Bayesian methods for missing data: part 2

Illustration of a General Strategy

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BAYES 2013, May 21-23, Erasmus University Rotterdam

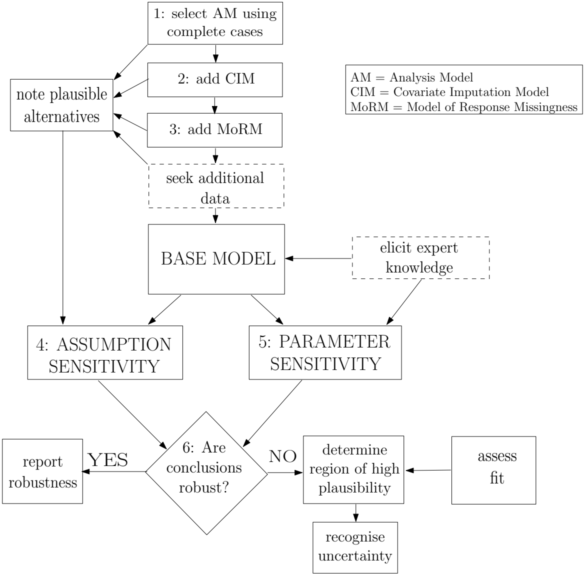
Introduction

- In part 1, we discussed the use of Bayesian joint models for dealing with missing data
- Considering a regression context, key points were:
  - subjects with missing responses can be modelled assuming ignorable missingness using just the analysis model
  - a missingness indicator must be modelled to allow for a non-ignorable missingness mechanism
  - a covariate imputation model must be built to include subjects with missing covariates
- In part 2, we will:
  - demonstrate how these ideas can be incorporated into a general strategy for modelling missing data
  - focus on sensitivity analysis
  - use the HAMD data as an illustrative example throughout

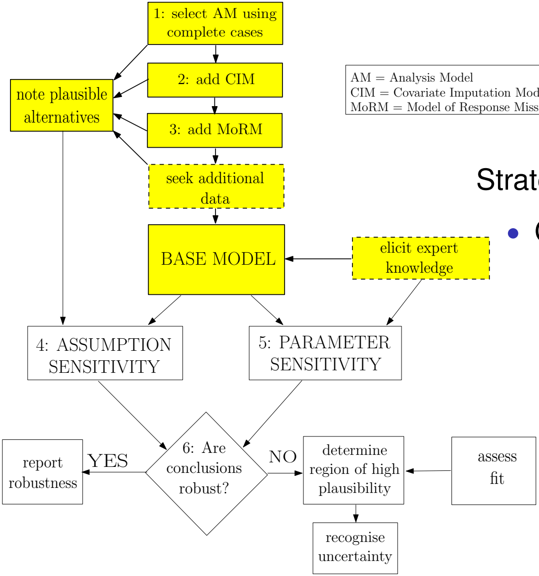
Strategy Overview

- The strategy (Mason et al., 2012b) consists of two parts
  - constructing a base model
  - assessing conclusions from this base model against a selection of well chosen sensitivity analyses
- It allows
  - the uncertainty from the missing data to be taken into account
  - additional sources of information to be utilised
- It can be implemented using currently available software, e.g. WinBUGS

Schematic Diagram



Schematic Diagram: constructing a base model

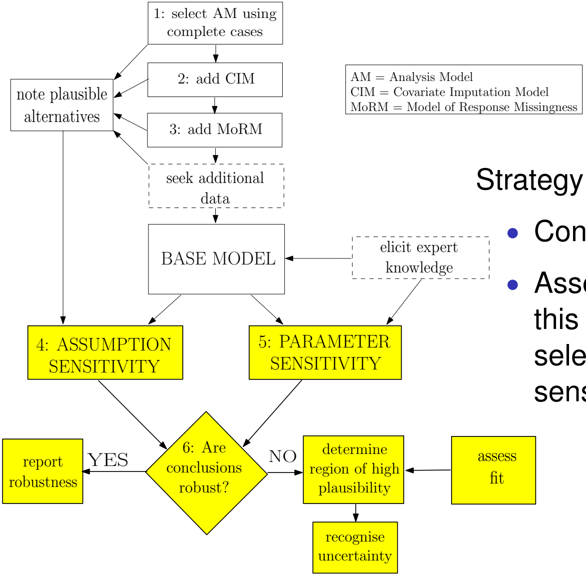


AM = Analysis Model
CIM = Covariate Imputation Model
MoRM = Model of Response Missingness

