EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Meta-analysis in EU regulation

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Disclaimer

The views expressed in this talk are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

Current practice in EU

Do not routinely ask for formal synthesis of evidence

Can require a MA at post authorisation stage

No preauthorisation MA done by EU regulators

No clear guidance on safety MA

Guidelines

ICH E9

PtC on applications with 1.meta-analysis; 2.One pivotal study

ICH E9 1998

Meta-Analysis The formal evaluation of the quantitative evidence from two or more trials bearing on the same question. This most commonly involves the statistical combination of summary statistics from the various trials, but the term is sometimes also used to refer to the combination of the raw data.

7.2 Summarising the Clinical Database

An overall summary and synthesis of the evidence on safety and efficacy from all the reported clinical trials is required for a marketing application (Expert report in EU, integrated summary reports in USA, Gaiyo in Japan). This may be accompanied, when appropriate, by a statistical combination of results.

PtC on applications with 1.meta-analysis; 2.One pivotal study

May 2001

Addresses only MAA

Accepted regulatory purposes include

- Overall effects in pre-specified subgroups
- Analyse rare secondary outcome variables
- Safety in subgroups of patients or with rare adverse events

More on PtC

- Does not address
  - Study selection
  - Statistical models
- Specifies need for protocol
  - Stresses timing of protocol
- Report to include
  - Comparability of individual studies
  - Impact of each on overall result
  - Impact of each on heterogeneity

Acceptability of MA for efficacy

Sets strong conditions for a MA of primary variable to support authorisation

- Some positive studies
- Inconclusive studies have positive trend
- No statistical heterogeneity
- Pooled result CI well away from null
- Justification that biased selection unlikely
- Demonstration of robustness

Too strong for safety

Pooled safety data

MA of all data may be infeasible

MA of all controlled trials may be valuable

Recommends prospective standard setting to make safety outcomes comparable

Warns about short duration

Intra-study comparisons a ‘minimum requirement’

BSWP Survey to clinical assessors 2014

Points to consider on application with 1. Meta-Analyses; 2. one pivotal study

6.a) Are you aware of the guideline?		
Answer Options	Response Percent	Response Count
Yes	63.4%	85
No	36.6%	49
answered question		134
skipped question		30

600 invited to reply => 22% response for this question. Considerable apathy!

Motivations for increased understanding

Many regulatory debates arise from academic meta-analyses

A few examples .....

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

S.E. Nissen, M.D., K Wolski, M.P.H. N Engl J Med 2007

More than 24 weeks of treatment

42 studies, 27848 patients.

OR for MI 1.43 (1.03 to 1.98 p=0.03)

OR for CV death 1.64 (0.98 to 2.74 p=0.06)

Marginal result in a large group of studies. Demonstrates need to be able to engage at detailed level with researchers.

Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality

Amit Patel, Michael A Laffan, Umeer Waheed, Stephen J Brett, *BMJ 2014; 349*

16 studies, 4190 patients with sepsis

RR of death versus control fluid 0.94 (0.87 to 1.01)

Marginal result with a trend favouring albumin but exclusion of large effect. No evidence to support treatment with albumin.

Risk of myocardial infarction associated with selective COX-2 inhibitors: meta-analysis of randomised controlled trials.

Chen LC, Ashcroft DM. Pharmacoepi Drug Saf. 2007 Jul;16(7):762-72.

- 55 studies, 99087 patients.
- OR any Cox-2 inhibitor vs placebo 1.46 (1.02 to 2.09)
- OR Rofecoxib vs naproxen 5.39 (2.08 to 14.02)

Combined problem of validation of MA methodology and subgroup selection.

Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis.

Singh S, Loke Y, Spangler J, Furberg C. CMAJ 2011;183(12):1359-66.

- 14 RCTs, 8216 patients
- 7 to 52 weeks of follow-up
- OR varenicline versus placebo 1.72 (1.09 to 2.71)
- Not enough power to assess mortality

Detailed review by combined statistical group from EU NCAs. BSWP.

Request for further analysis by manufacturer.

