Challenges and Opportunities with Decentralized Trials: Statistical Perspectives

Demissie Alemayehu, Pfizer Inc.

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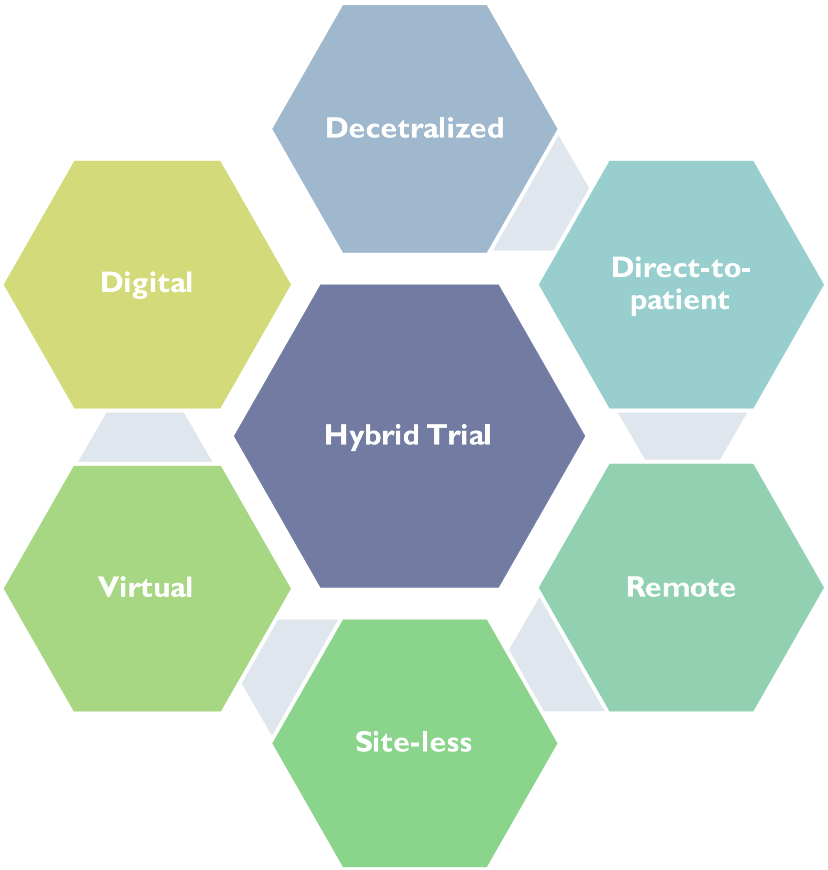
Outline

- Background
- Lessons from the REMOTE Trial
- Elements of DCTs with Statistical Import
- Modern Analytics to Advance DCTs
- Other Considerations in DCTs
- Concluding Remarks

Decentralized trials: Terminology

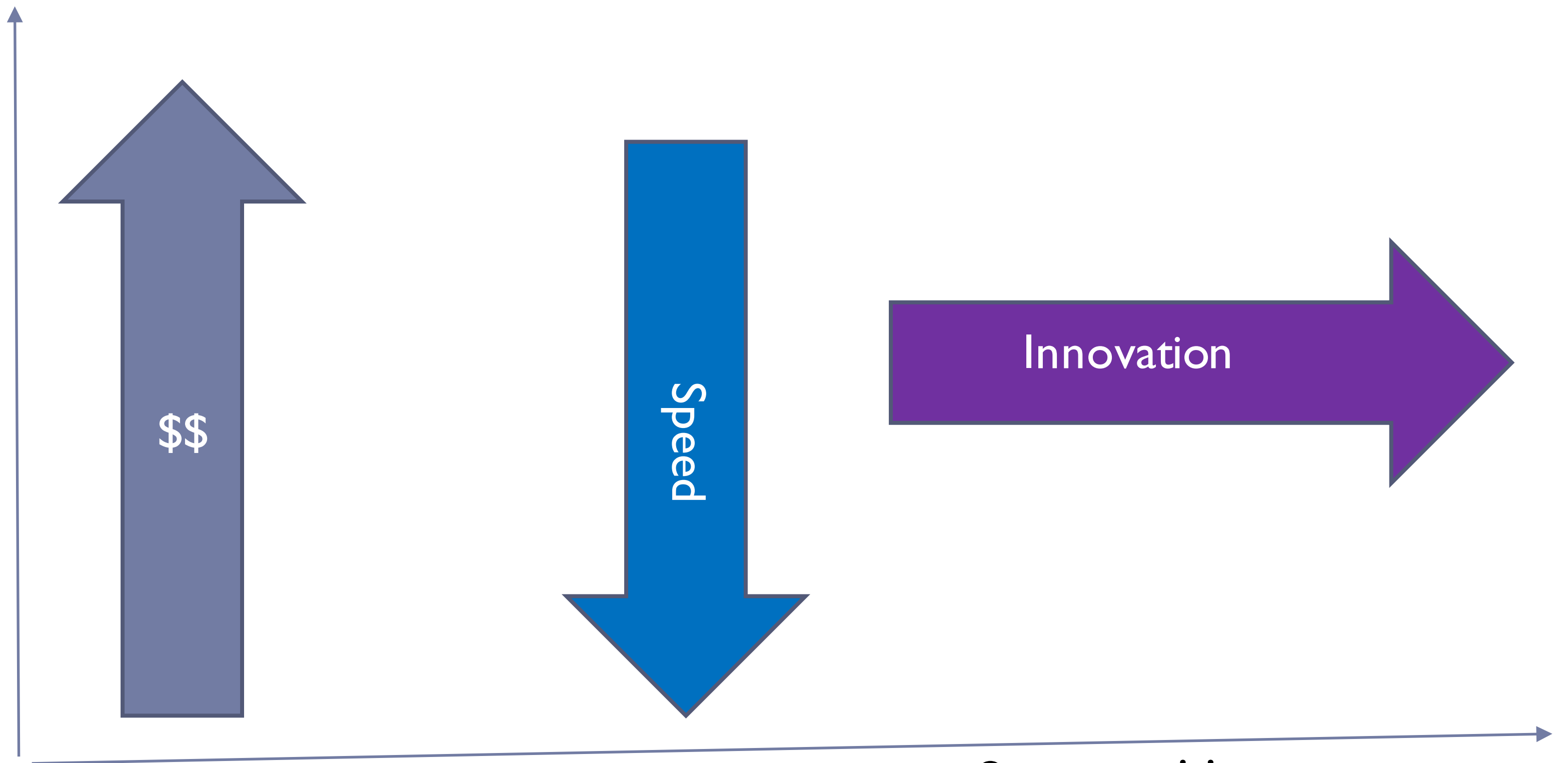


- **Variety of terms in use**
- **Hybrid approach preferable in certain situations**