Strategy consists of two parts:

- Constructing a base model

Schematic Diagram: sensitivity analysis



Strategy consists of two parts:

- Constructing a base model
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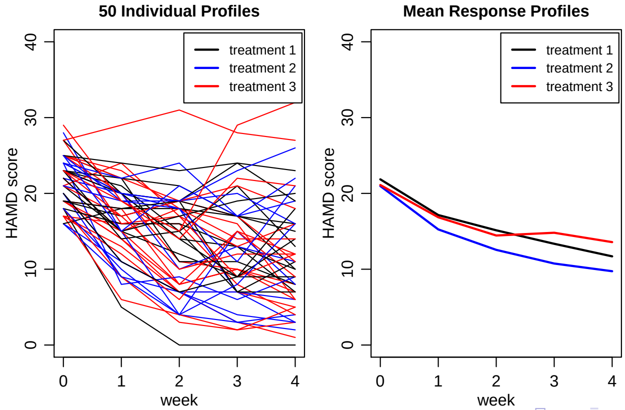
Illustrative Example: HAMD revisited

- Antidepressant clinical trial, comparing 3 treatments
- Subjects rated on HAMD score on 5 weekly visits
- Objective is to compare the effects of the 3 treatments on the improvement in HAMD score over time



Before the strategy: step 0

- The strategy consists of a series of model building steps
- Before starting, the missingness should be explored to determine
    - which steps are required?
    - are any other modifications needed?
- In particular
    - which variables have missing values?
    - what is the extent and pattern of missingness?
    - what are plausible explanations for the missingness?

HAMD example: step 0

Which variables have missing values?

- HAMD score (model response) missing in weeks 3-5
- No covariate missingness $\Rightarrow$ CIM not needed (omit step 2)

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What is the extent and pattern of missingness?

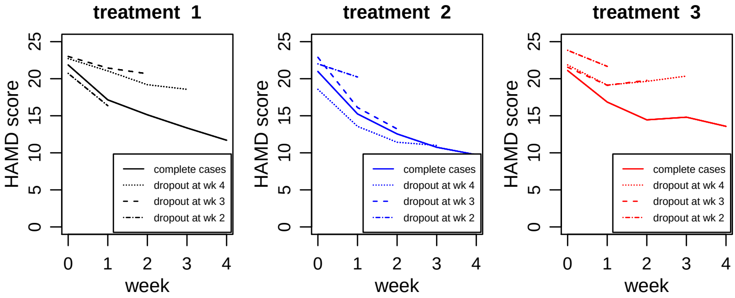
Percentage of missingness by treatment and week

	treat. 1	treat. 2	treat. 3	all treatments
week 2	11.7	22.0	9.3	14.2
week 3	19.2	29.7	16.3	21.5
week 4	36.7	35.6	27.1	33.0

- level and pattern of missingness inconsistent across treatments

HAMD example: step 0 continued

What is the extent and pattern of missingness? (continued)



- individuals have different profiles if they dropped out rather than remained in the study
- the treatments show different patterns

HAMD example: step 0 continued II

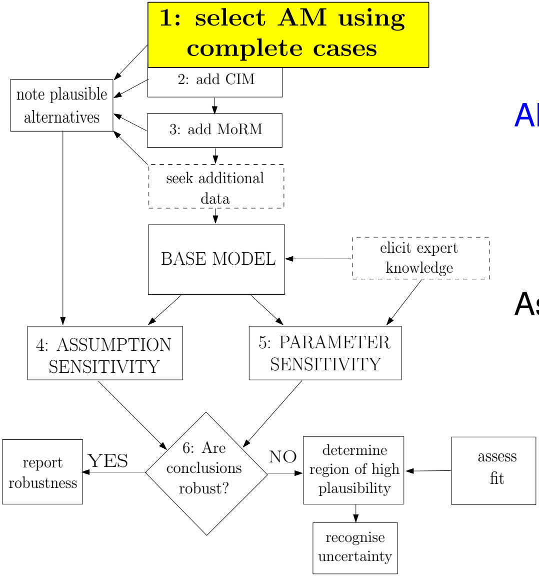
What are plausible explanations for the missingness?

