Missing outcome data in evidence synthesis with aggregate data

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What is this webinar about

- This workshop is about:

✓ missing outcome data

✓ meta-analyses of randomized clinical trials with aggregate data

- This workshop is **not** about:

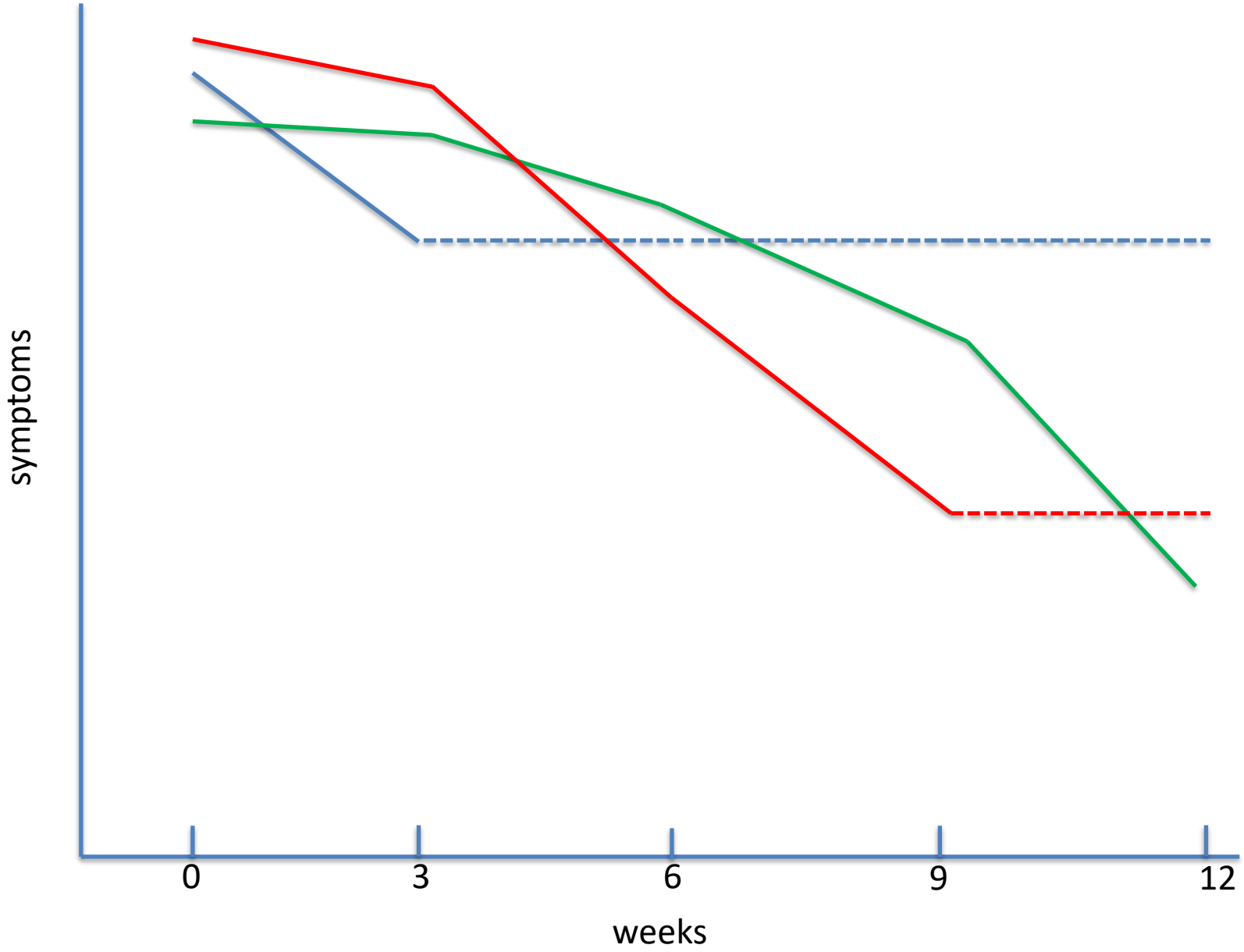
- missing studies
- selective outcome reporting
- missing statistics (e.g., standard deviation)
- missing covariates and auxiliary data

Why missing outcome data matter

It creates two main problems at RCT level:

- **Loss in power and precision**
  - Because the sample size decreases
- **Bias (maybe)**
  - Any analysis must make an untestable assumption about missing data
  - wrong assumptions may result in biased estimates
- There is **no remedy for missing data** - we can only do sensitivity analyses and see how much the results change under different assumptions

Last Observation Carried Forward (LOCF)



LOCF-imputed data

- A missing follow-up visit is replaced (imputed) by the subject's last observed value.

- If unobserved outcomes improve over time, then LOCF tends to favour treatment groups with less drop-out.

- If unobserved outcomes deteriorate over time, then LOCF tends to favour treatment groups with more drop-out.

For each study/arm we may have…

Study	Treatment	LOCF + competers			Completers			Missing
		LOCF + completers	MEAN	SD	N	MEAN	SD	
1	reboxetine	4+22=26	12.60	10.30	22	10.10	8.20	0
1	placebo	16+10=26	29.50	13.30	10	16.30	10.20	0
2	reboxetine	7+17=24	17.18	4.75	17	16.59	4.73	2
2	placebo	5+21=26	16.6	5.14	21	15.52	4.78	1

Assumptions about missing outcome data

Missing Completely At Random (MCAR)

The probability that data are missing does not depend neither on observed or unobserved variables

- In an RCT of antihypertensives that measures blood pressure (BP) data, the sphygmomanometer broke down unexpectedly and we lost some participants.

