MHRA
Regulating Medicines and Medical Devices

Rationale for Issuing the Guideline and Main Points

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Medicines and Healthcare Products Regulatory Agency

CHMP – Benefit-Risk decisions

- Committee for Medicinal products for Human Use (CHMP)
- **Legislation** requires that marketing authorisation for a medicinal product shall be **refused** if:

(a) the **risk-benefit** balance is not considered to be favourable; or

(b) its **therapeutic efficacy** is insufficiently substantiated by the applicant; or

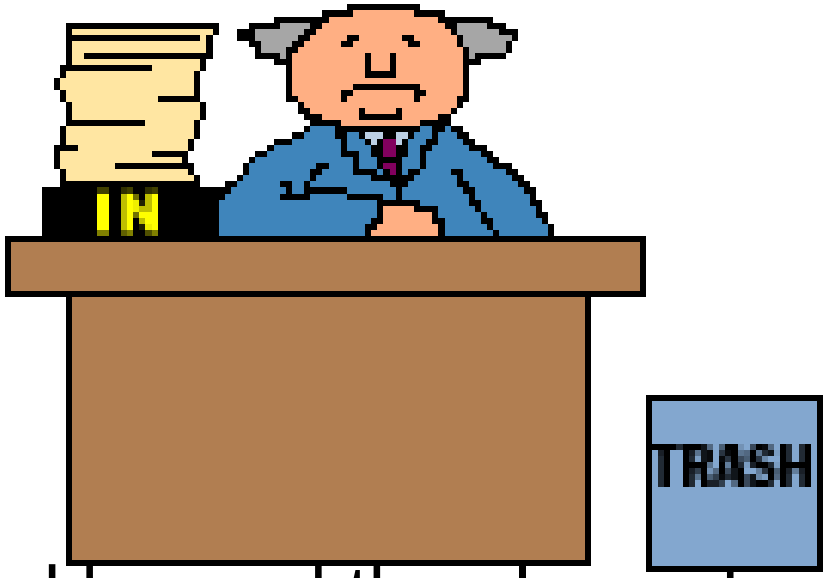
(c) its qualitative and quantitative composition is not as declared.

- **“therapeutic efficacy”** is considered in terms of the clinical relevance as well as statistical significance

CHMP – Benefit-Risk decisions

- P < 0.05 (two-sided)

P ≥ 0.05 (two-sided)



- Some discomfort to extend beyond the planned analyses into subgroups: lack of information and multiple testing

CHMP – Benefit-Risk decisions

- Marketing Authorisation is based on an SmPC (plus RMP etc.), including a description of the Therapeutic Indication in Section 4.1, where '**risk-benefit'** and **'therapeutic efficacy'** are met.

- The patient population does not automatically reflect the clinical trial inc/exc criteria; it is usually broader, but may be narrowed as the evidence dictates.

Exploratory subgroup analyses

- **Scenario 1: The clinical data presented are overall statistically persuasive with therapeutic efficacy demonstrated globally. It is of interest to verify that the conclusions of therapeutic efficacy (and safety) apply consistently across subgroups of the clinical trial population.**
- Scenario 2: The clinical data presented are overall statistically persuasive but with therapeutic efficacy or benefit/risk which is borderline or unconvincing and it is of interest to identify post-hoc a subgroup, where efficacy and risk-benefit is convincing.
- Scenario 3: The clinical data presented fail to establish statistically persuasive evidence but there is interest in identifying a subgroup, where a relevant treatment effect and compelling evidence of a favourable risk-benefit profile can be assessed.

What factors?

- Stratification factors
- Key demographic factors, including genomic factors, related to the mechanism of action / pharmacology would be included in this category.
- stage, severity or phenotype of disease
- use of concomitant medications
- possibly region or centre.

Warning…

“Analyses of subgroups cause some confusion and muddle in most reports of clinical trials, often with medically important adverse consequences. Subgroup analyses as currently practiced are a source of many importantly wrong clinical decisions and regulatory decisions. There are occasions on which they produce medically useful conclusions, but there are, at present, far more occasions on which they do the opposite.”

We have to choose – ignore subgroups because we may be mislead **(in either direction)** or tackle the challenges to try to make best informed evidence-based decisions?

Warning…

- If all patient groups benefit to same extent (same Δ) then will see smaller estimated effects, even –ve effects for some groups, **by chance**
  - Action leads to false –ve decision
- If some patient groups benefit to different extent (Δ1, Δ2, Δ3, possibly 0 or harm) then even more likely to see smaller estimated effects for some groups, **because it's real**!
  - To ignore leads to false +ve decision

Heterogeneity and Consistency

- Is my trial population heterogenous?
  - Yes, and (while there are limits) that is a good thing
- Will my treatment effect be consistent across the population?
  - No, but is the inconsistency important?