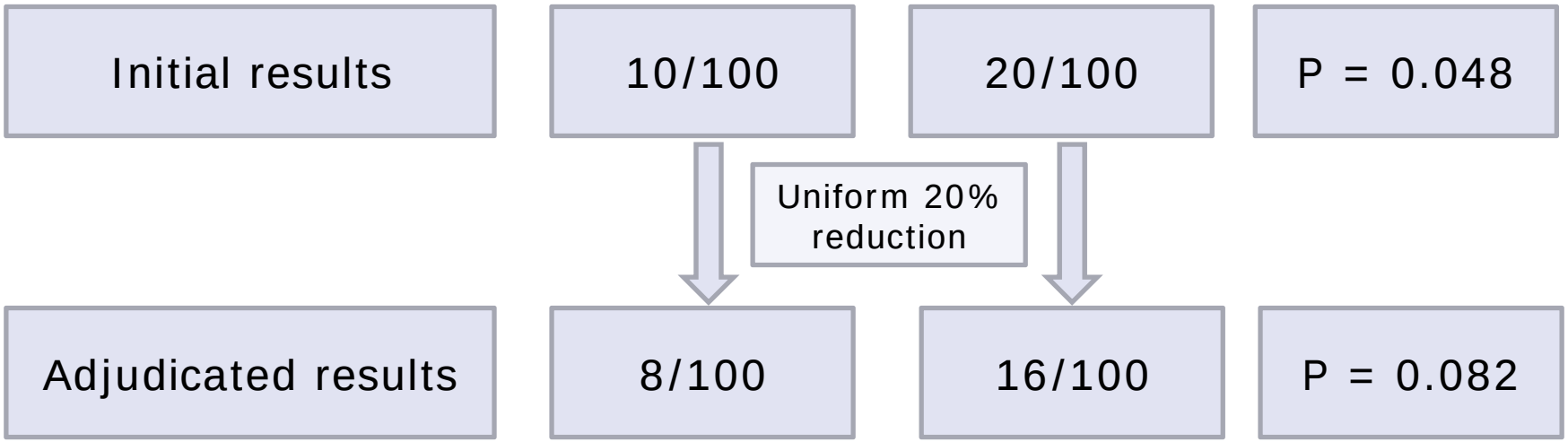
Pfizer meta-analysis

Company MA – ownership of data allowed readjudication of endpoints – good or bad?

Allowed assessment of first events and of accumulating events – good.

Company MA broadly in line with academic but causality and benefit/risk, even if causal, unclear.

Masked adjudication



Masking is not a guarantee against subversion

Questions

Do adjudicators look at events whether judged relevant or not in original studies? Or do they just look at events initially counted as relevant?

Do meta-analyses fully document the results of adjudication? Both downgrading and upgrading.

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REVIEW OF BSWP DELIBERATIONS IN LAST YEAR CONCERNING USE OF META-ANALYSIS

MA as a decision making tool

To establish best evidence for non-inferiority margin

Investigation of subgroups.

- To establish best evidence for extension of indication – may involve taking subgroups from several trials e.g. metastatic cancer
- To establish best evidence for paediatric population

Extrapolation of efficacy and safety in medicine development

One request from NCA for a network MA

DRAFT Guideline on the investigation of subgroups in confirmatory clinical trials

Plausibility of subgroups: Of course, when multiple trials are available that bear on the same question, a pooled analysis is possible. The possibility to look at two or more sources of evidence provides stronger evidence on the question of consistency, or otherwise, of effect in a subgroup than the mere presentation of a more precise estimate obtained through pooling of the respective subgroups from two trials.

Consistency of findings in relevant subgroups needs to be discussed in the analysis report: Forest plots graphing the treatment effect in a series of subgroups and statistical methods to assess heterogeneity of treatment effects estimated in subgroups play an important role for the provision of signals as to whether the overall treatment effect applies to the full trial population.

Concept paper on extrapolation of efficacy and safety in medicine development 2013

Second of two strategies: Some efficacy data are considered necessary in the target population the nature of which depending on the degree of extrapolation from the source population. Such a scenario could be supported by 'Bayesian' statistical approaches using prior information from the source population(s).

- E.g. Modelling prior information from existing data sets (Bayesian models, meta-analytic predictive).

To consolidate the reliability of conclusions based on extrapolation, collateral measures and criteria could be implemented such as:

- Prospectively planned meta-analysis including future trials.

DRAFT Reflection paper on assessment of cardiovascular risk of medicinal products for the treatment of cardiovascular and metabolic diseases

- Two potential approaches to assess clinical data
  - A meta-analysis of all ph II/III studies
  - A dedicated cv outcome study

Suggestions from companies

Network MA for comparison of new substance with all relevant comparators – to allow extension to as yet unidentified products.

Attempt to establish a relationship between surrogate endpoints and clinical outcome

Establishing best evidence on incidence or prevalence of contextual variables

WHAT GUIDANCE IS AVAILABLE OR UNDER DEVELOPMENT?

Current

Meta-analysis of Observational Studies in Epidemiology (MOOSE) guideline.

Non-Randomised Studies Methods Group (NRSMG) of the Cochrane Collaboration.

The Cochrane Adverse Events Methods group focuses on systematic reviews of the harms of interventions and covers all research designs from randomised trials to case reports and non-clinical data. Started 2007.

Draft Data Integration of controlled observational studies of the aetiology of harm. - ENCePP

The focus is on systematic review and meta-analysis of completed studies of adverse events

In contrast to CIOMS X the ENCePP guidance is focused exclusively on observational data.

Chapters on study identification and selection reflect the complexity associated with multiple possible designs and potentially greater publication bias.

Problem of missing data and data quality a major issue when data were not collected specifically for the studies.

Role of network meta-analysis? ENCePP positive.

CIOMS X

Covers randomised and observational studies

Examines issues from multiple angles – Industry, Regulators, Independent researchers …….

Talks about principles of analysis

Covers important issues of interpretation and communication

Messages

Growing awareness of need for meta-analysis when no single data source is sufficient

Reference to MA with regard to areas other than simple efficacy suggests a need to develop guidance

Statistical expertise is a limiting factor in EU regulation

THANK YOU