Missing At Random (MAR)

The probability that data are missing does not depend on the outcome or unobserved variables but can be fully accounted for by observed variables

- In an RCT of antihypertensives that measures blood pressure (BP) data, older participants are more likely to have their BP recorded. Missing data are MAR if at any age, individuals with low and high BP are equally likely to have their BP recorded

Missing Not At Random (MNAR) or Informatively Missing (IM)

The probability that data are missing depends on unobserved variables (e.g., the missing outcome itself)

- In an RCT of antipsychotics individuals with relapse are more likely to leave the study early in the placebo group

Complete case analysis (CCA)

- Analyze only those participants for whom we have observed the outcome.
- A CCA is valid when missing outcomes are MCAR
- It can be valid under certain MAR assumptions (e.g., when the probability of a complete case is independent on the outcome conditional on some explanatory variables).
- It is impossible to test whether missing data are MAR or MNAR

Risk of bias (RoB) for incomplete outcome data in RCTs

Examples of **low RoB**

- All participants completed the study, no losses to follow-up, no changes between groups
- Missing data are MCAR
- Reasons for missing data are reported and balanced across groups

Examples of **high RoB**

- Difference in missing rates across groups
- Reasons for missing data differ across groups
- Use imputation methods than treat imputed data as if they were observed (mean imputation, single imputation, LOCF etc.)

Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook

Intention-to-treat (ITT) analysis

- Requires measurement of all patient outcomes regardless of protocol adherence (in the groups to which they were randomized).
- The intention to treat approach is often inadequately described and inadequately applied.
- Many empirical studies show that most of the trials with missing outcome data do a CCA or a use a single imputation method.
- Single imputation methods replace the missing value by a value, they do not take uncertainty of imputation into account and consider imputed data as observed data, inflating sample size and producing spuriously narrow confidence intervals

- *Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ. 1999 11;319(7211):670-4.*
- *Wood A, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. Clinical Trials. 2004;1:368–376.*

Missing data at the meta-analysis level

- Systematic reviewers rarely distinguish between LOCF-imputed data and completely missing outcome data.
- Most systematic reviews either conduct a CCA or employ a single imputation strategy.
- Systematic reviews do not provide any justification on how they handled missing data.
- Few systematic reviews using an imputation strategy considered a sensitivity analysis.

- *Kahale LA, Diab B, Brignardello-Petersen R, Agarwal A, Mustafa RA, Kwong J, Neumann I, Li L, Lopes LC, Briel M, Busse JW, Iorio A, Vandvik PO, Alexander PE, Guyatt G, Akl EA. Systematic reviews do not adequately report or address missing outcome data in their analyses: a methodological survey. J Clin Epidemiol. 2018;99:14-23*
- *Spineli LM, Pandis N, Salanti G. Reporting and handling missing outcome data in mental health: a systematic review of Cochrane systematic reviews and meta-analyses. Res Synth Methods. 2015 Jun;6(2):175-87. doi: 10.1002/jrsm.1131.*

RCT: Haloperidol vs. placebo in schizophrenia

	Success	Failure	Missing
Haloperidol	29	18	22
Placebo	20	14	34

- Outcome: clinical global improvement (yes/no)
- RR (95% CI) = 1.05 (0.73, 1.50)
- Missing rates are 32% for haloperidol and 50% for placebo

How do systematic reviewers analyze these data?

RCT: Haloperidol vs. placebo in schizophrenia

	Success	Failure	Missing
Haloperidol	29	18	22
Placebo	20	14	34

Success rates: 29/47=0.62 vs 20/34=0.59 (Available Cases Analysis, ACA)

- RR (95% CI) =1.05 (0.73, 1.50)
- *Which is the assumption behind?*
  - *MCAR!*

Success rates: 29/69=0.42 vs 20/68=0.29

- RR (95% CI) = 1.43 (0.90, 2.27)
- *Which is the assumption behind?*
  - *All missing outcome values are failures!*

ANY analysis makes assumptions which, if wrong, produces biased results!

Mirtazapine vs Placebo for depression

Change in depression symptoms measured on the HAMD21 scale

Placebo				Mirtazapine			
Mean	SD	n	m	Mean	SD	n	m
-11.5	8.3	24	21	-14	7.3	27	18

What is the sample size you would use to estimate the weight of the mean difference (MD) in this study?

- ***Option 1***: the observed=24+27
  You assume MCAR! Complete Cases Analysis!

- ***Option 2***: the randomized=24+27+21+18
  You impute the observe mean in all missing participants –
  it is wrong as it produces spuriously small standard errors!

Single imputation methods

- **Dichotomous outcomes**
  - Best-case scenario: replace missing outcomes in the experimental group with “successes” and in the control group with “failures”
  - Worst case scenario: replace missing outcomes in the experimental group with “failures” and in the control group with “successes”
  - Replace all missing participants with failures

- **Continuous outcomes**
  - Last Observation Carried Forward (LOCF): replace missing outcome with last observed value
  - Mean/median Imputation: The missing value is replaced by the mean/median of the available cases

Summary table of possible analyses at the meta-analysis level (Cochrane Handbook)

Analysis	Outcome	Description of method/how it handles missing participants	Assumptions about missing outcome data	Adequacy for addressing missing data
CCA	Binary; Continuous	Ignores them	A random sample of all participants	Valid under missing completely at random (MCAR) – unbiased results but less powerful – MCAR rarely holds
Worst (best)-case scenario	Binary	Imputes failures in the treatment group and successes in the control (or vice-versa)	Worse in the experimental group (better in the experimental group)	*Inflates sample size and erroneously increase precision/reduce standard errors*
Mean imputation	Continuous	imputes the mean value	The same as observed	
Other single imputation	Binary; Continuous	Imputes specific number of successes/mean value	Explicit assumptions about them	
Gamble-Hollis	Binary	Downweigh studies according to best/worst case scenarios	Studies with large differences between best/worst case scenario are less reliable	Too extreme downweighting.
The suggested model	Binary; Continuous	Relate outcome in missing participants to outcome in completers. Downweigh studies with high missing rates.	Use expert opinion or sensitivity analysis to determine how missing outcomes relate to observed outcomes. The more the missing rate the less reliable is the estimate	**Accounts for uncertainty in the missing outcome data - Expert opinion can also be used.**

A general approach

We propose the Informative Missing (IM) parameter as a general way to think about missing data