Traditional vs. Decentralized Clinical Trials

	Traditional	Virtual
Recruitment, Enrollment	• Site visits by patients	Internet & Social Media • People's online searches and activities
Compliance & Retention	• Site visits by study monitors	• Remote data verification & patient monitoring
Safety/efficacy data capture & processing	• Measurements by trained personnel • SDV	• ePRO • Mobile devices
Design and data analysis	• Operational challenges for CID • Data sparsity limits ML implementation	• CID implementation • Massive data for training ML methods

Why Decentralized Trials in Drug Development?



Average cost of developing new drug > $1 billion

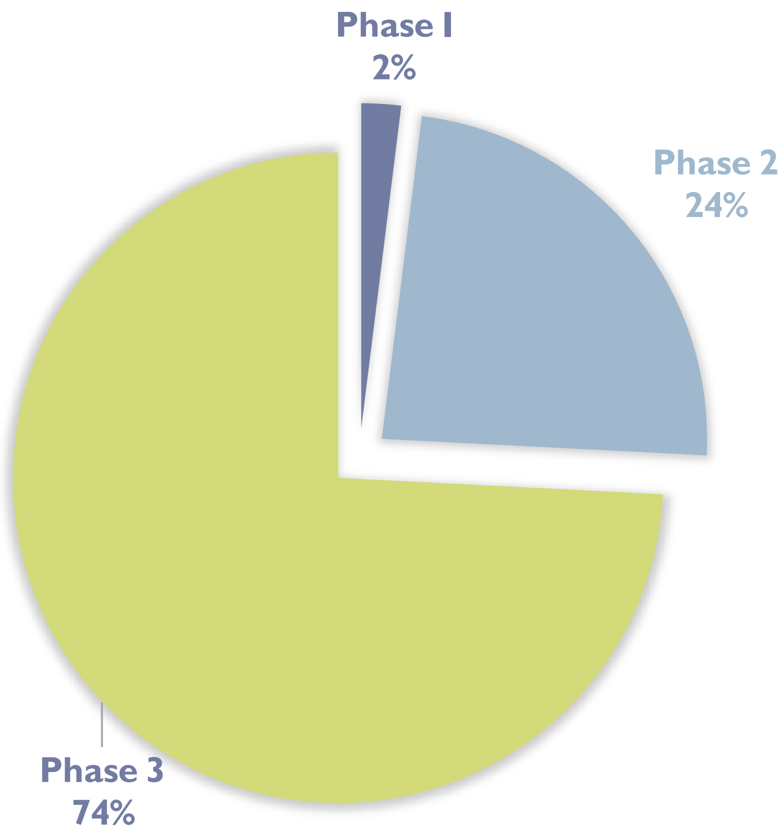
Total Duration: 10-15 Years

Opportunities:

- Unmet treatment needs: Neuroscience, Oncology, Rare Diseases
- Advance personalized medicine

