and consistency of the application of MID3; and iii) provide regulatory authorities with substrate to develop MID3 related and/or MID3 enabled guidelines.

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Abbreviations: ADME, Absorption distribution metabolism and elimination; **BLQ**, Below limit of quantification; **BOS**, Break-out session; **CE**, Comparative effectiveness; **COPD**, Chronic obstructive pulmonary disease; **CRCL**, Creatinine clearance; **CSR**, Clinical study report; **CTD**, Common technical document; **CTS**, Clinical trial simulation; **DDMoRe**, Drug Disease Model Resource http://www.ddmore.eu/; **ECG**, Electrocardiogram; **eCTD**, Electronic Common Technical Document; **EFPIA**, European Federation of Pharmaceutical Industries and Associations; **EMA**, European Medicines Agency; **Emax**, Maximum effect; **FDA**, Food and Drug Administration (United States); **FEV1**, Forced expiratory volume in 1 second; **FIP**, First-in-patient; **GCP**, Good Clinical Practice; **GnRH**, Gonadotropin-releasing hormone; **HbA1c**, Glycated hemoglobin; **HTA**, Health technology assessment; **HV**, Healthy volunteer; **ICH**, International Conference on Harmonisation; **IGI**, Integrated glucose insulin; **IGRH**, Glucose-red blood cell-HbA1c; **IMI**, Innovative Medicines Initiative; **iNOS**, Inducible nitric oxide synthase; **LDL-C**, Low density lipoprotein cholesterol; **LME**, Line mixed effect; **M&S**, Modeling and simulation; **MABEL**, Minimum anticipated biological effect level; **MBDD**, Model-based drug development; **MBDDx**, Model-based drug discovery; **MBMA**, Model-based meta-analysis; **MCPMod**, Multiple comparison and modeling; **MIDD**, Model-informed drug development; **MID3**, Model-informed drug discovery and development; **MPG**, Mean plasma glucose; **MSWG**, Modeling and Simulation Working Group; **NGF**, Nerve growth factor; **NLME**, Nonlinear Mixed Effects; **PBPK**, Physiologically-based pharmacokinetics; **PD**, Pharmacodynamics; **PK**, Pharmacokinetics; **PoC**, Proof of concept; **QA**, Quality assurance; **QC**, Quality control; **QTc**, Heart rate correct QT interval of the ECG; **R&D**, Research and development; **ROI**, Return on investment; **SAR**, Structure affinity relationships; **TrKA**, Tropomyosin receptor kinase A

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[1]Although the opinions expressed in the publication are the collective views of the individual contributing scientists aided by wider peer review, the intended aim was to provide a current state of good practice across the participating European Federation of Pharmaceutical Industries and Associations (EFPIA) companies.

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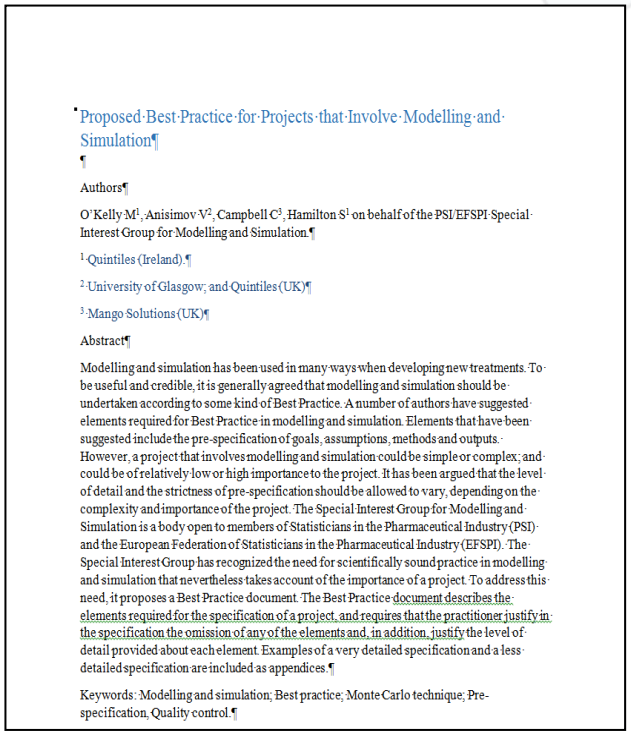
Proposed M&S BP



Proposed Best Practice for Projects that Involve Modelling and Simulation

Authors

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[3] Mango Solutions (UK)

Abstract

Modelling and simulation has been used in many ways when developing new treatments. To be useful and credible, it is generally agreed that modelling and simulation should be undertaken according to some kind of Best Practice. A number of authors have suggested elements required for Best Practice in modelling and simulation. Elements that have been suggested include the pre-specification of goals, assumptions, methods and outputs. However, a project that involves modelling and simulation could be simple or complex; and could be of relatively low or high importance to the project. It has been argued that the level of detail and the strictness of pre-specification should be allowed to vary, depending on the complexity and importance of the project. The Special Interest Group for Modelling and Simulation is a body open to members of Statisticians in the Pharmaceutical Industry (PSI) and the European Federation of Statisticians in the Pharmaceutical Industry (EFSPI). The Special Interest Group has recognized the need for scientifically sound practice in modelling and simulation that nevertheless takes account of the importance of a project. To address this need, it proposes a Best Practice document. The Best Practice document describes the elements required for the specification of a project, and requires that the practitioner justify in the specification the omission of any of the elements and, in addition, justify the level of detail provided about each element. Examples of a very detailed specification and a less detailed specification are included as appendices.

Keywords: Modelling and simulation; Best practice; Monte Carlo technique; Pre-specification, Quality control.

How…

- Basic standards in planning & reporting for MID3 activities
- Risk Based QC/verification
- Documentation of assumptions, evaluation & impact assessment of MID3 Activities

- Basic standards in planning & reporting M&S related to trial design
- Sensitivity analyses and operating characteristics
- M&S plans templates proposed

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