Fundació Doctor Robert
UAB

EURORDIS
RARE DISEASES EUROPE

Review of key concepts in clinical trial methodology

Markku Toivonen, MD, PhD
Scientific Director
NDA Regulatory Science Ltd

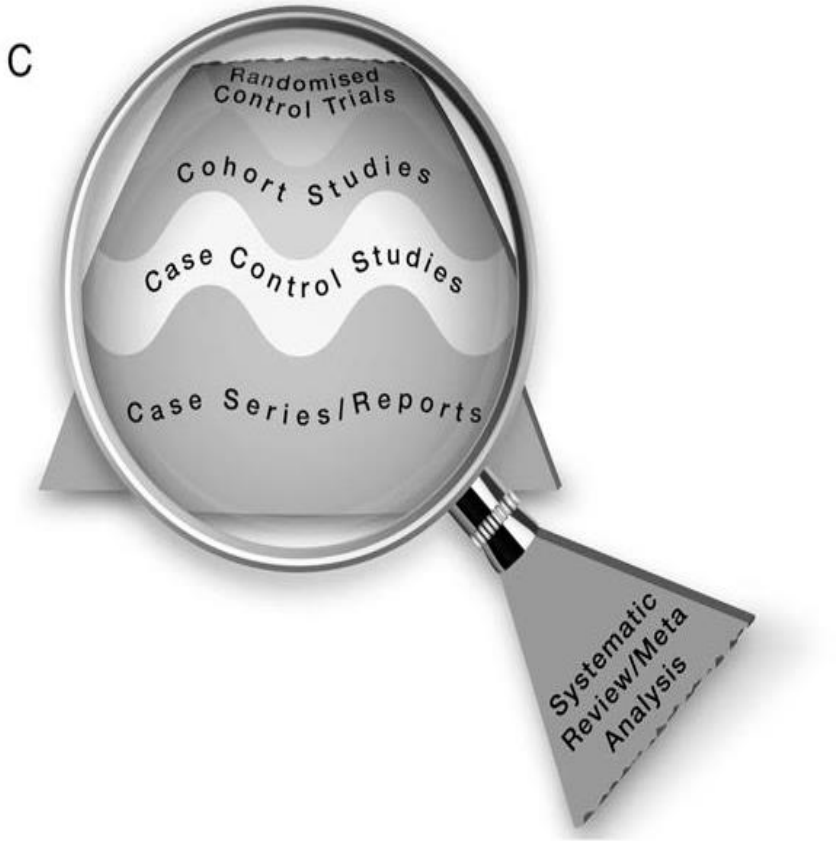
June 5, 2016, Barcelona

EURORDIS.ORG

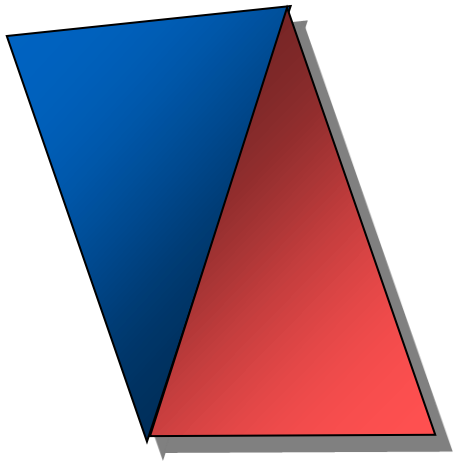
EVIDENCE-BASED MEDICINE

- Care of individual patients is based on evidence
  - From medical research
  - From medical expertise and experience
- Medical research "gold standard": randomised, controlled trial (RCT)

LEVELS OF EVIDENCE



Confidence



Risk of bias

http://dx.doi.org/10.1136/ebmed-2016-110401

Murad et al.

RANDOMISATION

- Study participants are identified based on clear criteria defined in advance (screening)
- Participants fulfilling study criteria are assigned to treatment groups randomly
  - Computerised systems
- Neither participants nor study investigators can influence treatment allocation

ADVANTAGES OF RANDOMISATION

Avoids selection-based bias (systematic error) – possibility that treatment outcome is influenced by selection

Objective: treatment groups within a clinical trial are balanced (similar) and only the treatment is different

SHORTCOMINGS?

- Randomisation does not guarantee that the study setting is free from bias, particularly if
  - The participant, the investigator or both know what treatment the individual will receive (open-label study)
- **Studies should be conducted "double-blind" whenever possible**

CONTROLLED

- Control group is a "yardstick" against which efficacy and safety of experimental therapy can be evaluated
- Control treatment (comparator) may be
  - Placebo
  - Standard care + placebo
  - Best supportive care
  - Established therapy – authorised or not authorised, but evidence-based

OUTCOME MEASURES/ENDPOINTS

- Often called variables
- Objective or subjective
  - Objective: impartial – based on observation/physico-chemical measure, low degree of interpretation
  - Subjective – important measure of perceived benefit/harm
- Surrogate endpoints
- Biomarkers

HIERARCHY OF ENDPOINTS

- Defined in advance in protocol
- Primary
  - Most important measure
  - Result defines study success/failure
- Secondary
  - Measure other important aspects of disease
- Tertiary/exploratory
  - Other measures of interest

NON-STANDARD SITUATIONS

- In priciple, development of orphan medicinal products is a standard situation
- Development may require non-standard solutions
  - Historical control group – natural history studies
  - No control group: single arm study
  - Adaptive studies
  - Sequential studies

TO CONCLUDE

Randomised, controlled, blinded studies provide best scientific evidence of benefit and risk

- Not always possible
- Alternative designs to be agreed with authorities in advance