2.6 Clinical Trials: Current + NextGen

Alihan Huyuk
ah2075@cam.ac.uk

Clinical trials

- Difficult, expensive, and ripe for disruption
- Average PoS per Phase II/III trial: 50-60%
- 1-2 years for trial
- Up to 2,000 trials per year
    - Half for oncology
- Opportunity
    - Despite flaws, RCTs remained dominant approach for decades
    - Innovation:
        - Improve patient benefit
        - Reduce required patient numbers
            - Replace controls and preventing dropouts
        - Reduce cost per patient
            - Improved recruitment, monitoring and operations
        - Improve PoS
            - Better recruitment, prediction, trial design, and analytics
    - Cost and time savings by running better trials
- Clinical trial phases

	Exploratory		Confirmatory	Extrapolatory
	Phase I	Phase 2	Phase III	Phase IV
Goal	Safety	Dose finding	Efficacy	Retargeting
# of patients	10 -100	~100	~1000	>1000
Regulations	Less regulated, company's own risk		Highly regulated	Regulated
Input data	• Pre-clinical (Animal models) • Related clinical trials • Baseline data (current practice) • PKPD models		• Results from Phase I/II • Interim analysis	• Real world usage (incl. Off-label data & other drugs)

- Steps taken for each phase of the study
    - Planning
        - Spec out the trial protocol
    - Conduct
        - Logistical challenges

    - Analysis
        - Produce trial findings
    - Clinical Use (for Phase IV)
        - Usage of the approved treatment
- Challenges and potential solutions felt through the clinical development journey
    - Step 1: Planning -> what data?
        - Causal ML
            - Determining endpoints
        - Transfer Learning
            - Incorporating observational data
            - Incorporating pre-clinical data
            - Incorporating cross-trial results
        - Optimal Design
            - Optimal design of trials
        - Synthetic Data
            - Augmenting preclinical/ cross-trial data
    - Step 2: Conduct
        - Reinforcement learning/ Multi-armed Bandits
            - Determining dosage
            - Discovering drug combinations
            - Identifying “good” subpopulations
            - Recruitment “right” patients
        - Inverse Reinforcement Learning
            - Retaining recruited patients
        - Synthetic data
            - Streamlining data sharing
                - internal/ external
                - Contractors
    - Step 3: Analysis
        - Treatment effect estimation
            - Predicting personalized response
            - Subpopulation analysis
        - Time series analysis
            - Time to event analysis
            - Competing risk analysis
        - Few-Shot learning
            - Combining models (e.g. PKPD)
        - Synthetic data
            - Anonymising results for reporting
    - Step 4: Clinical use
        - Treatment effect estimation
            - Refining guidelines (e.g. timing, dosage)
            - Indication expansion
        - Time series analysis

            - Effect and impact on comorbidity
            - Modeling disease progression
        - Few-shot learning
            - Rapid deployment
        - Synthetic Data
            - Facilitating RWD access and anlayiss
- Machine learning can help in two ways:
    - SyncTwin
        - https://proceedings.neurips.cc/paper/2021/hash/19485224d128528da1602ca47383f078-Abstract.html

Adaptive Recruitment

- Identifying good subpopulations fast with confidence

AdaGGI:
https://arxiv.org/pdf/2208.05844.pdf

Individualized treatment effect inference:
https://www.vanderschaar-lab.com/individualized-treatment-effect-inference/
Next generation clinical trial:
https://www.vanderschaar-lab.com/adaptive-clinical-trials/