The Ethical considerations of Placebo Study design in NMO

EMA view

Regulatory Workshop on Clinical Trials Designs in Neuromyelitis Optica

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Ethics

- Deontology
  - Clinicians
  - Investigators
- Virtue
  - Patients and society
    - Investigator integrity
    - Clinician integrity
- Teleology
  - Final outcome of development
    - Need to compare to approved agents
    - Easiness of investigation
    - Short time to market the final product

EMA view

Aspects to consider

- Benefit over present best standard of care
- Risk over present best standard of care
- Risk of withholding treatment

- Risk of uncertainty in knowledge of benefit / risk balance when establishing comparison to best care – external validity

- Study population
  - NMO / NMOSD
  - AQP4-IgG positive / negative
  - Previously immunosuppression / Ongoing / Naïve
  - Post Immunosuppressant failure
- Comparator availability
  - Which active comparators are available for best care
- Commitment
  - Patient
  - Clinician / Investigator
  - Sponsor

Schizophrenia EMA view

- Similar risk for withholding treatment
  - Increased acute risk
  - Increased disability if non treated
- FDA demand for placebo arm, in spite of other approved treatments
- Placebo arm not accepted
- Pseudoplacebo (low dose antipsychotic) accepted in some circumstances

EMA view

- Placebo controlled trial hardly acceptable for clinically confirmed NMO / NMOSD pts who are responding to immunossupressant tx:
  - Reasonable diagnostic certainty
  - Recognised efficacious therapeutic options with known risks

EMA view

- Placebo controlled trial also hardly acceptable for:
  - AQP4-IgG negative with NMO criteria
  - NMOSD if previously identified neurological impairment

EMA view

- Placebo controlled trial might be acceptable
  - In NMO / NMOSD patients who failed previous treatments (failure definition)
  - As add-on to ongoing immunosuppressant tx