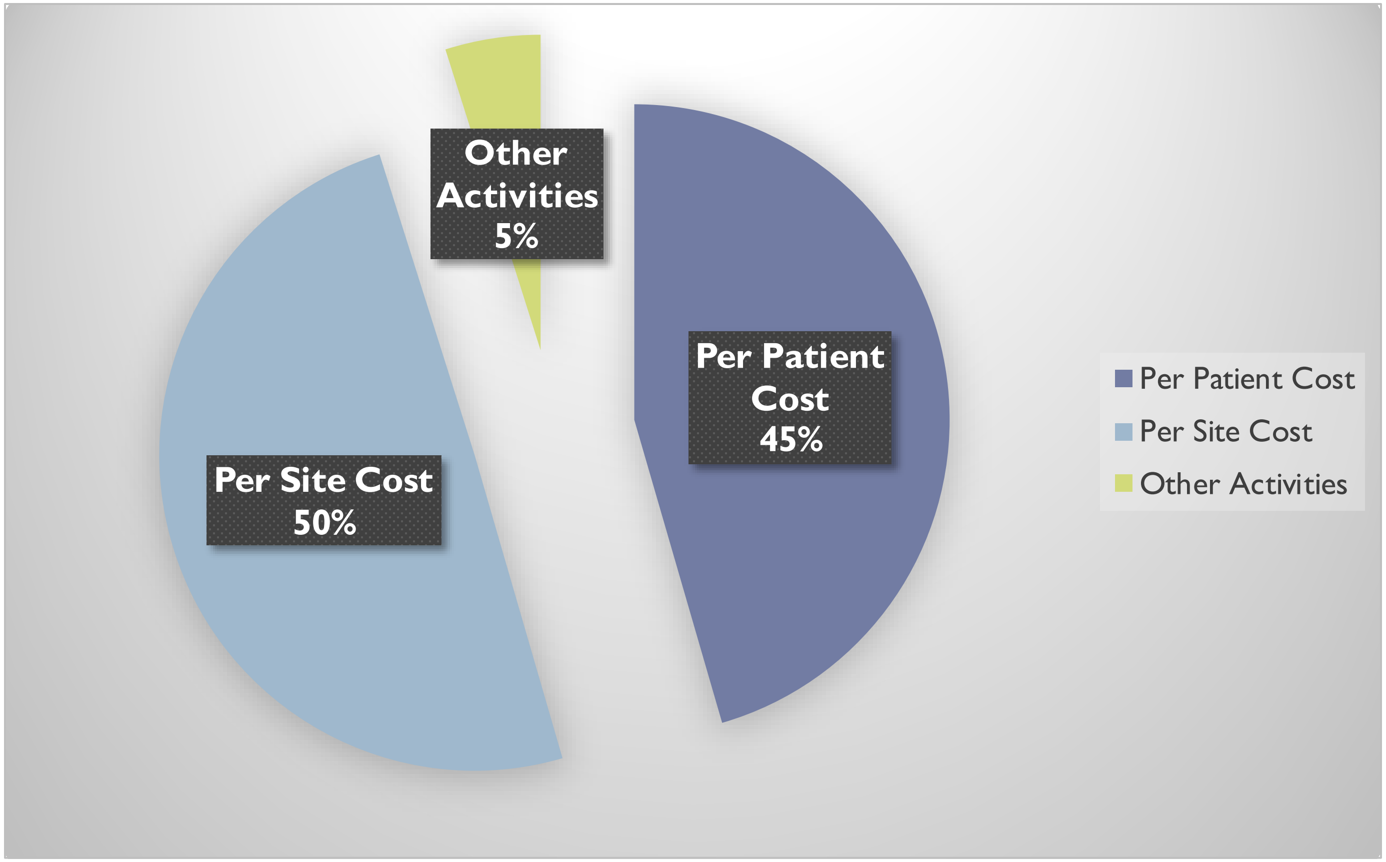
Cost of Pharmaceutical Clinical Trials

Pain and anesthesia studies



Source: Sertkaya A, Wong HH, Jessup A, Beleche T. Key cost drivers of pharmaceutical clinical trials in the United States. *Clin Trials*. 2016;13(2):117-126. doi:10.1177/1740774515625964

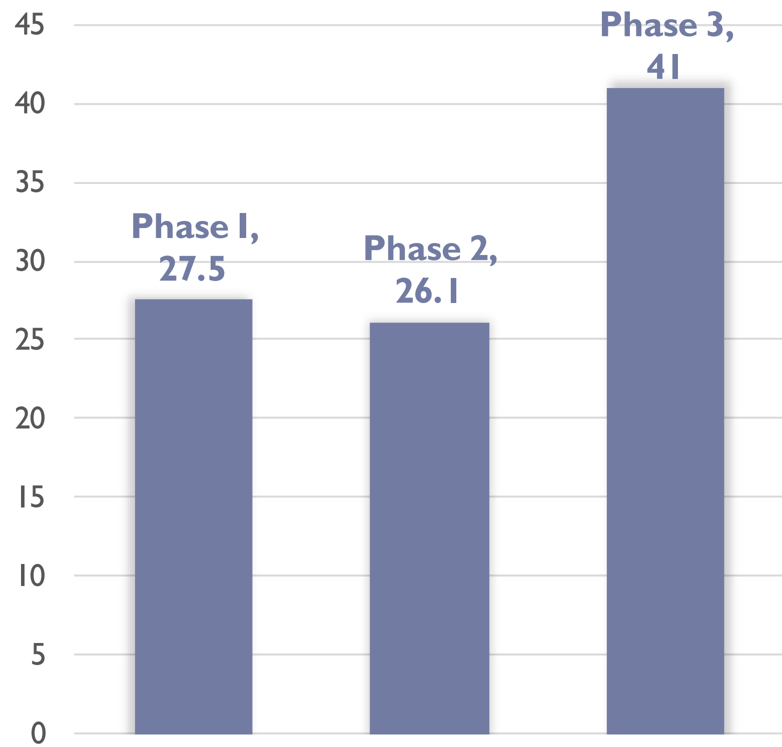
Cost Drivers of Pharmaceutical Clinical Trials



Source: https://pubmed.ncbi.nlm.nih.gov/26908540/

Average Duration (MM) of Oncology Clinical Trials

"... oncology clinical trial delays are a direct result of patient recruitment challenges."

