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Regulatory issues in the use of meta-analyses in drug approval

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Meta-analyses in clinical development

- Combining evidence from several trials that bear the same question to
  - Summarize efficacy
  - Analyze overall safety profile
  - Assess risk benefit
  - Support and justify clinical trial design
  - Extrapolate between populations/indications/endpoints

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Regulatory guidance

- ICH E9 (1998)
  - Meta-analytic techniques generally appreciated
  - Acceptability in specific circumstances not further discussed
- EMA Points to Consider (2001)
  - Meta-analysis (MA) as the sole base of pivotal evidence questioned
  - Different purposes identified for which MA are acceptable
  - Guideline for the conduct of MA given

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Purposes for MA

- EMA PtC:
  - Providing more precise effect estimates
  - Analyzing pre-specified subgroups
  - Analyzing additional efficacy outcome
  - Evaluating rare events
  - Evaluating dose-response
- Others:
  - Justification of non-inferiority margin
  - Surrogate endpoint evaluation
  - Extrapolation from one population to another (e.g. adults to children)

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Use of historical data (1)

- Support study design
  - Assumptions for statistical model
  - Evaluating operating characteristics
  - Endpoints, schedule
- Justify
  - Non-inferiority margin
  - Surrogate endpoint
- Use of historical data from another population (e.g. in pediatric submissions)

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Use of historical data (2)

- Maintain the paradigm of independent confirmation
  - Type-1 error should not be based on historical data
  - Non-inferiority:
    - Synthesis approach not acceptable
    - Fixed margin based on a MA
  - Surrogate endpoints
    - MA to validate
    - Type-1 error based on clinical study
- Extrapolation to children
  - Evidence synthesis approach (Bayesian MA) violates independent confirmation principle

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NI synthesis approach

- Indirect placebo comparison using data from several trials
- Combine treatment effects from historical and actual trial as well as their standard errors
  - test statistic (w/o adjustments):

$$\frac{d_{CP}+d_{AC}}{\sqrt{s_{CP}^{\ 2}+s_{AC}^{\ 2}}}$$

    - d_{CP} difference comparator – placebo with se s_{CP}
    - d_{AC} difference active drug - comparator with se s_{AC}
- Not acceptable for regulators
  - type-1 error depend on historical data

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Confirmatory pivotal use of MA

- Two pivotal studies as the standard of evidence
  - Independent confirmation of evidence more difficult if design/context/centers etc differ
  - Mainly: Maintaining the agreed level of evidence
- Preplanned MA that fulfils one-pivotal-trial criteria (maintaining the overall level of evidence) similar to the "convincing" one pivotal trial (which may be accepted)

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Basic principles in drug approvals

1. Define win criterion
2. Demonstrate efficacy using this win criterion
3. Show favourable risk benefit ratio
4. Additional claims need to be demonstrated in a confirmatory way after general efficacy (2) has been shown

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Consequences of approval principles

- Level of evidence / type-1 error / independent confirmation principle to be maintained for the prespecified win criterion:
  - Prob(win | no effect)
    = Prob(drug approved | drug ineffective) ≤ α
  - "Specificity"
    = Prob(drug not approved | drug ineffective) ≥ 1-α
- If trial successful according to win criterion risk benefit assessment using whole data base (e.g. by MA)

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Weakening requirements (1)

In some circumstances, especially

- Small populations
  - E.g. paediatric approvals
- Orphan drugs

modified requirement are discussed but not (yet) well specified.

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Weakening requirements (2)

Different options:

1. Lower level of evidence (one pivotal study, type 1 error)
   - ⇒ Decrease specificity to increase sensitivity (if drug is effective it should be approved, may be useful in orphan drugs)
   - ⇒ Acceptability of preplanned MA as one pivotal study approach
2. Modify paradigm of independent confirmation
   - ⇒ Historical data / prior beliefs may partially be used
   - ⇒ Acceptability of Evidence synthesis approach

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MA risks

Risks of meta-analytic efficacy assessment:

- Confirmation principles may be weakened
- Combining different designs may imply different questions
  - Low evidence for each of the questions
  - Difference may be subtle (scale, inclusion criteria = populations, slight differences in endpoints)
- Sequential use of MA/one-two pivotal trials increases type-1 error

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MA chances

- Sensitivity for difficult but important claims
- Assessment of heterogeneity
  - To which extent can we extrapolate the results to the general population?
  - Assessment of external validity
- Comprehensive risk benefit assessment
- Reasonable subgroup claims / exclusion of subgroups
- Proper assessment of rare adverse events

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MA for rare adverse events

- Importance of MED depend on information on rare adverse events
- Safety signals emerge at any point in the life-cycle:
  - Development program
  - Post-approval studies
  - Scientific publications
  - ⇒ Repeated MAs on safety signals using process control methodology
  - ⇒ Different sources / conditions as a methodological challenge

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Indirect comparisons

- Indirect comparisons are not robust:
  - Scale dependent
  - See NI discussion: Assay sensitivity and constancy assumption to be fulfilled in all indirect compariso
- Either rely on historical data or not really relevant:
  - Preplanned studies to be used for indirect comparison could, in general, also be planned as three-arm trials

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Summary

- MA to be used to fully use relevant data
  - Comprehensive risk benefit assessment
- MA to design properly to improve drug development
  - Justify endpoints / margins
- MA to assess external validity
- Internal validity / confirmation principle may be compromised if not properly planned
- Properly preplanned MA for confirmation not much different from one "convincing" pivotal trial