ISPOR-SMDM Joint Task Force Good Modeling Research Practices: Controversies

Jaime Caro MDCM, FRCPC, FACP, Chair
Uwe Siebert MD, MPH, MSc, ScD, Co-chair
Karen Kuntz ScD, Co-chair
Andrew Briggs DPhil, Co-chair

Madrid, November 8, 2011

Working Groups

Conceptual Modeling Working Group
Chair: Mark Roberts; Members: Murray Krahn; David Paltiel; Michael Chambers; Phil McEwan; Louise Russell

State-Transition Modeling Working Group
Chairs: Karen Kuntz; Uwe Siebert; Members: Oguzhan Alagoz; Doug Owens; David Cohen; Beate Jahn; Ahmed Bayoumi,

Modeling Discrete Event Simulation Working Group
Chairs: James Stahl; Jonathan Karnon; Members: Jörgen Möller; Javier Mar; Alan Brennan

Dynamic Transmission Modeling Working Group
Chairs: Richard Pitman; John Edmunds; Members: Maarten Postma; Greg Zaric; Marc Brisson; David Fisman; Mirjam Kretzschmar

Model Parameter Estimation & Uncertainty Working Group
Chair: Andrew Briggs; Members: Milt Weinstein; Mark Sculpher; Elisabeth Fenwick; David Paltiel; Jonathan Karnon

Model Transparency and Validation Working Group
Chairs: David Eddy; John Wong; Members: Joel Tsevat; William Hollingworth; Kathy McDonald

Review Process & Status

- All papers have undergone external review
  - Broad representation
  - Reviewed/approved by journal editors
  - Peer review comments documented as well as responses
- Papers posted for members' review & comment
- Submission jointly to MDM & ViH
- Editors review.

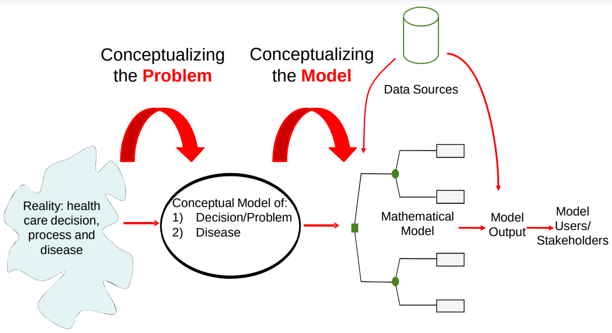
Conceptualizing the model

Mark Roberts

On behalf of

Working group

Conceptual Framework



Conceptualizing the Model

- **Collaborate and consult** to ensure that model adequately addresses decision problem & disease in question.
- Clear, written **statement of the decision problem**, objective and scope
  Multiple detailed sub-recommendations regarding these and other attributes
- **Conceptual structure** should
  - Be linked to the problem and **not based on data availability**
  - Be **used to identify key uncertainties in model structure** where sensitivity analyses could inform the impact of structural choices
  - Follow an explicit process to convert the conceptualization into an appropriate model structure: Influence diagrams, concept mapping, expert consultations
- Model **simplicity is desirable** for transparency, ease of validation and description, but
  - Must be **sufficiently complex to answer the question**
  - Should **maintain face validity**.

Choice of Model Type

Problem Characteristic	Model Type
Simple, non-dynamic	Decision tree
Based on "states" of health	State transition model
State explosion	Individual microsimulation
Interactions, event-based, time-to-event	Dynamic transmission models, DES, Agent-based
Resource constraints, interactions	DES, Agent-based, Dynamic Transition models

For some decision problems, combinations of model types, hybrid models, and other modeling methodologies are appropriate

Parameter estimation & uncertainty

Andy Briggs

On behalf of

Working group

Terminology

Preferred term	Concept	Other terms sometimes employed	Analogous concept in regression
Stochastic uncertainty	Random variability in outcomes between identical patients	• First order uncertainty • Variability • Monte Carlo error • Unexplained heterogeneity	Error term
Parameter uncertainty	The uncertainty in estimation of the parameter of interest	• Second-order uncertainty	Standard error of the estimate
Heterogeneity	The variability between patients that can be attributed to characteristics of those patients	• Variability • Observed or explained heterogeneity	Beta coefficients (or variability of fitted dependent variable)
Structural uncertainty	The assumptions inherent in the presentation of the decision modeling form	• Model uncertainty	The form of the regression model (linear/log-linear etc.)