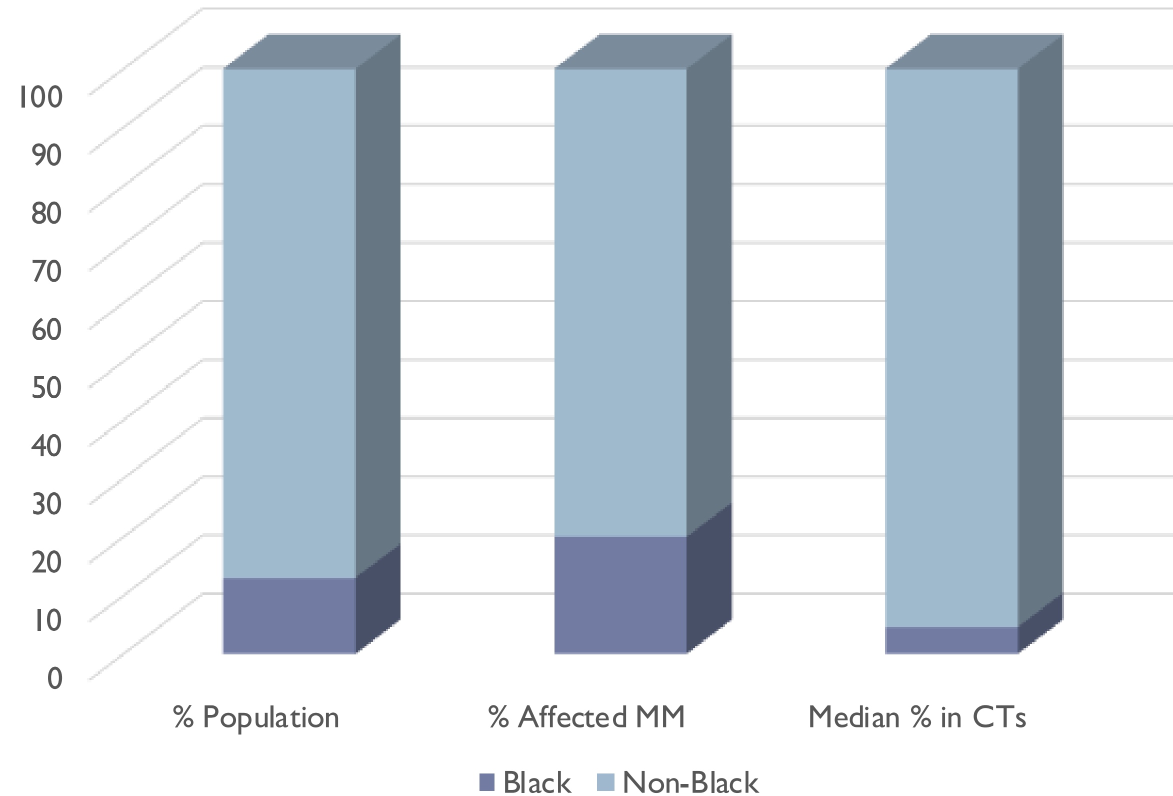


Source: http://ipimediaworld.com/wp-content/uploads/2013/06/2-Patient-Recruitment-Driving-Lenght-and-Cost-of-Oncology-Clinical-Trials.pdf

Challenges with Patient Recruitment: Diversity

FDA Analysis of Racial Demographics in Multiple Myeloma Trials

- Blacks constitute 20% MM, but 13% U.S. population
- Median% blacks enrolled in MM trials 4.5%.



Conclusion: Enrollment of black subjects in pivotal trials submitted to FDA not representative of MM population

Source: Bhatnagar, et al. FDA Analysis of Racial Demographics in Multiple Myeloma Trials, Blood, 2017

Benefits of Decentralized Trials

Patient Centricity
- Patients participate in trials from their home

Population Diversity
- Access to a larger geographical footprint

Patient Recruitment
- Access to a larger population, requiring less frequent site visits

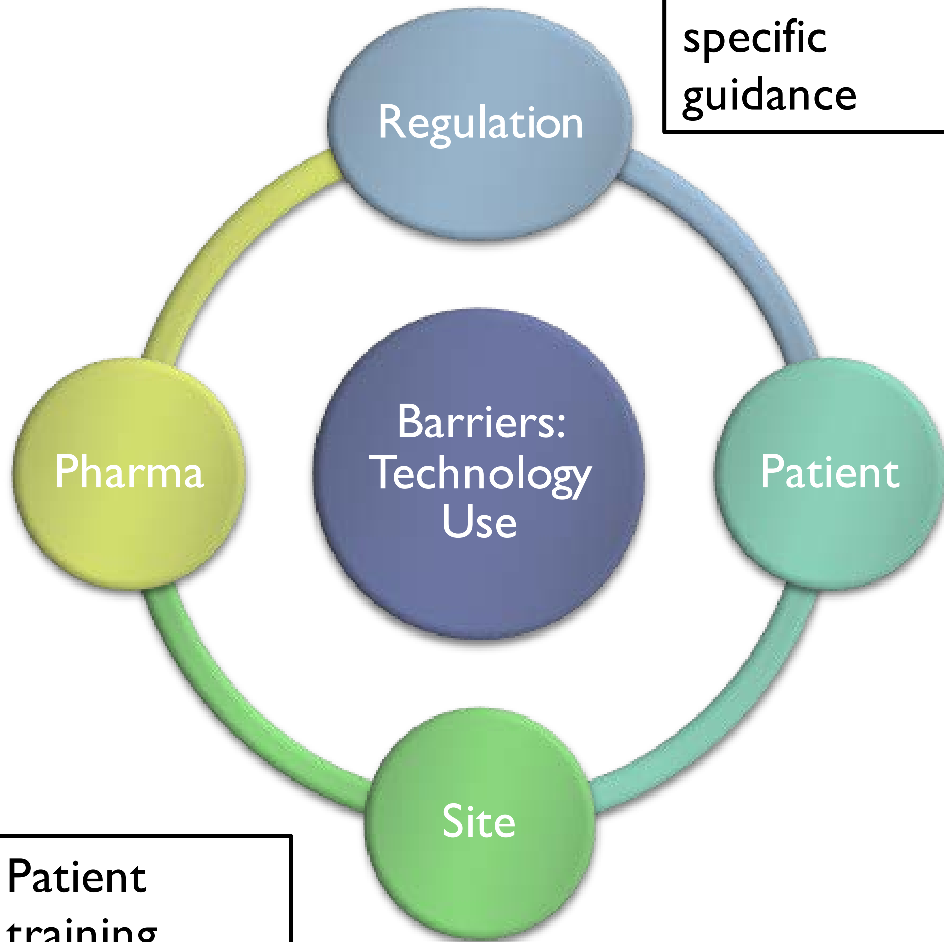
Retention
- DCTs decrease burden for both patients and caregivers, contributing to patient retention