- patients for whom the treatment is successful and get better may decide not to continue in the study
- patients not showing any improvement or feeling worse, may seek alternative treatment and drop-out of the study
- in either case, informative missingness
  $\Rightarrow$ MoRM needed (step 3)

Part 1 (steps 1-3): constructing a base model

- This part involves building a joint model as follows:
  1. choose an analysis model
  2. add a covariate imputation model
  3. add a model of response missingness
- Optionally, the amount of available information can be increased by incorporating data from other sources and/or expert knowledge
- The strategy
  - allows informative missingness in the response
  - but assumes that the covariates are MAR
- However, it can be adapted to reflect alternative assumptions

HAMD example: analysis model (step 1)

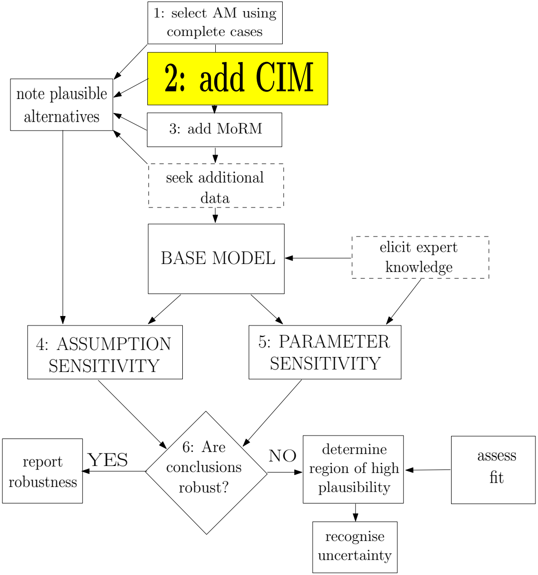


AM = Analysis Model

As discussed in part 1

- a hierarchical model with random intercepts and random slopes is reasonable

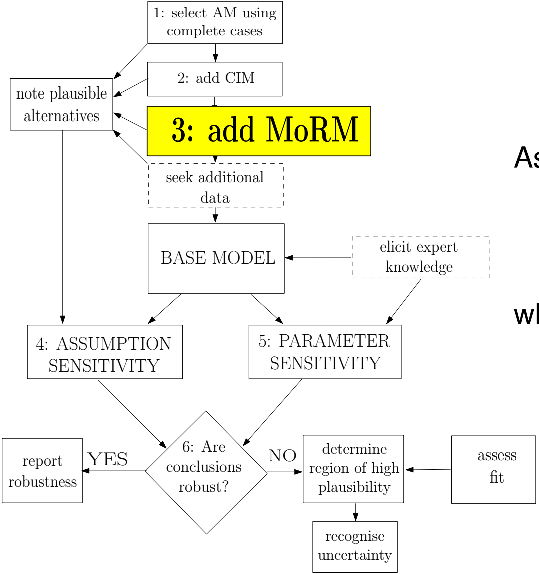
HAMD example: covariate imputation model (step 2)



CIM = Covariate Imputation Model

- No missing covariates in this example, so not required
- If data includes missing covariates, set up CIM to produce realistic imputations at this stage
- See part 1 for details
- Without a CIM, records with missing covariates cannot be included

HAMD ex.: model of response missingness (step 3)



MoRM = Model of Response Missingness

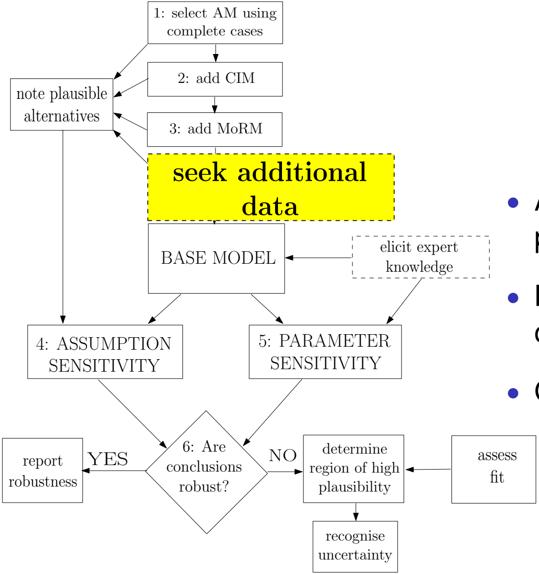
As discussed in part 1 use

$$m_{iw} \sim \text{Bernoulli}(p_{iw})$$
$$\text{logit}(p_{iw}) = \theta_0 + \delta(y_{iw} - \bar{y})$$

where $\bar{y}$ is mean of observed ys

- Allows informative missingness in the response
- Dependence is on current HAMD score

