Clinical evaluation of orphan devices

Specific considerations for MDR clinical evidence requirements

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An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

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Clinical evidence and OD – the challenge

MDR improvements

- Increased clinical evidence
- Additional scrutiny
- Mandatory clinical investigations
- Life-cycle clinical evaluation
- PMCF
- Transparency
- Safe, effective, performs as intended

OD Challenges

- Small population
- Unmet clinical need
- Insufficient alternatives
- Practical difficulties
- Risk of delay
- Costs
- Vulnerable populations

MDCG Draft guidance – Orphan Devices

- Guidance for manufacturers and NB on the application of clinical evaluation requirements to OD

- MDCG ODTF clinical evaluation drafting group
  - Regulatory representatives:
    - **IE**, BE, ES, FR, IT, NL, COM, EMA
  - External representatives:
    - Notified bodies, Industry, Academic and Clinical experts including ESC

- **PART A – Clinical Evaluation Considerations**

- **PART B – Procedural Considerations**

- Guidance in development

Clinical considerations for Orphan Devices

- Acceptable limitations in pre-market clinical evidence
- Non-clinical data
- Clinical investigations for OD
- Post-market clinical data / PMCF
- Extrapolation of data from non-orphan indications

Acceptable limitations in pre-market clinical evidence

- **Limitations acceptable if the following can be justified:**
  - Non-clinical and clinical data evaluated; limitations identified
  - Risks reduced as far as possible; GSPRs fulfilled
  - Non-clinical and limited clinical data provides sufficient evidence to expect that the device will provide a clinical benefit
    - considering the clinical condition, state of the art, and patient safety
  - Not feasible or proportionate to generate further pre-market clinical data
  - PMCF plan to generate additional clinical data
    - to address specific limitations within an acceptable timeframe
  - Users of the device adequately informed
    - e.g., information in IFU

Clinical investigations

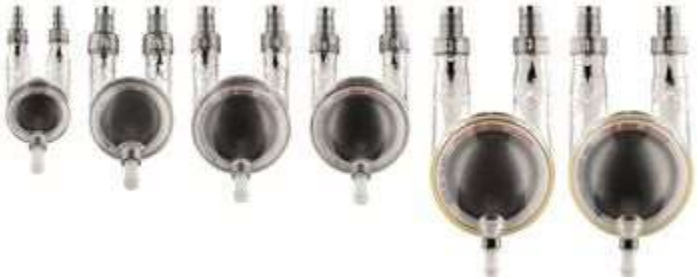
- **Specific considerations for studies in rare populations**
  - Population / Cohort
  - Comparator / Control
  - Outcomes
  - Endpoints
  - Design
    - Cross-over, N-of-1
    - Adaptive and sequential designs
    - Bayesian approaches

Post-market clinical follow-up

- **PMCF must generate additional clinical data**
  - Appropriate timeframe
  - Address pre-market limitations in clinical evidence

- **PMCF plan should be clear, well designed, prescriptive, and achievable**
  - PMCF investigations
  - Registries and registry-based studies
  - Real world evidence & PMS
  - Off label use

e.g. US FDA - EXCOR Pediatric VAD



- **HDE Approval 2011**
- IDE - Multi-centre, single arm study
  - 48 paediatric subjects – 2 cohorts (BSA)
    - 3rd cohort – compassionate use
  - Endpoints
    - Effectiveness – survival to 30 days/explant vs historical control (ECMO – ELSO registry)
    - Safety – SAE rate vs performance goal of 0.25 SAEs per patient-day (ppd) of support
  - Results
    - 30-day mortality higher in ECMO vs EXCOR (Cohort 1 – 10x, Cohort 2 – 50x)
    - SAE rate acceptable – Cohort 1 - 0.068 ppd, Cohort 2 – 0.079 ppd
    - Limitations – historical control, duration of ECMO vs EXCOR, L/T survival

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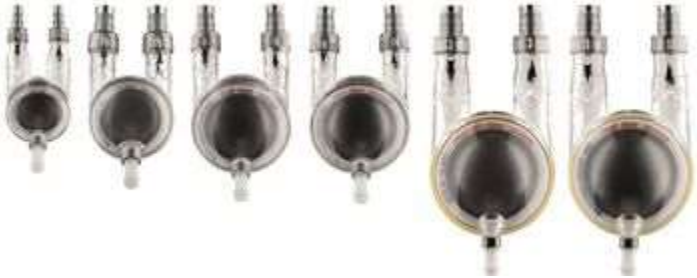

- **PMA Approval 2017**
- Clinical data from 565 patients
  - IDE – 148 subjects
    - including 54 in Cohort 3 - compassionate use
  - HDE Post-approval study
    - 39 subjects across 19 sites
    - Followed up to 24 months post-explant
  - Compassionate use data – 187 total
  - Other - 245 patients implanted across 45 hospitals

Conclusion

- Clinical evidence challenges for OD
- Balance: clinical evidence vs unmet clinical need
- Acceptable limitations in clinical evidence
- Alternative clinical investigation approaches
- PMCF essential

Thank you

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