- Definition: IM parameter relates a summary statistic in the missing group to the corresponding summary statistic in the observed group
  - **IMOR -** Informative Missing Odds Ratio: the odds of success in the missing group over the odds of success in the observed group
  - **IMDOM -** Informative Missing Difference of Means: mean in the missing group minus the mean in the observed group
- IM parameters may be different in intervention & control arms
- Not known, but we can suggest clinically plausible values

Assumptions about the informatively missingness parameter (IMP) – we call it λ for brevity (IMOR or IMDOM)

- MCAR $\lambda_{ij} = 0$
- Free $\lambda_{ij}, \lambda_{ij} \sim N(\mu_{\lambda_{ij}}, \sigma^2_{\lambda_{ij}})$
- Study specific λ: $\lambda_i \sim N(\mu_{\lambda_i}, \sigma^2_{\lambda_i})$
- Correlated λ's

$$\begin{pmatrix} \lambda_{iC} \\ \lambda_{iT} \end{pmatrix} \sim \mathrm{N}\left(\begin{pmatrix} \mu_{\lambda_{i\mathrm{C}}} \\ \mu_{\lambda_{i\mathrm{T}}} \end{pmatrix}, \begin{pmatrix} \sigma^2_{\lambda_{iC}} & \rho_\lambda \times \sigma_{\lambda_{iC}} \times \sigma_{\lambda_{iT}} \\ \rho_\lambda \times \sigma_{\lambda_{iC}} \times \sigma_{\lambda_{iT}} & \sigma^2_{\lambda_{iT}} \end{pmatrix} \right)$$

i refers to studies
j refers to arms

Dichotomous outcome
Informative Missingness Odds Ratio (IMOR)

$$\text{IMOR} = \frac{\text{odds of success in missing}}{\text{odds of success in observed}}$$

- **IMOR=2** the odds of success in the missing participants is twice that of the observed ones *(e.g., for a beneficial outcome, maybe people leave the study because of early response!)*

- **IMOR=0.5** the odds of success is half in the missing participants rather than the observed *(e.g., for a beneficial outcome, maybe people leave the study because of they are disappointed as they don't see any improvement!)*

- **IMOR=1 the data is missing completely at random**

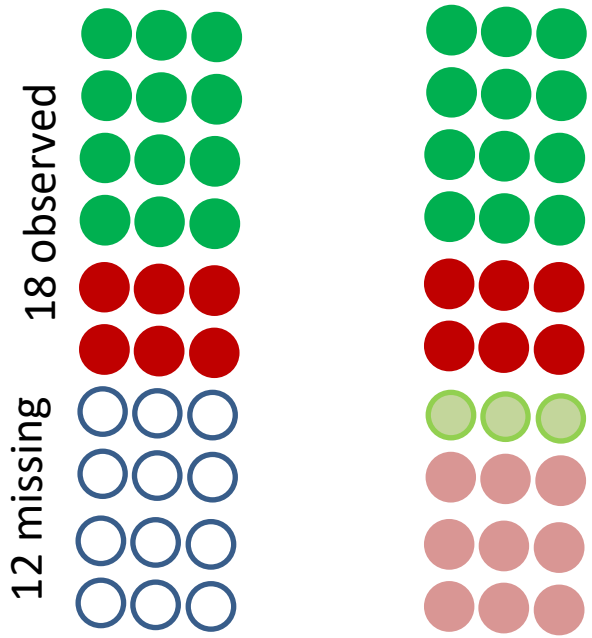
We work out the total odds starting from IMOR!

- We asked a clinician (or several!) with experience in clinical trials in the field:

"Out of 100 patients randomized in drug X, 40 recovered,20 did not recover and we have no information about 40 patients. How many of those 40 patients do you believe they have recovered?"

- He replied *"10 patients."*

$$\text{IMOR} = \frac{\text{odds of success in missing}}{\text{odds of success in observed}} = \frac{10/30}{40/20} = \frac{1}{6}$$



When we know IMOR, then we can work out successes and failures in the entire sample!

Odds in observed	2
Odds in missing	1/3
Total odds	1
IMOR	1/6

Continuous outcome
Informative missingness difference in means

$$\text{IMDOM} = \text{mean in missing - mean in observed}$$

- **IMDOM=1** the mean in the missing participants exceed the mean in the observed participants by one unit
- **IMDOM=-1** the mean in the missing participant is one unit less compared to the mean of the observed participants
- **IMDOM=0 the data is missing completely at random**