Optional step: seek additional data

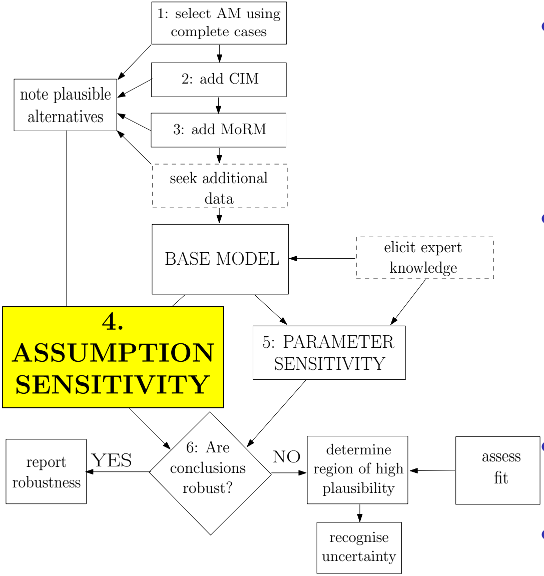


- Additional data can help with parameter estimation
- Most useful with missing covariates
- Omitted for HAMD example

Part 2 (steps 4-6): sensitivity analysis

- Sensitivity analysis is essential because assumptions are untestable from the data
- There are many possible options, and the appropriate choice is problem dependent
- We propose two types of sensitivity analysis:
  1. an assumption sensitivity
  2. a parameter sensitivity

Step 4 - assumption sensitivity



- Assumption sensitivity forms alternative models by changing the assumptions in the different base sub-models
- Key assumptions include:
  - AM error distribution
  - transformation of the AM response
  - functional form of the MoRM
- Stage 1: change single aspect to assess effect
- Stage 2: combine several changes

HAMD example: assumption sensitivity (step 4)

There are many options, including but not limited to the following

- Analysis model:
  - use a t_4 rather than normal error distribution
  - use an autoregressive model, AR(1), rather than random effects
  - include centre effects
  - allow for non-linearity by including a quadratic term
- Model of response missingness:
  - allow dependence on change in HAMD score
  - allow dependence on treatment
  - allow for non-linear relationship (piece-wise linear)

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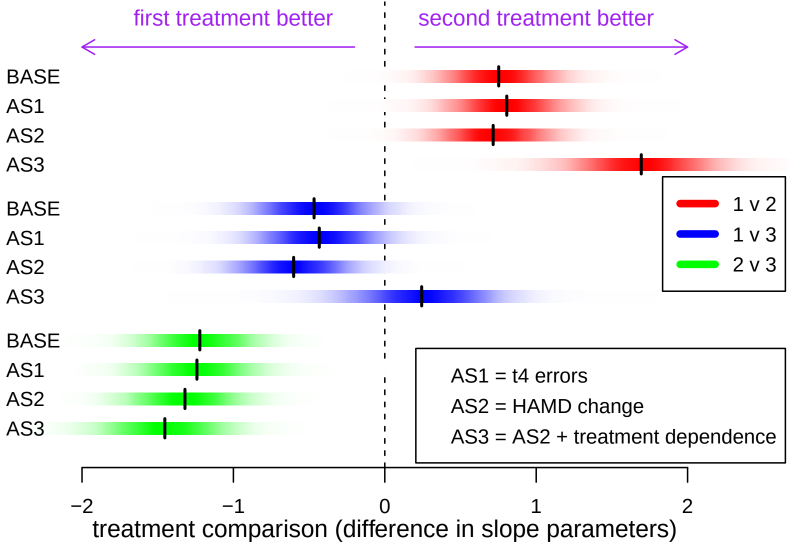
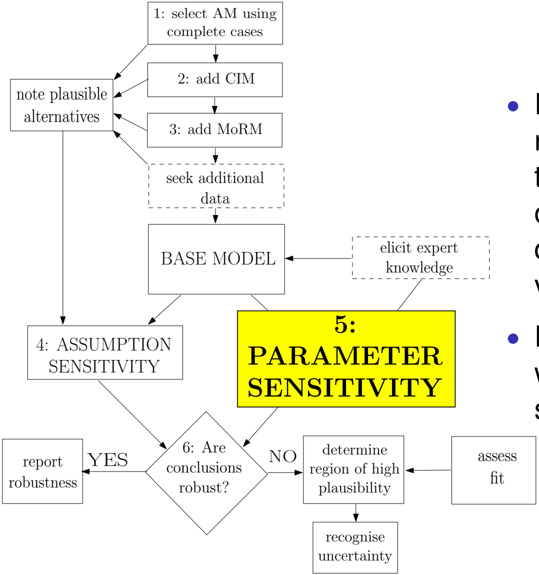
Example: results from assumption sensitivity