Data Collection
- Wearables, sensors, EDC

Digital Solutions

Need for specific guidance

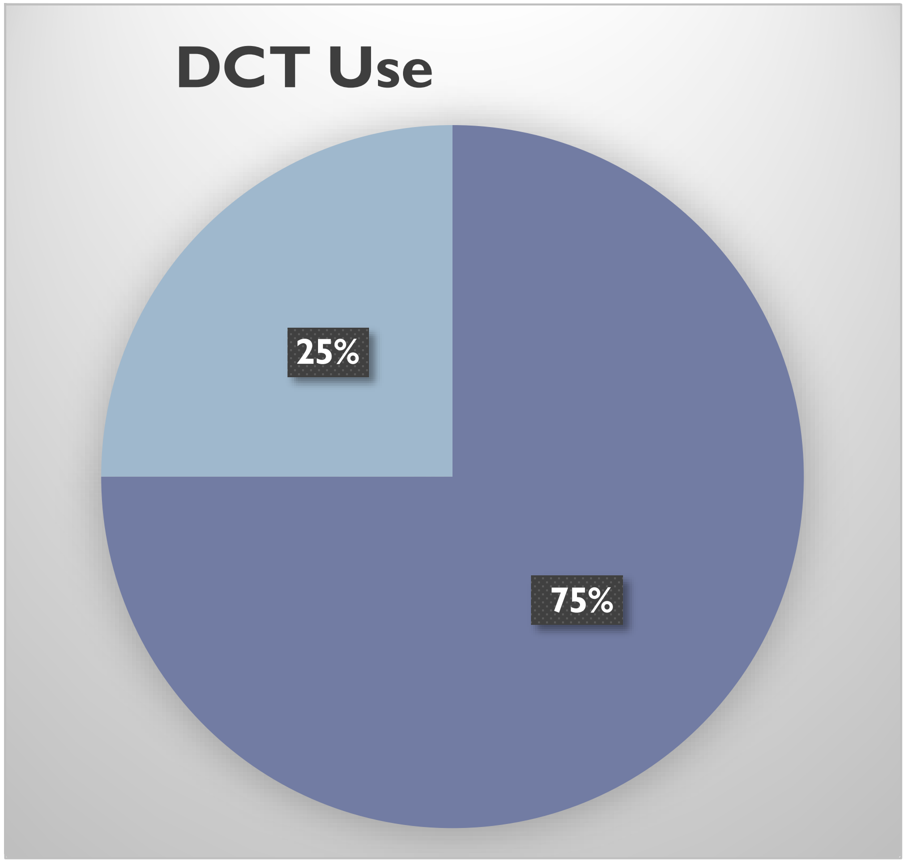
- Risk aversion
- Lack of corporate strategy
- Investment risk

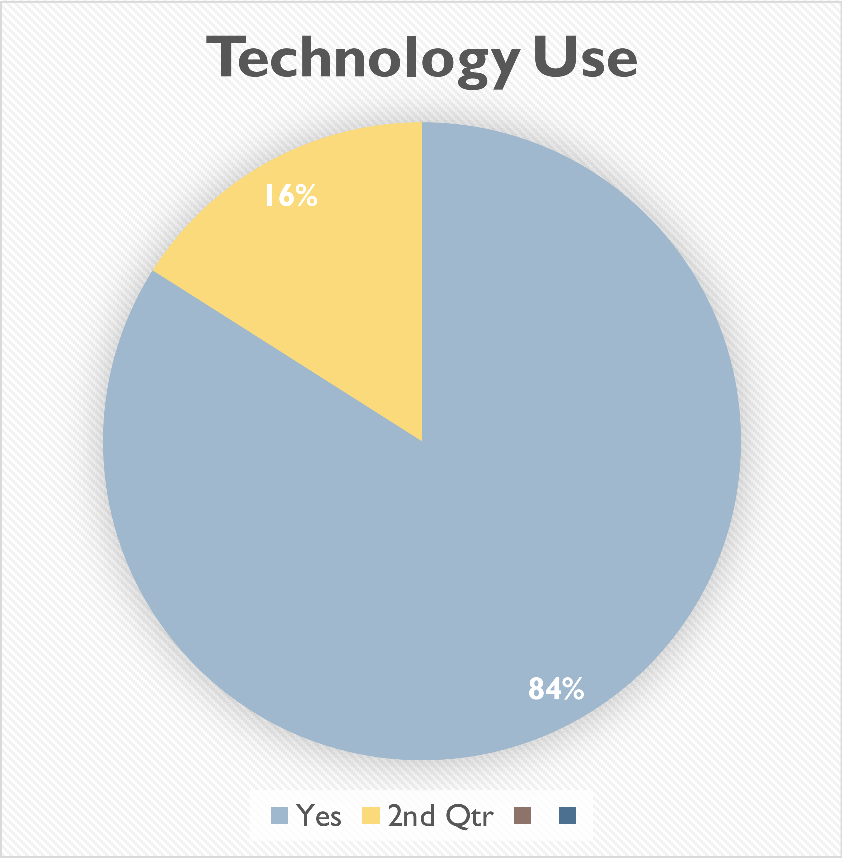


- Access to Internet
- Time, effort, for learning use of technology.

- Patient training
- Tech support

Industry Trends





> 75% pharma respondents favor adoption DCTs following pandemic

Source: Oracle. Survey: COVID-19 the Tipping Point for Decentralized Clinical Trials, November 18, 2020

> 84 % pharma sponsors and CROs seek technology use to support DCTs.

Rethinking Data Quality Best Practices in the Era of Decentralized Clinical Trials (premier-research.com)

An Early Example of DCTs: REMOTE

Research on Electronic Monitoring of Overactive Bladder Treatment Experience (REMOTE) trial (Orri et al. 2014).

- Initiated by Pfizer in 2011
- Designed to replicate previous clinic-based trials of tolterodine ER (Detrole)
- First web-based study conducted under an IND application

Main Result:
Efficacy observed consistent with results from conventional trials

Features

- Participants recruited and informed consent obtained electronically
- Labs in facilities near their homes
- Drugs shipped directly to participants
- Interactive voice response system (IVRS) used for randomization,
- EDC utilized for data collection and management

