Safeguarding public health

MHRA

Key messages from the CHMP guideline and the NAS report on Missing Data

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Disclaimer

- Views expressed are personal opinion and do not necessarily reflect those of the MHRA/EMA/CHMP/BSWP etc

Content

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- Adopted by CHMP in June 2010
- Came into effect in January 2011
- Drafting process had been ongoing since 2007
- Updates the original 2001 Points to Consider document

Key highlights (for me) from the guideline

- Quote from the introduction “The manner in which missing data are handled can have, depending upon the amount and type of missing data, a crucial influence on the final results of a clinical trial and on the certainty with which conclusions can be drawn.”

- Example – anonymised drug. 2 trials. 2 doses

- Outcome - Change from baseline to week 6 – Study 1

– ITT LOCF

	Placebo	X mg	Y mg	Active
Change from baseline (SE)	-10.7 (1.57)	-16.2 (1.66)	-14.9 (1.69)	-15.4 (1.63)
p-value		p=0.0145	p=0.0680	p=0.0342

– ITT Mixed model (CV=AR(1))

	-15.6 (1.36)	-21.3 (1.43)	-21.3 (1.38)	-20.2 (1.41)
		p=0.0043	p=0.0035	p=0.0193

– ITT Mixed model (CV=UN)

	-13.8 (1.66)	-21.2 (1.76)	-19.5 (1.73)	-19.9 (1.75)
		p=0.0024	p=0.0182	p=0.0118

MMRM v LOCF – An example

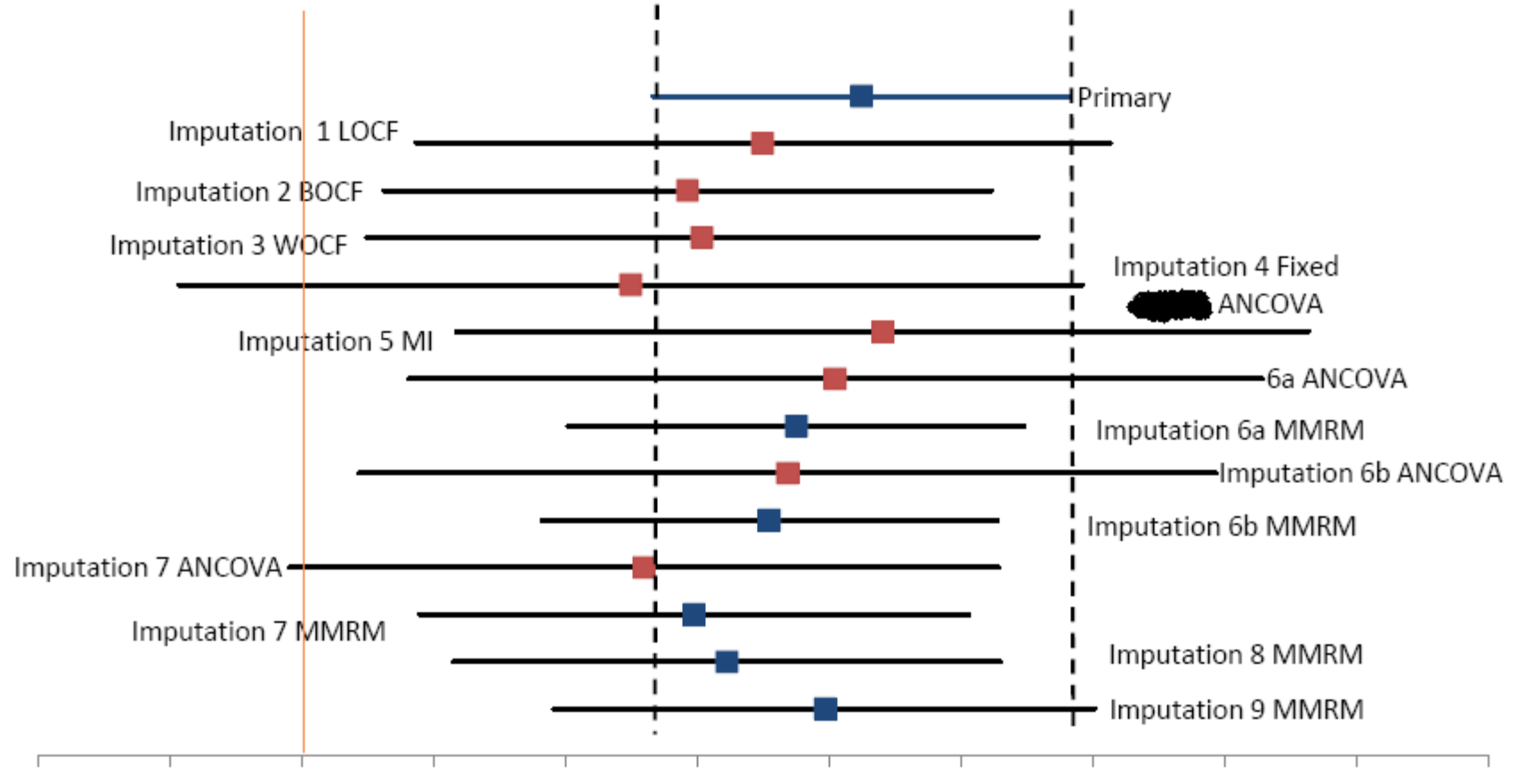
- Change from baseline smaller for all groups, including placebo for MMRM v LOCF
- Difference between treatment group smallest for LOCF
- Standard error for LOCF between that for the 2 different MMRM models
- Regulatory opinion is that LOCF may be the most appropriately conservative method in this particular situation, and thus presented in the SmPC, regardless of the pre-specification of MMRM as the primary analysis