AS3: δ_{T1} 0.33 (0.01,0.62); δ_{T2} -0.41 (-0.63,-0.20); δ_{T3} -0.23 (-0.42,-0.02)



Step 5 - parameter sensitivity



- Parameter sensitivity involves running the base model with the MoRM parameters controlling the extent of the departure from MAR fixed to values in a plausible range
- Expert knowledge can help with setting the parameter sensitivity range

HAMD example: parameter sensitivity (step 5)

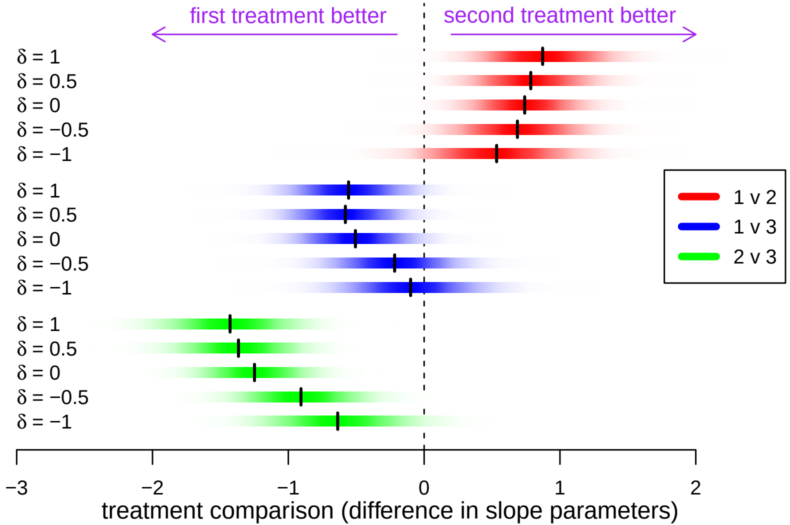
MoRM equation for Base Case

$$\text{logit}(p_{iw}) = \theta_0 + \delta(y_{iw} - \bar{y})$$

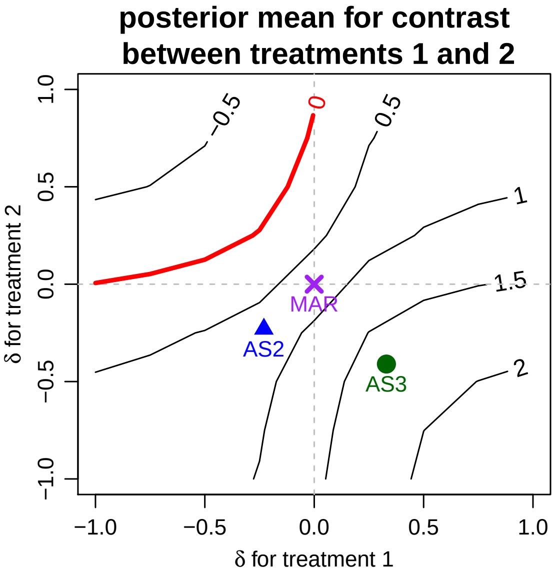
- δ estimated as 0.08 (0.04,0.11) in Base Case
- The value of δ controls the degree of departure from MAR missingness
- δ is difficult to estimate for a model with vague prior
- Run a series of models with δ fixed using point prior
  - 5 variants: values $\{-1, -0.5, 0, 0.5, 1\}$
  - δ corresponds to the log odds ratio of a missing response per point increase in HAMD score
  - range (-1,1) corresponds to assuming odds of non-response per unit increment in HAMD score ranges from ≈ 3 to $\frac{1}{3}$
  - $\delta = 0$ variant is equivalent to assuming the response is MAR