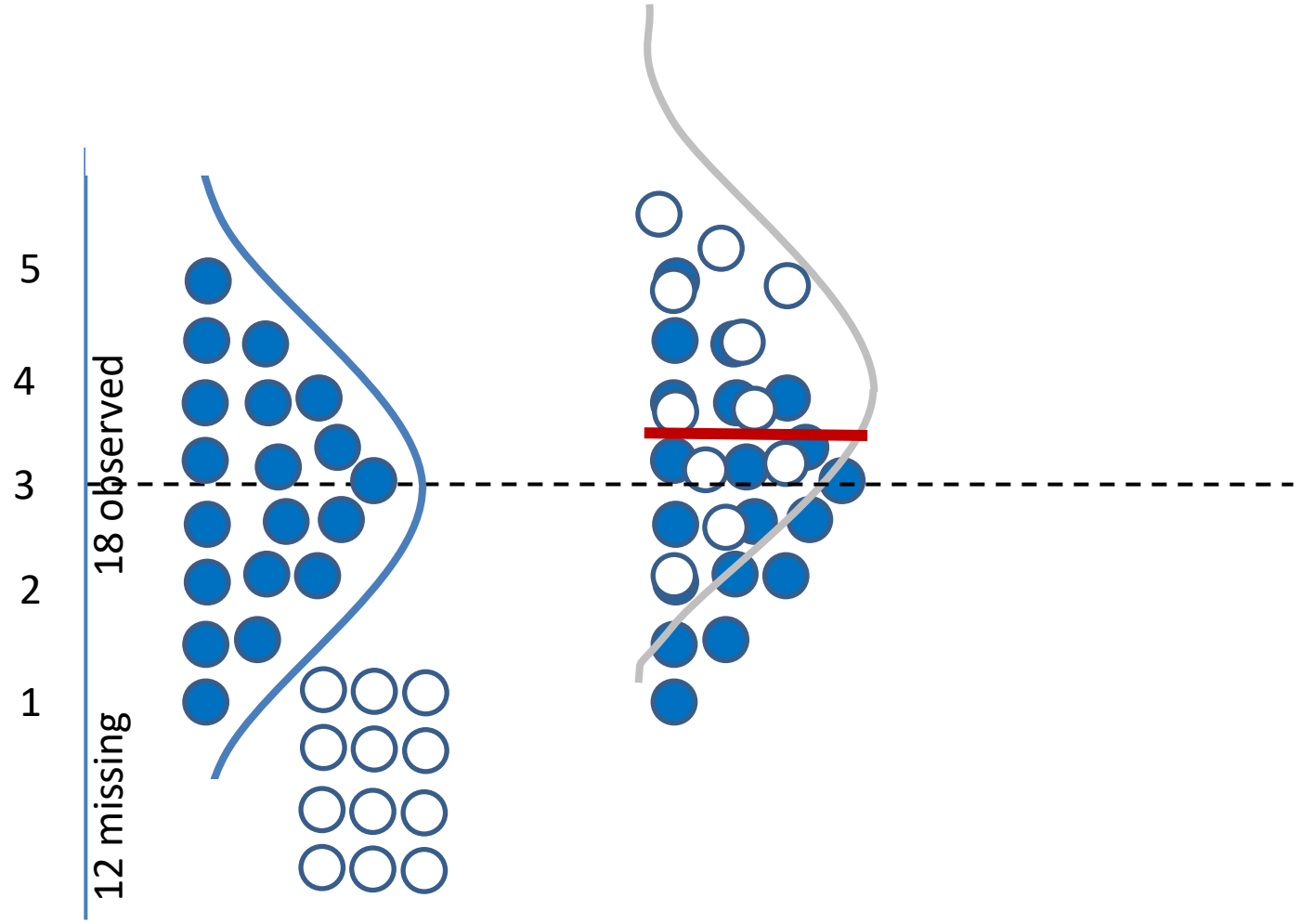
We work out the total means starting from IMDOM!

- We asked a clinician (or several!) with experience in clinical trials in the field

"Out of 100 patients randomized in drug X, 60 finished the study and had a mean score 3 whereas 40 patients did not finish. What do you guess would be the mean score in those who did not finish?"

- He answered *"The mean score in those who did not finish is on average 4."*

IMDOM = mean in missing-mean in observed=4-3=1



Observed mean= 3	Observed mean = 3
Mean of missing	Observed mean +IMDOM =4
Total mean	**3.4**
	(3×18+ 4×12)/30
IMDOM λ	1

Mirtazapine vs Placebo for depression

Study	Placebo				Mirtazapine			
	Mean	SD	n	m	Mean	SD	n	m
1	-11.4	10.2	19	26	-14.5	8.8	26	19
2	-11.5	8.3	24	21	-14	7.3	27	18
3	-11.4	8	17	13	-13.2	8	12	18

We assume **IMP=1 for Placebo** (the symptoms increased in the missing participants) and **IMP=-1 for Mirtazapine** (missing participants left because of early response)

Study	Placebo		Mirtazapine		MD
	Missing mean	Total mean	Missing mean	Total mean	
1	-10.4	-10.82	-15.5	-14.92	-4.10
2	-10.5	-11.03	-15	-14.40	-3.37
3	-10.4	-10.97	-14.2	-13.80	-2.83

Meta-analyze these!
(you need their SEs)

Consider a study comparing Mirtazapine to Placebo in patients with depression and the outcome is measured using HAMD21 scale at 6 weeks.

In the mirtazapine group:

- *some participants provide the outcome (completers)*
- *others dropped out of the study without providing outcome data (non-completers).*

In the completers we observe a mean drop of 14 in HAMD21 compared to baseline and a 95% CI for the mean drop is (11,17).

Some participants dropped out of the study without providing outcome data (non-completers) and we want to guess their outcomes. The table below gives some possible outcomes for a non-completer.

What proportion of the non-completers will have a reduction in HAMD21 scale falling in the categories described below?

	What proportion of the non-completers in the Mirtazapine group would have a reduction in HAMD21 in each of the following categories?								
	Interval of mean change for the non-completers (percentage improvements with respect to baseline score are given in parentheses)								
	More than 19	**Between 19 and 17**	**Between 17 and 15**	**Between 15 and 13**	**Between 13 and 11**	**Between 11 and 9**	**Between 9 and 7**	**Less than 7**	**Total**
Your answers	5	10	15	20	20	15	10	5	100%

White IR, Carpenter J, Evans S, Schroter S. Eliciting and using expert opinions about dropout bias in randomized controlled trials. Clin Trials. 2007;4(2):125-39. doi: 10.1177/1740774507077849.

$$\lambda \sim N(0, 2^2)$$

General characteristics of the approach

- We don’t impute missing data!
- We simply make assumptions about the outcome in the missing data and its relation to the observed data
- In the entire procedure we account for the fact that data are not fully observed
  - **This is very important in order to obtain correct standard errors from studies! (see later…)**

Pattern mixture models

$$Y = \left(Y^{obs}, Y^{miss}\right)'$$

$$R_{ijk} = \begin{cases} 1 & if\ outcome\ is\ reported \\ 0 & otherwise \end{cases}$$