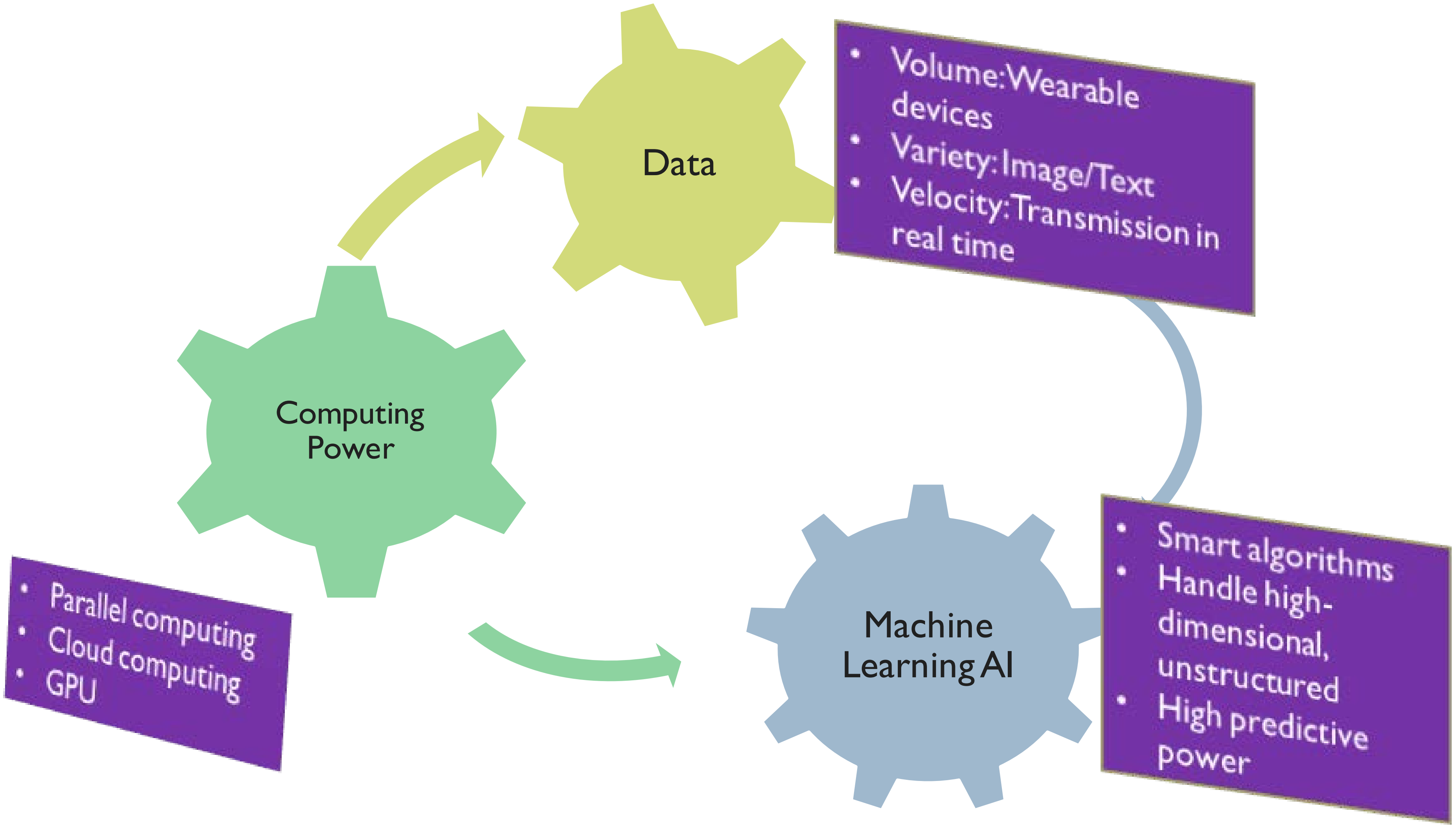
Challenges

- Complicated screening process: Security measures to verify participant identification online
- Slow enrollment rates
- Drop-out rate much higher than conventional trials

Lessons learned

- Need to simplify screening criteria.
- User-friendly and state-of-the-art technology

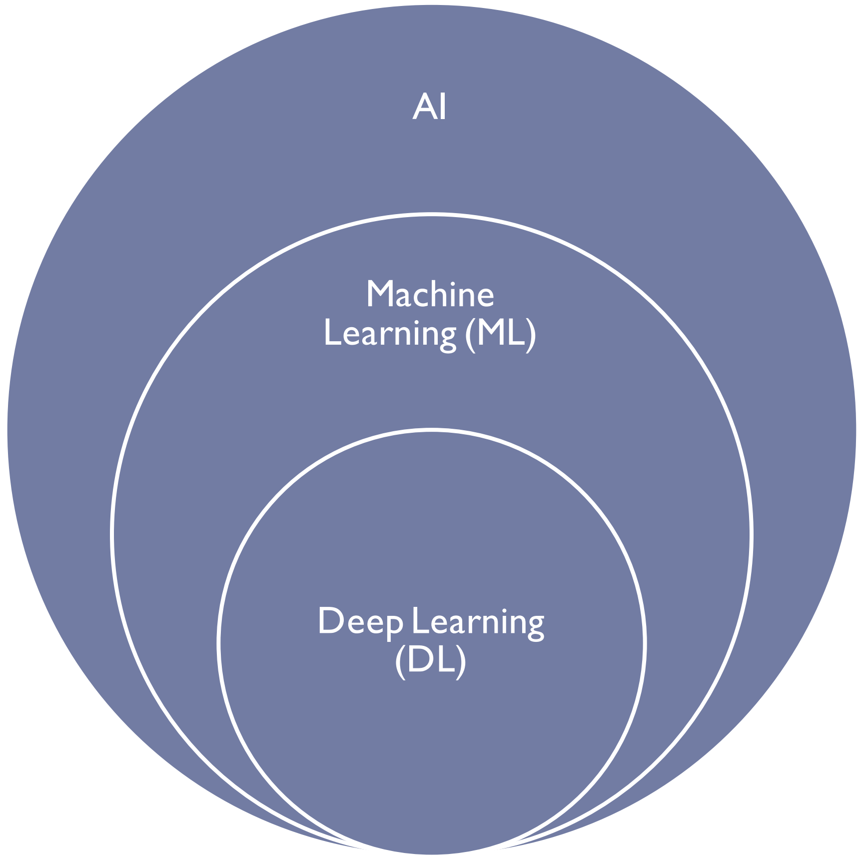
Key Drivers of DCTs: Technology & Analytics



Modern Analytics in Advancing DCTs

Traditional ML

- ANN: Artificial Neural Network
- SVM: Support Vector Machines
- PCA
- k-NN
- Regularized regression,