HAMD example: results from parameter sensitivity

MoRM equation: $\text{logit}(p_{iw}) = \theta_0 + \delta(y_{iw} - \bar{y})$

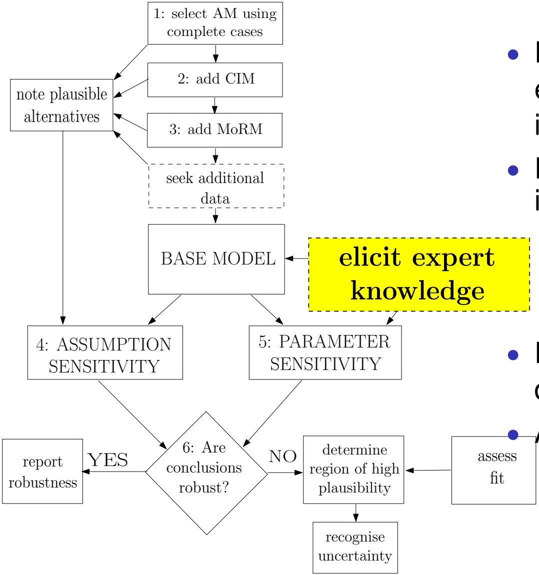


HAMD example: results from parameter sensitivity II



- Second parameter sensitivity based on AS3 (separate δ for each treatment)
- Investigate difference between treatments 1 and 2
- Fix δ_1 and δ_2 to values in range (-1,1)
- Fix $\delta_3 = -0.2$ (value suggested by AS3)

Optional step: elicit expert knowledge



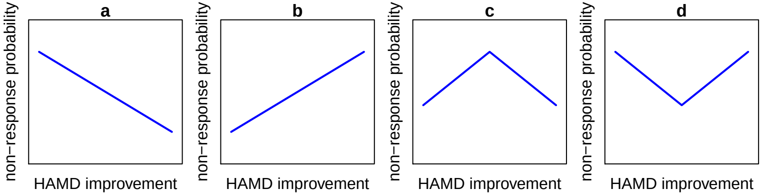
- Expert knowledge can be elicited and incorporated using informative priors
- Focus on parameters not well identified by the data
  - particularly those associated with the degree of departure from MAR
- Eliciting priors on parameters directly is difficult
- A better strategy is
  - elicit information about the probability of response
  - convert to informative priors

HAMD example: sample elicitation questions

Q1 Which variables do you think will help explain non-response?

A improvement in HAMD score since last visit (HAMD improvement)

Q2 What shape do you expect for the relationship between HAMD improvement and the probability of non-response?



A (d) ‘v’

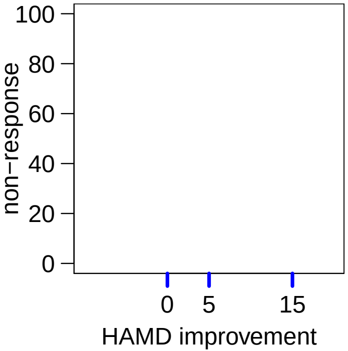
Q3 What value of HAMD improvement will minimise non-response?

A improvement of 5 points

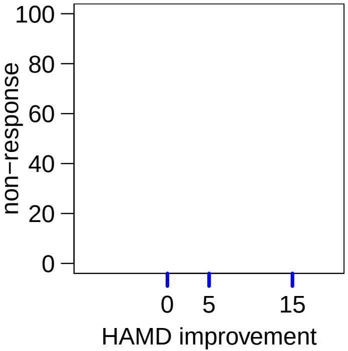
Q4 What other values of HAMD improvement should be used for elicitation?

A no improvement and improvement of 15 points

HAMD example: sample elicitation continued

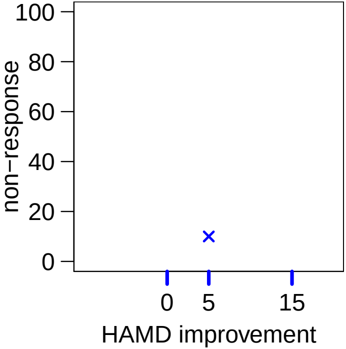


HAMD example: sample elicitation continued



Q5 Out of 100 subjects, how many would you expect not to respond if their HAMD score improves by 5?