i: study
j: arm
k: individual

$$P\left(R_{ijk} = 1\right) = \pi_{ij}^{obs}$$

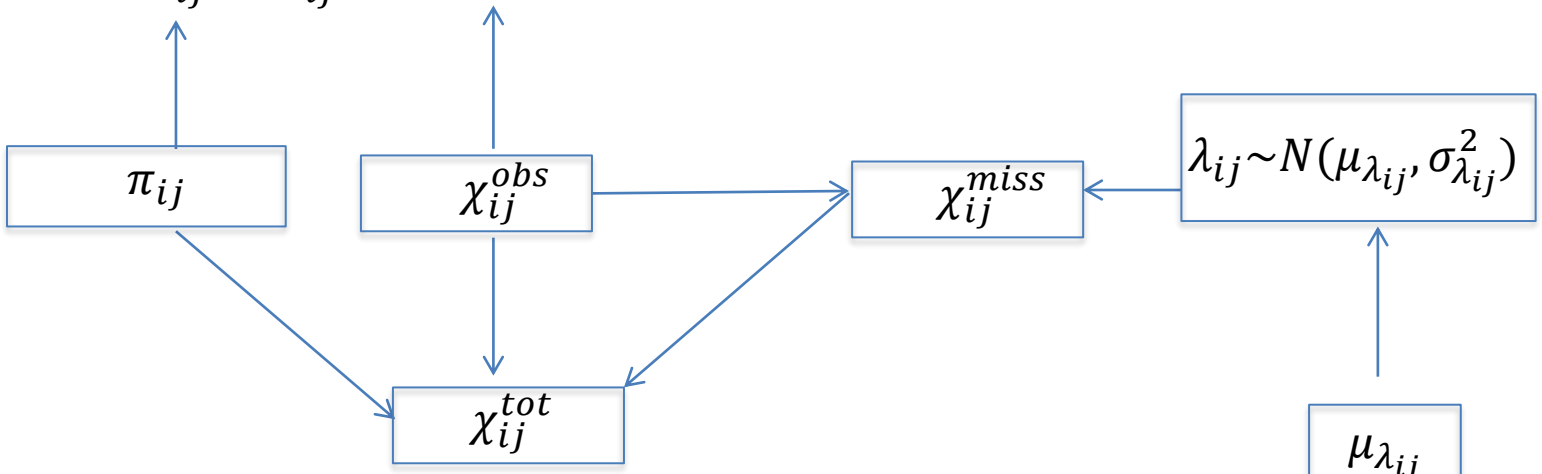
$$E\left(Y_{ijk} \middle| R_{ijk} = 1\right) = \chi_{ij}^{obs}$$

$$E\left(Y_{ijk} \middle| R_{ijk} = 0\right) = \chi_{ij}^{miss}$$

$$f(Y, R) = f(Y|R) \times f(R)$$

Model for arm j of study i pattern mixture model

$$p_{ij} = \frac{n_{ij}}{n_{ij} + m_{ij}} \qquad x_{ij}^{obs}, s_{ij}^{obs} \qquad g(\chi_{ij}^{miss}) = \lambda_{ij} + g(\chi_{ij}^{obs})$$



$$x_{ij}^{tot} = p_{ij} \times x_{ij}^{obs} + (1 - p_{ij}) \times x_{ij}^{miss}$$

$$x_{ij}^{tot} = p_{ij} \times x_{ij}^{obs} + (1 - p_{ij}) \times g^{-1}\left(\lambda_{ij} + g(x_{ij}^{obs})\right)$$

studies i, arms j

Estimating E(β) and var(β)
Taylor Series Approximation/Monte Carlo

$$ES_i = f(\chi_{\iota \mathrm{T}}^{\mathrm{tot}}) - f(\chi_{\iota \mathrm{C}}^{\mathrm{tot}})$$

$$\chi_{ij}^{tot} = \mathrm{p_{ij}} \times \chi_{ij}^{obs} + (1 - p_{ij}) \times g^{-1}\left(\lambda_{ij} + g(\chi_{ij}^{obs})\right)$$

- E(β) and var(β) are straightforwardly calculated if *f* and *g* are identity functions

$$ES_i = \chi_{\iota \mathrm{T}}^{\mathrm{tot}} - \chi_{\iota \mathrm{C}}^{\mathrm{tot}}$$

$$\chi_{ij}^{tot} = \mathrm{p_{ij}} \times \chi_{ij}^{obs} + (1 - p_{ij}) \times (\lambda_{ij} + \chi_{ij}^{obs})$$

$$\chi_{ij}^{tot} = \chi_{ij}^{obs} + (1 - p_{ij}) \times \lambda_{ij}$$

$$\mathrm{E}(ES_i) = x_{iT}^{obs} + (1 - \mathrm{p_{iT}}) \times \mu_{\lambda_{iT}} - x_{ic}^{obs} - (1 - \mathrm{p_{iC}}) \times \mu_{\lambda_{ic}}$$

$$var(ES_i) \approx \sum_{j=C,T} \left[\frac{p_{ij} \times (1 - p_{ij})}{n_{ij} + m_{ij}} \times \left(\mu_{\lambda_{ij}}^2 + \sigma_{\lambda_{ij}}^2\right) + \frac{s_{ij}^2}{n_{ij}} + \sigma_{\lambda_{ij}}^2 \times (1 - p_{ij})^2 \right] - 2 \times \rho_{\lambda} \times \sigma_{\lambda_{iC}} \times \sigma_{\lambda_{iT}} \times (1 - \mathrm{p_{iT}}) \times (1 - \mathrm{p_{iC}})$$

How to estimate the corrected SE of the MD after accounting for missing data: an approximation

MD = total mean in Mirt(azapine) - total mean in Pla(cebo)

Naïve SE^2(MD)≈ SE^2(observed mean Mirt) + SE^2(observed mean Pla)

"correct" SE^2(MD)≈SE^2(observed mean Mirt)+SE^2(observed mean Pla)

$$+f(proportion\ missing\ Mirt) + f(SE(\lambda))$$
$$+f(proportion\ missing\ Pla) \times f(SE(\lambda))$$

Adjustment factor!

Adjustment factor: accounts for both sources of uncertainty

The larger the proportion of missing data, the larger the SE(MD)

The more uncertain we are about the mean in the missing data, the larger the SE(MD)

Fictional example: Studies with same standard deviations and observed sample sizes per arm, but different missing rates

Study	Observed	ES	Naïve SE (relative weight)	Randomized
1	100	0.20	0.07 (20%)	100
2	100	0.10	0.07 (20%)	120
3	100	0	0.07 (20%)	150
4	100	-0.10	0.07 (20%)	200
5	100	-0.20	0.07 (20%)	300

Would you give each study the same weight?

