Meta analysis of a small number of small studies: methods and added value

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Example in regulatory setting

Wakix (pitolisant) in narcolepsia, authorised March 2016

Adults for the treatment of narcolepsy with or without cataplexy.

8 Clinical studies in narcolepsy (578 randomised patients),of which 4 db placebo controlled.

Wakix in narcolepsia

- Primary endpoint: the difference in Epworth Sleepiness Scale at follow-up (ESSF) between pitolisant and placebo.
  - Using a linear mixed affects model, adjusted for ESSB with treatment and centre as fixed and random effects, respectively.

- The sample size:
  - Minimum clinically relevant difference on ESSF at 3,
  - Standard Deviation assumed to be $\sigma=5$,
  - Estimated coefficient of correlation r(ESSB, ESSF) = $\rho=0.65$,
  - Compound symmetry for the repeated measurements.

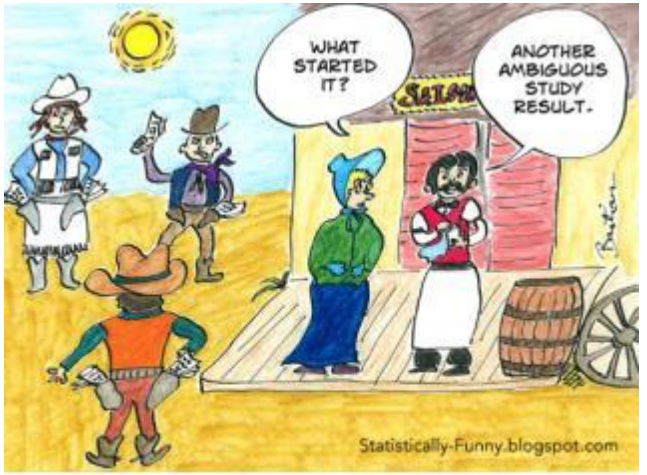
Results (EPAR)

Wakix in narcolepsia (versus placebo)

	Difference	**95% CI**	**p-value**
Harmony I (ITT 64 vs 30)	-3.0	(-5.6, -0.4)	0.024
Harmony I BIS (ITT 67 vs 33)	-1.94	(-4.05, 0.07)	0.065
[[post-hoc I BIS (re-allocation of small centers)	*-2.19*	*(-4.17, -0.22)*	*0.030]]*

Wakix in narcolepsia

Analysis performed across trials (pooled analyses and meta-analysis)



THINGS GOT TENSE FOR THE TOWNSFOLK WHEN THE THIRD META-ANALYST GANG RODE INTO TOWN.

To address this contradiction between results, …….

Individual Patient Data Analysis model using ……. O'Brien OLS test combining ESS, MWT and SART.

……This analysis showed that both low and high doses (20 and 40 mg) were better than placebo.

Meta-analysis in regulatory setting

- More precise estimate of the treatment effect.
- Positive effects are also seen in pre-specified subgroups.
- Evaluate an additional efficacy endpoint requiring more power.
- Evaluate safety in a subgroup of patients or a rare event in all patients.
- Improve the estimation of the dose-response relationship.
- Evaluate apparently conflicting study results.

Asterix ambitions - hopes

- Meta-analysis is employed to *integrate the evidence* after the trials are completed (whether prospectively planned or not).

- *Prospectively planned meta-analysis* are conducted at the end of the trial program as part of – or even as sole basis of – providing confirmatory proof of efficacy.

- The *program of clinical trials is prospectively planned*, with sequential (meta-) analysis to both allow early stopping of the program (after a study) as well as basis to provide primary evidence of efficacy.

Asterix ambitions - hopes

- Pro-actively use (sequential) meta-analysis to strenghten evidence in rare diseases.
- Incorporate previous (trial) results in design of future study to increase efficiency.
- Extend these efforts to multiple endpoints

Key challenges

- Heterogeneity fundamentally difficult in settings with a small number of small studies.
  - Solutions?
  - Robustness possible?

- Concepts of proposed methods
  - Sequential / incorporate historical data: weighting studies or yes/no included?
  - Independent studies? Separate studies versus adaptive design?