Most contentious issues

- While completely **arbitrary analyses** (e.g., varying an input parameter by +/- 50%) can be used as a measure of sensitivity, they **should not be used to represent uncertainty**.
- Consider using **commonly adopted standards from statistics**, such as 95% confidence intervals, or distributions based on agreed statistical methods for a given estimation problem.
- Where there is very little information, **analysts should adopt a conservative approach**
- In choosing distributional forms for parameters in a probabilistic sensitivity analysis, favor should be given to continuous **distributions that provide a realistic portrayal of uncertainty** over the theoretical range of the parameter of interest.
- **Correlation** among parameters should be considered.
- When more than two comparators are involved, CEACs for each comparator should be plotted **on the same graph** (avoid pairwise comparisons)

Structural Uncertainty

- Where **uncertainties in structural assumptions** were identified in the process of conceptualizing and building a model, those assumptions **should be tested in a sensitivity analysis**
  - Consideration should be given to opportunities to **parameterize these uncertainties** for ease of testing.
  - Where it is not possible to perform structural sensitivity analysis it is nevertheless important that analysts be aware of the **potential for this form of uncertainty to be at least as important as parameter uncertainty** for the decision maker.

State-Transition Models

Uwe Siebert

On behalf of

Working group

Structure

- Cohort or individual simulation?
  - **Cohort**: if the decision problem can be represented with a **manageable number of health states** incorporating all characteristics relevant to the decision problem
  - **Individual**: if **unmanageable number of states**
- **Validity should not be sacrificed for simplicity**
- Specification of **states and transitions should** generally **reflect** the biological/theoretical understanding of the **disease** or condition being modeled
- **States need to be homogeneous** with respect to the observed and unobserved (i.e., not known by the decision maker) characteristics that affect transition probabilities
- **Cycle length** should be **short enough to represent** the frequency of clinical events and interventions.

General Reviewer Comments

- Be more normative, use „models should …“ rather than „models are …“ → will be changed
- Explain terms (e.g., probabilistic sensitivity analysis, predictive validity) before use → refer to the other task force papers?
- Add example, add examples, add examples …
  → space problem, need to prioritize
- Audience? Too much/too little detail? → ?
- Are all issues STM-specific? → add explanation in beginning
- Requests for recommendations on topics covered in other papers (e.g., uncertainty analysis, validation) → include reference on other papers of the series

Reviewer Comments on States

- **Specification of states and transitions should generally reflect the biological/theoretical understanding of the disease or condition being modeled**
- *R: Mention that modeling natural disease progression in the absence of intervention is not absolutely necessary because to model can focus on comparing two or more active treatments. Natural progression data are hard to obtain.*
- *R: Do the authors really mean 'generally'? Are there instances where states and transitions should NOT reflect the biological/theoretical understanding of the disease or condition?*

Discrete Event Simulation

Jörgen Möller

On behalf of

Working group

Areas of Application

- Constrained resource scenarios
  - Optimising the delivery of services
    e.g. Clinic... gets seen by whom, when, where, and what happens to...
  - tec... . different refe...
  - tim... ts on costs and/or outcomes
  - Consider health outcomes not just throughput
- Non-c...
  - M...
  - An...
    - ...

> *"When modelling applied clinical practice, it should not be assumed that relevant published guidelines are applied in the system of interest."*

> It is disappointing not to see a firmer statement on when DES should be the preferred approach in non-constrained models
> The comment is appreciated and some on the task force would agree. There were also strong contrary opinions and it was decided, in the interest of being able to complete the task force's work, that the papers would avoid strong statements of preference of one technique over another.