- **No, because uncertainty should be larger when you have more missing data!**
  - **The observed sample size is not the only source of uncertainty!**
  - **First source of extra uncertainty:** Proportion of missing data!

Fictional example: Studies with same standard deviations and observed sample sizes per arm, but different missing rates

Study	Observed	ES	Naïve SE (relative weight)	Randomized
1	100	0.20	0.07 (20%)	100
2	100	0.10	0.07 (20%)	120
3	100	0	0.07 (20%)	150
4	100	-0.10	0.07 (20%)	200
5	100	-0.20	0.07 (20%)	300

We want to assume λ=0 (IMDOM=0)

- We can NEVER be sure that the mean in the missing is the same as in the observed
- We have some **uncertainty as to what exactly is the mean in the missing data**
- **We assume λ=0 with uncertainty interval (-1, 1)**
- **This is translated to $\lambda \sim N(0, 0.5^2)$**

– **Second source of extra uncertainty:**

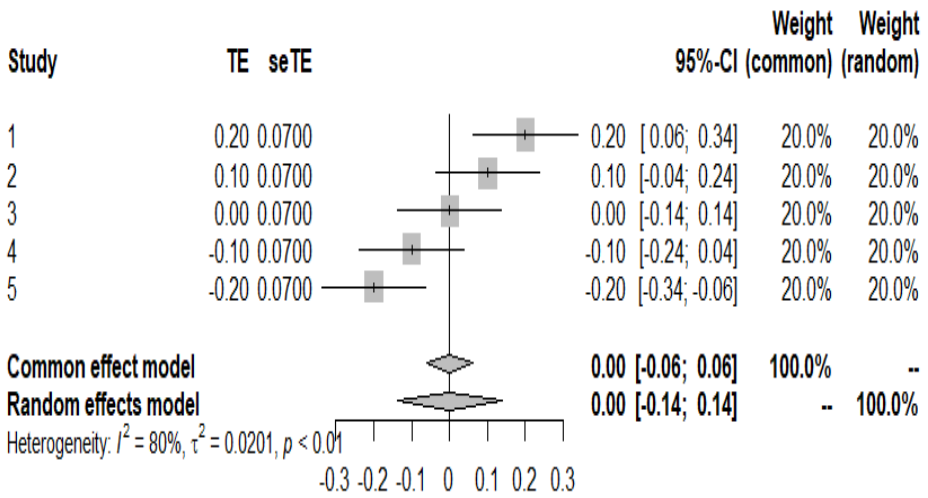
– Uncertainty about the assumption and IM parameter

Fictional example: Studies with same standard deviations and observed sample sizes per arm, but different missing rates

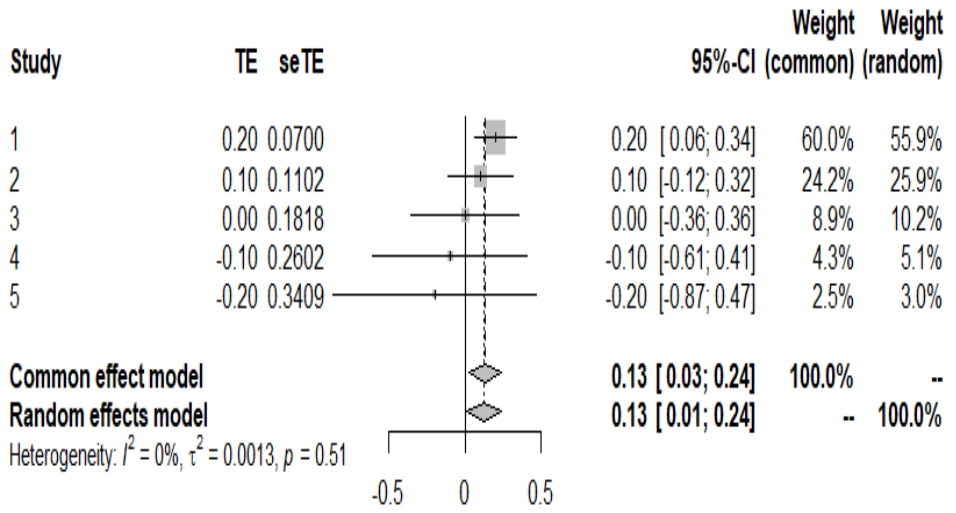
Study	Observed	Mean	Naïve SE (relative weight)	Randomized	Corrected SE (relative weight)
1	100	0.20	0.07 (20%)	100	0.07 (60%)
2	100	0.10	0.07 (20%)	120	0.11 (24%)
3	100	0	0.07 (20%)	150	0.18 (9%)
4	100	-0.10	0.07 (20%)	200	0.26 (4%)
5	100	-0.20	0.07 (20%)	300	0.34 (3%)

