
Short topics

Basel September 13, 2016



Quantitative Safety and
Epidemiology

Short Topics

Safety Screening for DSUR or DSUR for Safety Screening?

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Background

DSUR ... to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reported period, related to a drug under investigation, whether or not it is marketed.

However, Its current format causes **challenges to reviewers**, namely to **synthesize large amounts of data** provided in Appendices

System Organ Class	Total up to 31-Dec-09			
	[Study drug]	Blinded	Active comparator	Placebo
Investigations	18	4	7	2
Alanine aminotransferase increased	9	2	4	1
Aspartate aminotransferase increased	9	2	3	1
Nervous System Disorder	2	2	4	7
Syncope	2	2	4	7

MHRA proposes to **pilot a simple statistical approach** as described in Davis & Southworth 2016 **to** enable and **support/guide** their regulatory analysis.

Pilot approach and questions

Proposed stats approach in a nutshell

- Draw attention to Serious Adverse Event PTs where the point estimate of relative risk (vs. control) is ≥ 3.0 or its lower 90% CI bound is ≥ 1.0 .

Note: This is regardless of designs of studies included, without multiplicity adjustment, applied to 'event' (rather than case) level data, and disregarding the events for 'blinded treatment'.

Questions

The proposed pilot consists of applying a one-size fits all method on data prepared for simple reporting. Is this appropriate?

How well does it cover expectations of the European regulatory agencies in terms of **quantitatively-aided safety signal detection** in ongoing/completed clinical trials ?

Thank you

EFSPI Workshop on Regulatory Statistics **Basel, 13th September 2016**

Carol Reid



Background

- In a rare disease setting a single pivotal trial missed statistical significance,
with $0.05 < \text{p-value} < 0.1$
- A second pivotal trial is planned but adequately powering the trial due to the limited population is challenging
- Does the second trial need to be powered as a standalone study with $\text{p-value} < 0.05$

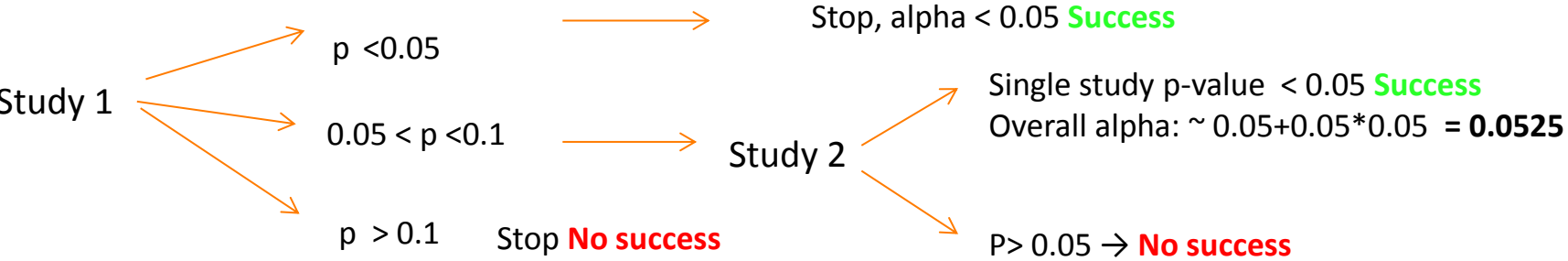
OR

- Is a meta-analysis approach, combining evidence from the two studies sufficient to provide evidence of efficacy (e.g. inverse normal p-value combination)?
 - E.g. Would a **combined** p-value < 0.05 be sufficient?
 - Would, in addition, a consistency consideration be needed e.g. 2nd study has p-value also below 0.1 or point estimates in same range?