HAMD example: sample elicitation continued



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A 10

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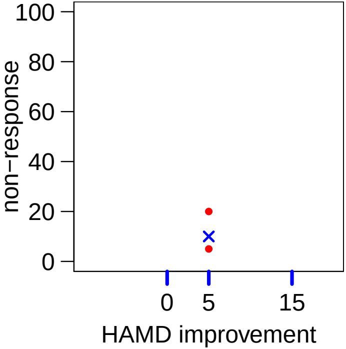

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- Similar questions can be used to elicit uncertainty

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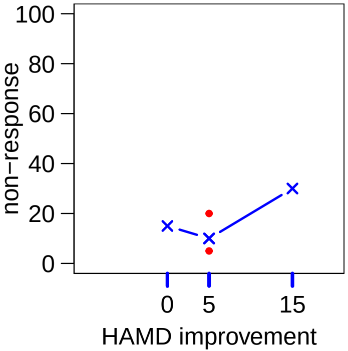

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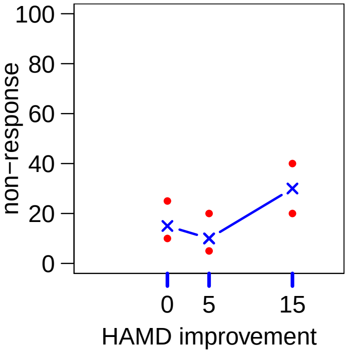
- Similar questions can be used to elicit uncertainty
- Elicit information at other values of HAMD improvement in the same way

HAMD example: sample elicitation continued



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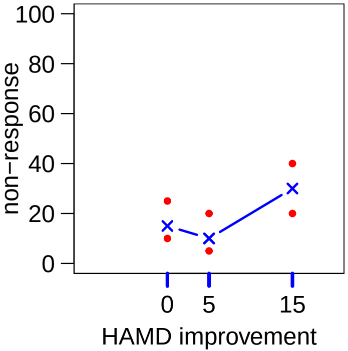

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- This information can be converted into informative prior on δ

$$\text{logit}(p_i) = \theta_0 + f(y_{iw}, y_{i(w-1)}; \delta)$$

- Can be incorporated as part of base case or used to inform sensitivity analysis

HAMD example: potential complications

- Probability of non-response may depend on other factors, e.g.
    - treatment
    - how depressed patient was previous week
- Multiple factors complicate elicitation
    - need to allow for an interaction between factors
    - ask questions of the form:

      Out of 100 subjects, how many would you expect not to respond if their HAMD score improves from 20 to 15?'

    - convert to joint rather than independent priors

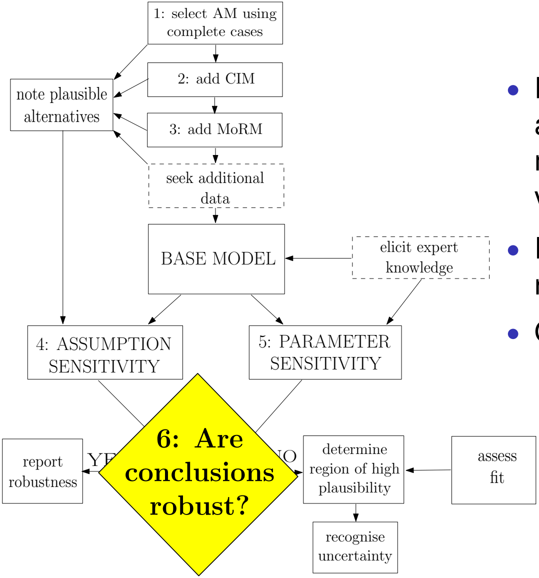
Elicitation: comment

Recall MoRM equation for Base Case

$$\text{logit}(p_{iw}) = \theta_0 + \delta(y_{iw} - \bar{y})$$

- The parameters associated with the response, δ, are identified by the parametric assumptions in
  - the analysis model (AM)
  - the model of response missingness (MoRM)
- This information is limited, so estimation difficulties can be encountered with vague priors
- If detailed elicitation is impractical, some information still helps
- In particular, ask questions that provide guidance on
  - variables to include in the model of response missingness
  - shapes of relationship between variables and probability of non-response
  - signs of parameters