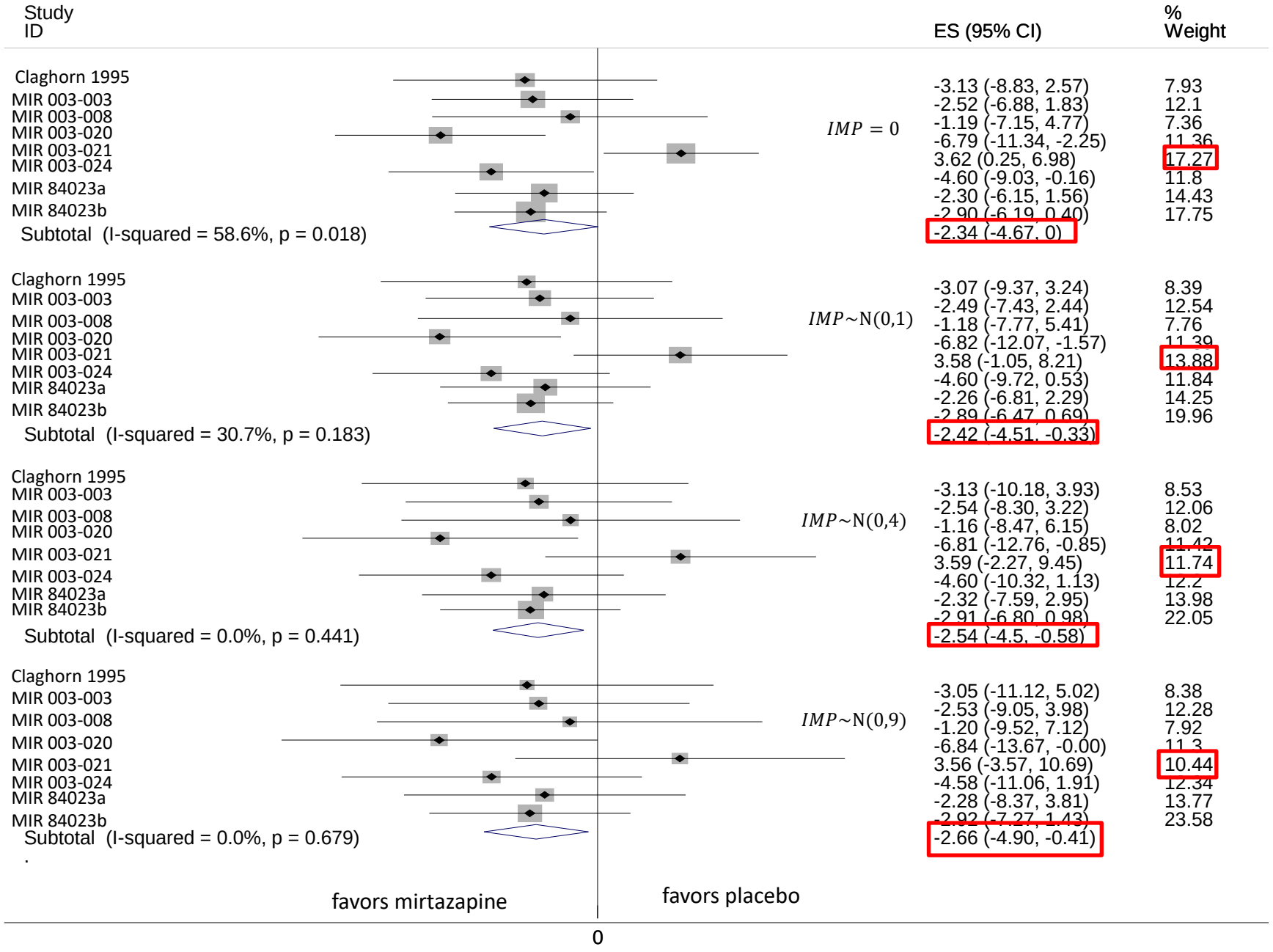
- We assume λ=0 with uncertainty interval (-1, 1), $\boldsymbol{\lambda \sim N(0, 0.5^2)}$
- Studies with more missing data get less weight!

Complete case analysis
$\lambda = 0$



$\lambda \sim N(0, 0.5^2)$




Study ID
ES (95% CI)
% Weight
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
Subtotal (I-squared = 58.6%, p = 0.018)
$IMP = 0$
-3.13 (-8.83, 2.57) 7.93
-2.52 (-6.88, 1.83) 12.1
-1.19 (-7.15, 4.77) 7.36
-6.79 (-11.34, -2.25) 11.36
3.62 (0.25, 6.98) 17.27
-4.60 (-9.03, -0.16) 11.8
-2.30 (-6.15, 1.56) 14.43
-2.90 (-6.19, 0.40) 17.75
-2.34 (-4.67, 0)
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
Subtotal (I-squared = 30.7%, p = 0.183)
$IMP \sim N(0,1)$
-3.07 (-9.37, 3.24) 8.39
-2.49 (-7.43, 2.44) 12.54
-1.18 (-7.77, 5.41) 7.76
-6.82 (-12.07, -1.57) 11.39
3.58 (-1.05, 8.21) 13.88
-4.60 (-9.72, 0.53) 11.84
-2.26 (-6.81, 2.29) 14.25
-2.89 (-6.47, 0.69) 19.96
-2.42 (-4.51, -0.33)
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
Subtotal (I-squared = 0.0%, p = 0.441)
$IMP \sim N(0,4)$
-3.13 (-10.18, 3.93) 8.53
-2.54 (-8.30, 3.22) 12.06
-1.16 (-8.47, 6.15) 8.02
-6.81 (-12.76, -0.85) 11.42
3.59 (-2.27, 9.45) 11.74
-4.60 (-10.32, 1.13) 12.2
-2.32 (-7.59, 2.95) 13.98
-2.91 (-6.80, 0.98) 22.05
-2.54 (-4.5, -0.58)
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
Subtotal (I-squared = 0.0%, p = 0.679)
$IMP \sim N(0,9)$
-3.05 (-11.12, 5.02) 8.38
-2.53 (-9.05, 3.98) 12.28
-1.20 (-9.52, 7.12) 7.92
-6.84 (-13.67, -0.00) 11.3
3.56 (-3.57, 10.69) 10.44
-4.58 (-11.06, 1.91) 12.34
-2.28 (-8.37, 3.81) 13.77
-2.92 (-7.27, 1.43) 23.58
-2.66 (-4.90, -0.41)
favors mirtazapine
favors placebo
0

