Clinical trials (for registration): which future?

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Disclaimer

- The views expressed in this lecture are personal. They do not necessarily reflect EMEA, CPMP or the Portuguese Agency positions on the same matters.

Summary

- Proof of efficacy - clinical trials
  - Problems
    - Perceived
    - Foreseen
  - Solutions
    - Logistic
    - Technical

My personal stance I

- Medicinal products (MP) should NOT be just another item to be consumed.
- Medicinal products' development should be prioritised by clinical need instead of potential revenues (if both come together - no problem!)

My personal stance II

- There is no point to allow on market a MP that has no advantage over what is already available. The potential advantage can be on:
  - Efficacy
  - Safety / tolerability
    - Commodity
      - Cost-effectiveness

Accordingly

- The setting where the risk-benefit relationship of a new medicinal product is favourable should be clearly defined within reasonable uncertainty margins, at time of approval. This includes:
  - targeted population
  - dose range
  - duration of treatment
  - effect size / safety profile
  - unknown or grey zones

Hierarchical organisation of evidence

From clinical trials: upward and downward

Clinical trial (randomised and controlled) is a true EXPERIMENT. Causality relationships may be established.

- **UPWARD**
  - Systematic review (including or not a
- **DOWNWARD**
  - Observational studies
    - cohort studies
    - case-control
    - series
    - case-reports

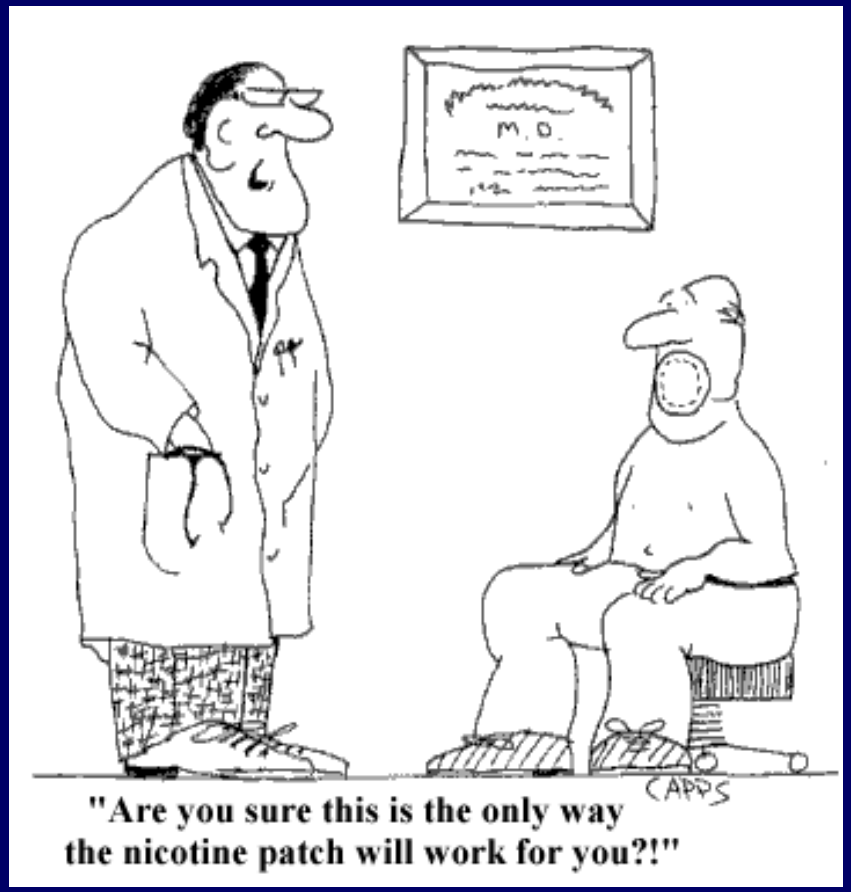
Proof of efficacy

- *Must be based in experimental studies = **Clinical trials.***
- **Levels of evidence**
  - **Efficacy**
  - **Safety**
  - **Effectiveness**

Proof of efficacy (clinical trials): perceived problems

- Goals out of focus
  - need to study niches
  - need to confirm
- Comparators
  - placebo
  - active comparators

Proof of efficacy "need to study niches"I



- Goal:
  - to show a relevant effect size in a clinical meaningful outcome.

Proof of efficacy "need to study niches"II

- Effect size: usual small in any field.
  - Unlikely paradigms
- Preferred targets:
  - population
  - type of health problems

Proof of efficacy "need to study niches"III

- Possible technical solutions:
  - add-on studies
  - test drug as rescue medication
  - factorial designs (testing associations of several MP at the same time).

  [*Mergers and Acquisitions make this possibility more realist]*
  - planned sub group analysis

Proof of efficacy
"Need to confirm..."

- Exploratory trials should not be transmutated in confirmatory trials.
- Dose-finding needs to be better done

Proof of efficacy
Comparators

- Need for active comparators:
  - In many medical fields long duration placebo controlled trials are no long ethically feasible or scientifically desirable.
    - Implies true comparisons.

Proof of efficacy
Comparators

- Choice of the comparator
  - Should reflect state of the art in clinical practice instead of the closest in the pharmacological class.

Proof of efficacy
Comparators

- Non-inferiority
  - absolutely exceptional
  - only if an advantage in other domain is foreseen
  - only if possible comparators are reliable and have consistent efficacy

Proof of efficacy
Comparators

- Placebo
  - ethical acceptability when standard treatments are available
  - variation of placebo effect size
    - mean effect
    - rate of placebo responders
    - need to explain variation

Proof of efficacy: foreseen problems

- Organisational
  - logistics/ professionalism
  - breach of quality standards / fraud
- Technical
  - optimisation of new designs
  - failure of some innovative tentatives
  - settings of increased complexity

Conclusions

- CT (for registration) should:
  - address focused questions to in need populations or subgroups.
  - reflect the mechanistic data available
  - reflect an well-informed prevision of future
  - incorporate design innovations to face the new challenges.
- Foreseen problems need prophylactic measures in place ASAP