Structure

- To simplify debugging and updating, sub-models should be used.
  - Structure ... some strategies should be defined once and ...
- If down... cts on costs or outcomes, structure should facilitate analyses of alternative downstream decisions
- Mechanism for applying ongoing risks should remain active over the relevant time horizon
- For structural sensitivity analyses, alternative structures should be implemented within a single DES.

> These papers are not meant to be tutorials and space limitations preclude providing detailed examples.

Parameterisation

- With competing risks, parameterisation approaches that represent correlations between the competing events are preferred
  - Rather than specifying separate time to event curves for each event.
- Where possible, progression of continuous disease parameters and the likelihood of related events should be defined jointly
  - e.g. sample the level of the continuous measure at which an event occurs, then sample the time at which the level is reached

Implementation

- Software choice depends on importance of flexibility & execution speed (general programming) vs. efficiency, automated structure and transparency (dedicated DES software)
  - Spreadsheet software is inappropriate for implementing DES
- Outputs should
  - be stored as ... es are required, otherwise ag... om each run
  - account for t...
- When run times are constrained,
  - optimal combination of run size & numbers of alternative input parameter sets tested should be estimated empirically
    - variance reduction techniques should be implemented
  - factorial des... and optimum seeking approaches can be used
  - meta-modellin... used
- If system is n... period if:
  - it can be ... remained constant over time
  - or the history of the key parameters can be incorporated into the warm-up period

> Spreadsheet part still in text but not in recommendation

> *Use of variance reduction techniques is recommended*

Reporting

- Animated representation that displays the experience of events by individuals is recommended as a means of engaging with users, as well to helping to debug the model through the identification of illogical movements
- Both general and detailed representations of a DES model's structure and logic should be reported to cover the needs of alternative users of the model.

Transparency & Validation

Jaime Caro

On behalf of

Working group

Importance

- **Trust and confidence** are **critical** to the success of models
- Three main methods
  - **Transparency** of model
    - People can see how it is built
  - **Validation** of model
    - People can see how well it reproduces reality
  - **Reporting** of methods and analyses
    - People can see specific assumptions, etc

Transparency

- **Ideally**, make everything **public**
  - Structure, equations, sources, assumptions, code
- However
  - Can be huge, highly **technical**
  - Usually requires **special knowledge**
  - May need to protect **intellectual property**
- Recommend
  - Non-technical description
  - Technical description.

Transparency

- Every model should have **non-technical documentation** that should
  - Describe in non-technical terms the type of model and intended applications; funding sources; structure of the model; inputs, outputs, other components that determine the model's function, and their relationships; data sources; validation methods and results; and limitations
  - Be **freely accessible** to any interested reader
- Every model should have **technical documentation** that should
  - Be written in sufficient detail to enable a reader with the necessary expertise to evaluate the model and potentially reproduce it.
  - Be made available **at the discretion of the modelers** either
    - **openly or**
    - **under agreements that protect intellectual property**.

Transparency

- Depending on the complexity of the model, **not all will be transparent to all people**
- If a model is **not transparent to some** people, that **does not mean the model has no value**
- Transparency is a description of a model; it does not show how well the model functions
- **Transparency** of documentation is necessary, but is **not a substitute for validation**.

Validation

- **Face validity** of structure, evidence, problem formulation, results
  - Desirable but **not sufficient**
  - is most important for evidence, data sources, and problem formulation
- **Verification**
  - Should be **described** in the non-technical documentation
  - Necessary but **not sufficient**
- **Cross-validity**
  - Published models of same or similar problems should be sought and similarities and differences discussed
  - **Neither necessary nor sufficient**
- **External validation**.

External Validation

- **Formal process** for conducting external validation that includes:
  - **Systematic identification & justification** of data sources
  - **Specification** of whether a data source is
    - dependent,
    - partially dependent, or
    - independent;
  - Description of which parts of the model are evaluated by each
  - Simulation of each data source and comparison of results
  - Measures of how results match observed outcomes
- Description of external validation & results **available on request**
- When feasible, test for prediction of future events
- Seek opportunities to conduct predictive validations as part of the overall validation process.

Dynamic Transmission Models

Andy Briggs

On behalf of

Working group