Standalone vs Combined

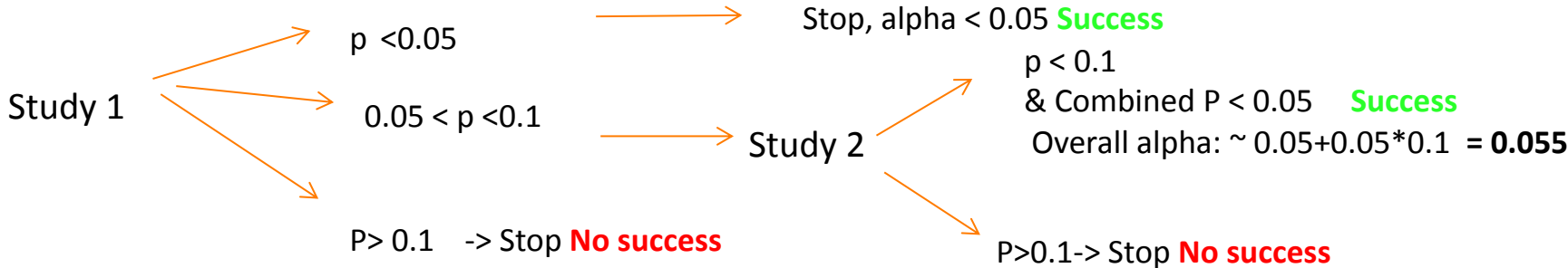


Standalone



Combined

Assume results will only be combined if 2nd study results are consistent with 1st study, i.e. $p < 0.1$



Thank You!

BMS Statistical Questions for EU

Question 1:



Immuno-Oncology (IO) endpoints

OUTLINE:

- In the new IO environment, some drugs have shown prolonged Overall Survival in multiple indications compared to standard treatment
- We could sometimes observe on the Kaplan-Meier curves:
 - a delayed effect, (i.e. hazard ratio close to 1 for a few months) followed by clear separation of the curves
 - IO curve ending with a “plateau”, i.e. larger number of long term survivors compared to control

In those cases, proportional hazards assumption may not hold.

QUESTION: Given that both the delayed effect and the “plateau” effect may be directly related to the mechanism of action of those compounds, could we use a weighted logrank test to compare treatment arms if pre-specified in protocol/SAP?

BMS Statistical Questions for EU

Question 2:



Immuno-Oncology (IO) endpoints

OUTLINE:

- In multiple clinical trials testing new IO compounds vs standard treatments, it was frequently observed that a large overall survival benefit didn't necessarily translate into a large difference in Observed Response Rate (ORR) or Progression Free Survival (PFS).
- This is somewhat unprecedented compared to the typical chemotherapy setting, again potentially due to the mechanism of action of IO compounds.

QUESTION: Having in mind approval acceleration in EU for those breakthrough therapies, would there be other shorter term endpoints recommended (e.g. Disease Control Rate, AUC of tumor size over time, durable responders rate ...)?

BMS Statistical Questions for EU

Question 3:



Single arms trials (SAT) in Oncology

OUTLINE:

- As presented by Francesco Pignatti at the EMA workshop on single-arm trials in cancer drug evaluation (London, 30 June 2016), SAT may be the only acceptable option for some patients.
- Use of SAT for regulatory approval in EU, in specific indications or for some breakthrough therapies, may therefore increase over time.

QUESTION: In case of EU submission using SAT only, would you recommend including historical trials & Real World data to strengthen the dossier?

OUTLINE:

- While OS generally remains the gold standard in oncology, there is clinical interest for patients to not only live longer, but also to have a good QoL.

QUESTION: Given the non-comparative setting and generally the relatively small sample size, do you recommend presenting QoL data for SAT in Study Reports as interpretation may be difficult?

BMS Statistical Questions for EU

Question 4:



Health Authorities and HTAs

OUTLINE:

- There have been recent examples in oncology where, despite regulatory approvals based on large well conducted randomized phase 3 trials demonstrating statistically significant and clinically meaningful superiority vs standard treatment, it was not necessarily followed by reimbursement in some EU countries.
- With the potential increase of single arm trials as basis for regulatory approvals in specific indications or for some new breakthrough therapies, reimbursement may even be more difficult to get in some countries, as discussed in the EMA workshop on single-arm trials in cancer drug evaluation (London, 30 June 2016).

QUESTION:

- **What could statisticians do to make packages not only acceptable towards Health Authorities, but also towards HTAs?**

BMS Statistical Questions for EU

Question 5:



First In Human (FIH) trials

OUTLINE:

- The Guideline on 'Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' is currently under revision.
- The Concept paper mentions an extension of the guidance to early phase CTs.

QUESTION:

- **Will the use of Bayesian designs be considered in the guidance, for example for dose finding studies?**