Clinical Trials - Methodological Considerations & Challenges

Ralf-Dieter Hilgers

Realise D

compRehensive mEthodological and operational Approach to cLinical trIalS in ultra-rarE Diseases

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Content

- General Challenges in RD and Ultra-Rare Disease
- Drug Trial Challenges
- Surgical Trial Challenges
- Device Trial Challenges
- Conclusion

General Challenges in (u) RD

- Operations aspects:
  - Structured and predictable system for referral of patient
  - Certified/qualified clinical trial sites
  - Reducing burden of trial participation
- Unclear natural history
  - Unclear outcome
  - without any clear path to treatment
- heterogeneity of disease population
- unclear target population (inclusion, exclusion)
- Improve Design and Analysis of trial data
  - Control groups

To address the IHI Call 4, Topic 4: Establishing novel approaches to improve clinical trials for rare and ultra-rare diseases.

Augustine EF, Adams HR, Mink JW. Clinical trials in rare disease: challenges and opportunities. J Child Neurol. 2013 Sep;28(9):1142-50. doi: 10.1177/0883073813495959. PMID: 24014509; PMCID: PMC3964003.

RealiseD …

will implement a collaborative and comprehensive method-logical and operational approach to clinical trials in ultra-rare diseases

Key Elements

- **Focus on ultra-rare diseases ((U)RD)**
- **Operational tools for recruitment and certified cites**
- **Design and Analysis Tools for (U)RD clinical trials > *paradigm shifts***
- **Cocreation of Tools with 6 Stakeholders (Pharma, Clinicians, Methodologists, EMA, HTA, Patients)**
- **Established Tools for Drug Development**

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Methodological Development Areas

Innovative clinical trial designs

- E.g. **master protocols, platform trials, single arm trials**
- **Randomization**
- framework on **individualized disease-modifying therapy**
- **similarity between disease**
- **RCT‘s with historical data**

Innovative analysis and data use strategies

- inference tools for the **joint /federated data analysis**
- investigate the **effect of overlapping symptoms**;
- framework for relevant **outcome measures**
- validity of methodology with **incomplete data**

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Surgical Trial Challenges

- Rapid developing “treatment” without stable state
- Timing of trial – to early versus to later
  - Fast changing technology
- Defining the Research Question
  - Choice of Comparator
- Learning curve

Trial Design issues
blinding
randomisation
outcomes

Tracker Trials

Expertise Based Trials

Comprehensive cohort design

randomisation by consent (Zelen) Design

Expertise Based Trials

Cook JA. The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. Trials. 2009 Feb 6;10:9. doi: 10.1186/1745-6215-10-9.

Trials with medical devices

MDR:
Extended clinical testing of justifiable risks balanced with clinical benefit
- **Statistical approaches**
- **Design incl. sample size**
- **Comparator**
- **Endpoint (clinically relevant)**

Substantial Equivalence
Surveilance for entire lifecycle

- Randomized trials difficult with medical devices
  - randomization impossible
  - difficulty of double-blinding
  - Fast changing technology; device's short life-cycle
  - the small size of the target population
  - the choice of comparator
  - the low acceptability of patients and practitioners
  - the operator-dependent nature

Tracker Trial
Adaptive/Sequential Trial
MAMS

Crossover trial
N-ot-1 trial > SnSMART Trial

Zelen Plan
Comprehensive Cohort Study
Trial based on Expertise

Bretthauer M, Gerke S, Hassan C, Ahmad OF, Mori Y. The New European Medical Device Regulation: Balancing Innovation and Patient Safety. Ann Intern Med. 2023 Jun;176(6):844-848. doi: 10.7326/M23-0454.
Vidal, C., Beuscart, R. and Chevallier, T. Contribution of Methodologies Adapted to Clinical Trials Focusing on High Risk Medical Devices. DOI: 10.5220/0009374503370343

Technology-Enabled Clinical Trials

- Electronic Health Records (real time digital records, mobile apps, wearables, etc)
- Patients diagnoses, treatments laboratory tests, administer drugs, clinical encounters (endpoints)
- Impact of patient enrolment
- Determine clinical event rates
- Reduce operational burden
  - Minimize time burden for conduct
  - Support implementation of randomization
  - Facilitate informed consent
  - Use for training
- support generalizability
- Accuracy and continuous monitoring of (novel) clinical trial endpoints (body function, vital signs, behaviors, metrics of daily activity with biosensors)

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Conclusions

- RealiseD will establish a new pathway for drug development in (u)RD clinical trials
- Major differences with evaluations of surgical treatments and Medical Devices
  - E.g. Development of Fast changing technology, limited life cycle, etc.
  - But some similarities like Bias Assessment
- Impact of MD for EHR on CTs are expected to increase, while facilitating CT conduct in particular in (U)RDs

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