Scenario 1: The tension…

- “I don’t believe in subgroup analyses because we know they mislead and cause ‘error’”

- “I do believe in individuality, biology, pharmacology, pharmacogenomics, epidemiology etc. so I am interested to investigate subgroups to improve understanding of benefits and risks”

Scenario 1: The tension…

- "I don't believe in subgroup analyses because we know they mislead and cause 'error'"
  - It's not so interesting to discuss this further.

- "I do believe in individuality, biology, pharmacology, pharmacogenomics, epidemiology etc. so I am interested to investigate subgroups to improve understanding of benefits and risks"
  - It's rather non-negotiable.

Scenario 1: The tension…

Still not convinced…

- "I don't believe in subgroup analyses because we know they mislead and cause 'error'"
  - Yes, but even if none of your spanners fit, you have to fix the leaky pipe.

- "I do believe in individuality, biology, pharmacology, pharmacogenomics, epidemiology etc. so I am interested to investigate subgroups to improve understanding of benefits and risks"
  - Why would you assume 'consistency'?

Stereotypes of current practice

- Sponsors – *"**the wish is father of the thought**"*:
  - Planning: Consider stratification of randomisation, analysis. Otherwise ignore. Don't investigate inconsistency. Keep fingers crossed.
  - Inference: Dismiss inconvenient findings as chance
- *"we have performed many exploratory analyses therefore we will find some false negative results therefore … ignore"*
- *"this analysis was not pre-specified therefore … ignore"*
- **= disincentive to think scientifically (which the guideline may not remove!)**

Stereotypes of current practice

- Regulators
  - Leap on concerning trends ask questions and restrict indications*
  - * in fact this is not so common.

- **This difficult problem deserves more attention → more attention should lead to more good decisions → proposal for guideline**

One type of inconsistency

- (**Scenario 3**) In a ‘failed’ trial, with a ‘positive’ subgroup, it seems to be easy to find arguments that the finding is plausible and that the analysis is reliable.
  - Including ‘pre-specified’ (= mentioned somewhere in the protocol)
- (**Scenario 1**) In a ‘positive’ trial, with a ‘failed’ subgroup, it seems harder for the sponsor to find arguments that the finding is plausible, but to argue that the analysis is not reliable.
  - ‘Not pre-specified’ (= not part of confirmatory strategy)

The guideline

- What is described in the guideline is, largely, not new, but …
  - opportunities for harmonisation within regulators
  - framework to enrich submissions

- One notable distinction between ‘confirmatory’ and ‘exploratory’ subgroup analyses relates to the efforts devoted to planning.

- As usual this is principles to support planning and assessment, not a methods textbook.

The guideline

- **Think about your trial population** – e.g. demographic factors, including genomic factors, factors related to the mechanism of action / pharmacology, stage, severity or phenotype of disease, use of concomitant medications and possibly region or centre; the extent of expected heterogeneity dictates the effort to expend on planning, analysing and reporting findings in subgroups.

- **Assessors should expect to find discussion in the trial protocol of the expected degree of heterogeneity of the patient population** in terms both of factors likely to be prognostic for outcome and those that are plausibly predictive of different response to treatment.

The guideline

- **A strategy that simply assumes homogeneity of a population in terms of its likely response to treatment, without discussion and without further investigation, is not sufficient.** Similarly, **it is not sufficient to dismiss, withou due consideration, all findings that indicate heterogeneity of response as being spurious.**

- **The benefits of this additional discussion are to maximise the *a priori* discussion of the importance of certain subgroups and thus to minimise the *a postiori* discussion** in an attempt to promote rational consideration of subgroups and to reduce the risk for erroneous conclusions. **Done properly, this should minimise the need for data-driven investigations**, relying instead on a well reasoned pre-specified strategy.

Conclusions

- The majority of clinical trials are designed based on the assumption, whether taken explicitly or through neglect, that patients recruited to the trial will be homogenous and will respond homogenously, or at least without important heterogeneity.
- Investigation into the effects of treatment in well-defined subsets of the trial population is an integral part of clinical trial planning, analysis and inference.
- Pharmacology, biology and clinical practice are complex and it may be argued that an assumption of complete homogeneity is not credible.

Conclusions

- The question is not whether or not to explore important subgroups, but a framework for how to do this and for **decision making under uncertainty**.
- Improved decision making by promoting regulatory consistency and enriching company submissions.
- Need to **prove** ($p<0.05$) efficacy in every subgroup? No
- Are regulatory hurdles increasing?
  - In principle, no, but evolutions in science increase awareness of potential heterogeneity and regulation follows science