Advanced Methods

- FFNN
- RNN
- CNN
- Deep Auto Encoders

Adversarial Training

- GANs: Generative adversarial networks

Recent developments:

- Inference involving ML models

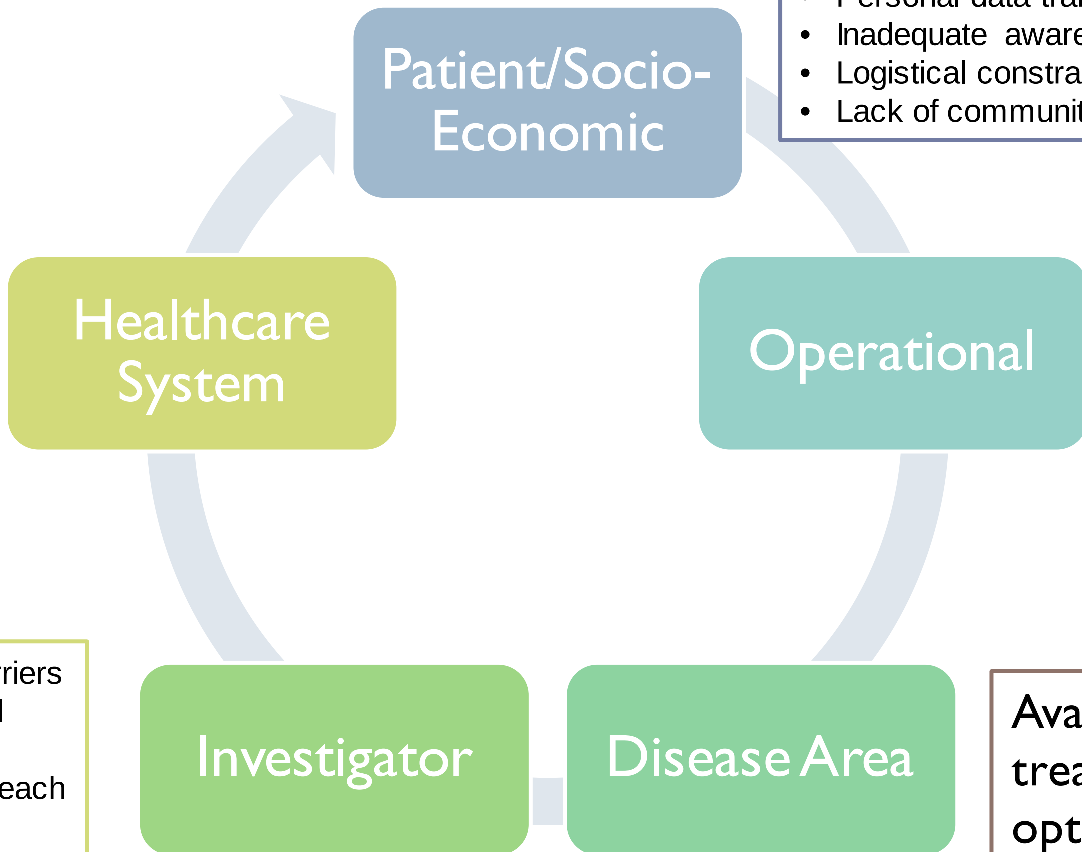
Statistical/Digital Opportunities with DCTs

- Patient recruitment
- Data capture and processing
- Advance in innovative trial design and analysis

Potential Barriers to Recruitment

- Lack of trust in pharma and/or government
- Personal data transparency concerns
- Inadequate awareness of clinical trials
- Logistical constraints
- Lack of community support

Lack of incentive to engage diverse patients in clinical trials



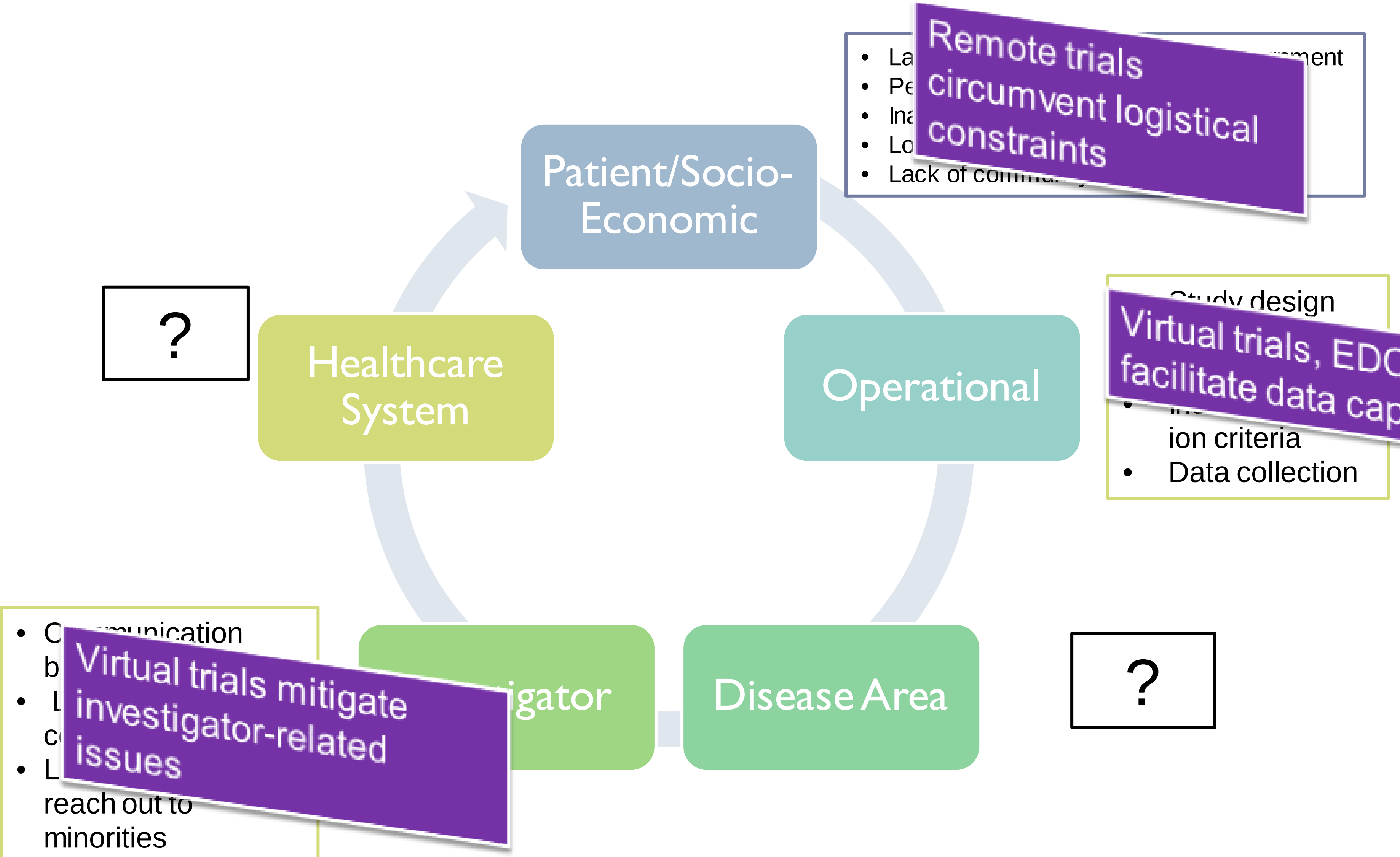
- Study design and protocol complexity
- Inclusion/ exclusion criteria
- Data collection