The key is the estimation of the SE of the effect size

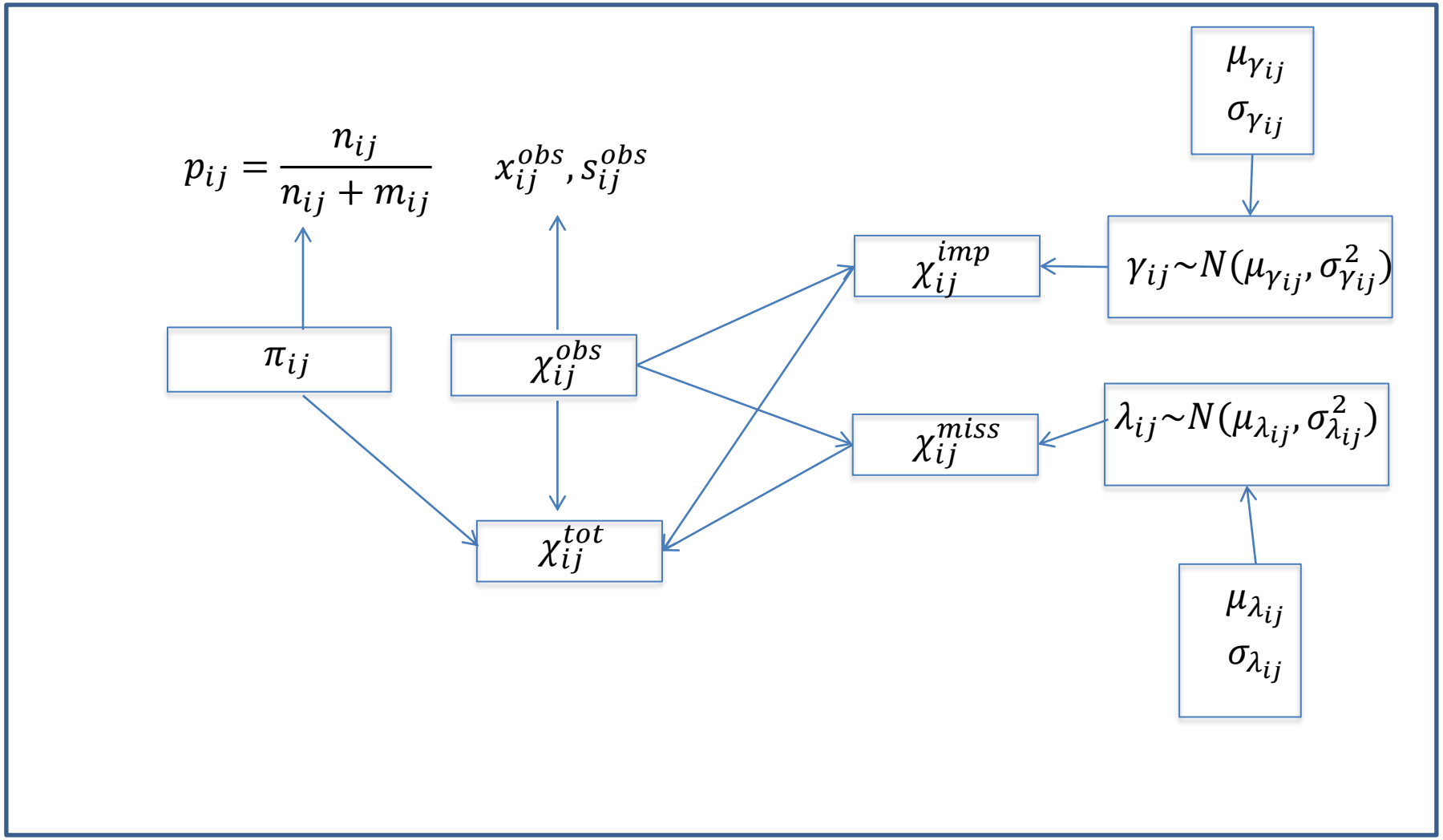
- To estimate SE(logRR), SE(logOR) and SE(SMD) you need mathematical manipulations or simulations (rather cumbersome!)

- Likely, Stata (metamiss2 command) and R will do the trick for you!
  - Using Monte Carlo
  - Using a Taylor series approximation

For all mathematical details see:

- *Mavridis D., White I., Higgins J., Salanti G* ***Addressing continuous missing outcomes in pairwise and network meta-analysis*** *Statistics in Medicine 2015,* ***34****:721-41*
- *White IR, Higgins JPT, Wood AM:* ***Allowing for uncertainty due to missing data in meta-analysis-Part 1 : Two-stage methods.*** *Statistics in Medicine 2008,* ***27****:711-727*

Model for arm j of study i pattern mixture model



studies i, arms j

The BILOCF parameter

- Bias in the LOCF outcome

$$BILOCF = \gamma = true\ mean\ outcome - LOCF\ imputed\ outcome$$

Assumptions about the BILOCF parameter

- MCAR $\gamma_{ij} = 0$
- Free γ_{ij}: $\gamma_{ij} \sim \mathrm{N}\left(\mu_{\gamma_{ij}}, \sigma^2_{\gamma_{ij}}\right)$
- Study specific γ: $\gamma_i \sim N(\mu_{\gamma_i}, \sigma^2_{\gamma_i})$
- Correlated γ's $\begin{pmatrix}\gamma_{iC}\\ \gamma_{iT}\end{pmatrix} \sim \mathrm{N}\left(\begin{pmatrix}\mu_{\gamma_{iC}}\\ \mu_{\gamma_{iT}}\end{pmatrix}, \begin{pmatrix}\sigma^2_{\gamma_{iC}} & \rho_\gamma \times \sigma_{\gamma_{iC}} \times \sigma_{\gamma_{iT}}\\ \rho_\gamma \times \sigma_{\gamma_{iC}} \times \sigma_{\gamma_{iT}} & \sigma^2_{\gamma_{iT}}\end{pmatrix}\right)$

Expert opinion

- *Participants randomized to fluoxetine were observed to have a mean score of 25 at the HAMD21 scale with 95% confidence interval [20-30] at 6 weeks after onset of the treatment.*
- *What is your prediction about their outcome at 12 weeks?*

Conclusions

- We suggest models that can:
  - Account for the fact that the presence of missing and LOCF-imputed data introduce uncertainty in the study estimates
  - Naturally downweight studies with lots of missing and imputed data
- metamiss2 command in STATA
- rnmamod library in R
- R library in construction (to allow also for LOCF imputed outcomes)

- *Chaimani A, Mavridis D, Higgins JPT, Salanti G, White IR. Allowing for informative missingness in aggregate data meta-analysis with continuous or binary outcomes: Extensions to metamiss. The Stata Journal 2018 18(3) 716-740.*
- *Spineli L, Kalyvas C, Papadimitropoulou K, rnmamod: Bayesian Network Meta-Analysis with Missing Participants. https://CRAN.R-project.org/package=rnmamod*

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Thank you!

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