Step 6 - determine robustness of conclusions



- Examine results of sensitivity analyses to establish how much the quantities of interest vary
- If the conclusions are robust, report this
- Otherwise
  - seek more information (optional steps)
  - determine a region of high plausibility
  - recognise uncertainty

Assessing model fit

- A model's fit to observed data can be assessed
- However, its fit to unobserved data cannot be assessed

  $\Rightarrow$ sensitivity analysis is essential
- DIC is routinely used by Bayesian statisticians to compare models, but
  - using DIC in the presence of missing data is not straightforward
  - the DIC automatically generated by WinBUGS is misleading (Mason et al., 2012a)
- Data not used in model estimation may be helpful in assessing model fit
  - compare model predictions against additional data

HAMD example: are conclusions robust? (step 6)

Consider comparison of Treatment 1 (T1) and Treatment 2 (T2)

- Base case - strong evidence T2 is more effective than T1
- Assumption sensitivity suggests strength of effect is uncertain
- In particular, AS3 suggests larger difference between T2 and T1
  - T1: $\delta > 0 \Rightarrow$ patient less likely to dropout if treatment effective
  - T2: $\delta < 0 \Rightarrow$ patient more likely to dropout if treatment effective
  - is this plausible?
  - different side-effects associated with each treatment?
  - are side-effect data available?
- Parameter sensitivity analysis examined AS3 further
  - ordering is only reversed if signs of δ are switched
  - if implausible, conclude treatment ordering robust to plausible sensitivities
  - otherwise report assumptions required to reverse ordering

Adaptions and extensions

- There are situations where it may be necessary to adapt this strategy
- Step 2 can be elaborated to allow MNAR covariates
- Steps 3 and 5 can be omitted if informative missingness in the response is implausible
- Could distinguish between different types of non-response
  - set up a missingness indicator with separate categories for each type of non-response
  - model using multinomial regression
- Bayesian models have the advantage of being fully coherent, but with large datasets or large numbers of covariates with missingness may be computationally challenging to fit

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- Offers possibility of including informative prior information about missing data process

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- Bayesian approach lends itself naturally to sensitivity analysis through different choices of prior distributions encoding assumptions about the missing data process
- Offers possibility of including informative prior information about missing data process
- But models can become computationally challenging...

Acknowledgements and References

- Thanks to Sylvia Richardson

- Funding by ESRC: the BIAS project (PI N Best), based at Imperial College, London

`www.bias-project.org.uk/research.htm`

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Two-pronged strategy for using DIC to compare selection models with non-ignorable missing responses.
Bayesian Analysis, **7**, (1), 109–46.

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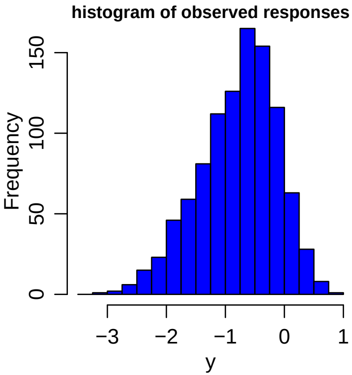
Strategy for Modelling Nonrandom Missing Data Mechanisms in Observational Studies Using Bayesian Methods.
Journal of Official Statistics, **28**, (2), 279–302.

How the AM distributional assumptions are used

Illustrative example (Daniels & Hogan (2008), Section 8.3.2)

- Consider a cross-sectional setting with
  - a single response
  - no covariates
- Suppose we specify a linear MoM,

$$logit(p_i) = \theta_0 + \delta y_i$$



- If we assume the AM follows a normal distribution, $y_i \sim \mathrm{N}(\mu_i, \sigma^2)$
  - must fill in the right tail $\Rightarrow \delta > 0$
- If we assume the AM follows a skew-normal distribution
  - $\Rightarrow \delta = 0$

Summary of required sub-models for a Bayesian analysis

Type of Variable with Missing Values	Missingness Type	Analysis Model	Covariate Imputation Model	Missing Mechanism Model
response	ignorable	✓	✗	✗
response	non-ignorable	✓	✗	✓
covariate	ignorable	✓	✓	✗
covariate	non-ignorable	✓	✓	✓