Key Highlights - Sensitivity analyses

- “sensitivity analyses should investigate the robustness of the conclusions of the study, and it is essential that an analysis can be identified which is assessed not to be biased to an important degree in favour of experimental treatment”

- “Obtaining similar results from a range of methods that make similar or the same assumptions does not constitute an adequate set of sensitivity analyses. The sensitivity analyses should show how different assumptions influence the results obtained.”

Sensitivity Analyses – an example



- Both statistical significance *and* point estimate
- Not necessarily the smallest point estimate
  - Most *suitably* conservative
  - E.g. if an extreme imputation leads to a point estimate that does not seem realistic given all the other analyses, would not mandate its inclusion in the SmPC
- Important to allow comparisons with other SmPCs
- Even with overwhelmingly significant results that are not statistically in doubt, we need sensitivity analyses

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Factors that affect the acceptability of individual methods include:

- differences between the treatment groups in the proportion of patient withdrawals,
- differences between the treatment groups in the timing of withdrawals,
- the reason for the patient withdrawals,
- the direction of any spontaneous changes over time.

Reason for patient withdrawal

- Usually very well documented
- If there are missing data, might expect it to be for lack of efficacy on placebo, safety reasons on active
- Other patterns may be of more concern
- Very well covered in simulation studies assessing bias of particular methods

Proportion and timing of withdrawals

- Proportion usually well described in dossiers
- Timing less well, but anecdotally seems to be improving
- *A priori* expectations should be discussed, in light of data
- Generally well covered in simulation studies assessing bias of particular methods

Spontaneous changes over time – Bias?

- “MMRM has been shown to be unbiased” is not a sufficient reason to specify as primary analysis
- Regulatory consideration is that not reasonable to assume patients behave the same as those in the trial once they have dropped out of the trial (both on active and placebo)
- Regulatory decision is based on a suitable estimate as to what would have happened conditional on them *not* finishing the trial.
- In the absence of knowledge on whether they would have improved, got worse or stayed the same, which is most appropriate assumption?

- What if we do know what would happen to patients?

  "if the patient's condition is expected to deteriorate over time (for example in Alzheimer's disease) an LOCF analysis is very likely to give overly optimistic results for both treatment groups, and if the withdrawals on the active group are earlier (e.g. because of adverse events) the treatment comparison will clearly provide an inappropriate estimate of the treatment effect and may be biased in favour of the test product."

Spontaneous changes over time – Bias?

- Guideline further considers situations where it *might* be conservative
- LOCF acknowledged to not be appropriate under many conditions
- Does not mean it is not inappropriate under many others
- Only place in guideline where the appropriateness of methods is extensively discussed, is in the context of the spontaneous changes over time

- Definition of estimand – question you are trying to answer
- For example what is the main aim of conducting a 12-week trial in chronic pain?
- If a patient withdrawal due to adverse events after 6 weeks what does this say about the likely long-term efficacy for this subject if given this treatment?
- Are we primarily interested in a) difference in pain for all participants? b) completers? or c) evaluating this treatment success rate (e.g. proportion of patients who can tolerate therapy, remain in the study and achieve adequate pain relief over 12 weeks)?

- States option b) and c) answer key regulatory questions. What about a)?
- Which estimand should be primary for regulatory decision making?
- What is the efficacy of a drug if 70% get a good response and remian on treatment for 12 weeks and 30% can’t tolerate it for 12 weeks?
  - It depends!

- Strongly support recommendation 6
  - Trial protocol does need to include a detailed section that addresses missing data

- Recommendation 8 warrants further discussion

  - "All trial protocols should recognise the importance of minimising the amount of missing data, and, in particular, they should **set a minimum rate of completeness for the primary outcome(s),** based on what has been achievable in similar past trials."

- Broad agreement with CHMP guideline on the need to pre-specify methods and to describe why methods have been chosen in the protocol.
- Also agreement that a range of sensitivity analyses are generally required and should be pre-specified.
- Very important to clearly and precisely describe the question you are trying to answer when a trial is conducted. You should also precisely state the primary analysis that is going to be used to investigate this aim.
- Analyses may need to explore more than one estimand to provide sufficient evidence for regulatory approval.

Conclusions

- Missing data is both a point estimate and a p-value ‘problem’ – **sensitivity analyses are key**
- Lots of effort has been spent looking at the effect on the analysis based on the reasons for the missing data, and the proportion withdrawing
- Some effort on timing of withdrawals per arm.
- Much less effort spent on the spontaneous changes over time
- Still a key issue of regulatory concern

Conclusions

- Plans for future updates of the CHMP guideline?
- Has there been any changes in the regulatory assessment of confirmatory clinical trials following the CHMP guideline coming into effect?

Thank you

Any Questions?