- Communication barriers
- Language / cultural competency
- Lack resources to reach out to minorities

Availability of treatment options

Adapted from Clark et al. (2019)

Digital Solutions to Recruitment Barriers



Digital Solutions: Lessons from Other Industries

- **Business**: AI in marketing (Ma et al. 2020)
  - ➢ Customer segmentation and engagement
  - ➢ Application in Banking, retail, hospitality, etc.

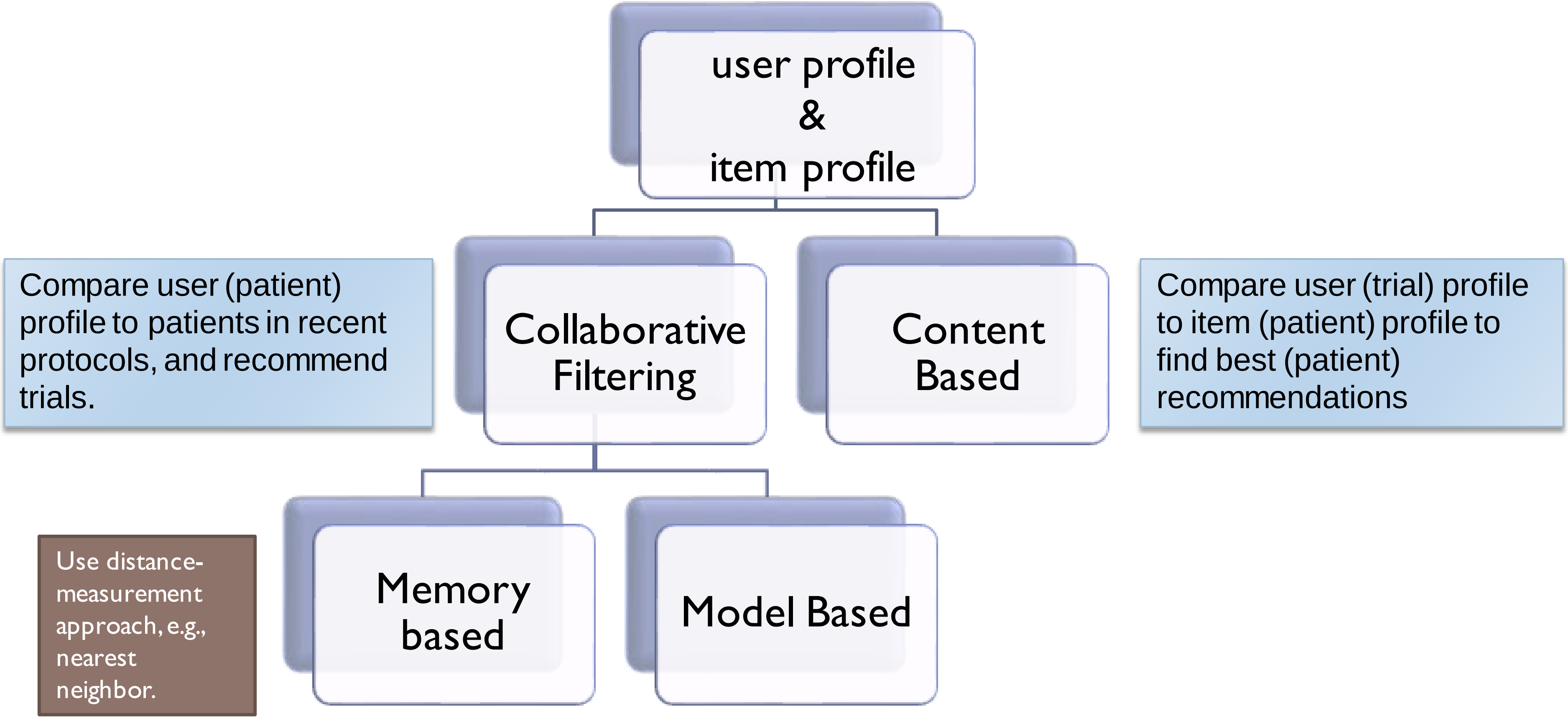
- **Human resources:** AI to enhance DEI
  - ➢ Recommender systems to raise awareness of job opportunities: Implications for recruitment
  - ➢ Mitigation of unconscious bias in performance evaluation: Implication for investigator bias (Zhang et al. 2019).

- **Cautionary measures**: AI perpetuation of harmful biases (Daugherty et al. 2018)

Recommender System for Patient Recruitment

- Approach widely used in other industries
- Recommender system to match patients to clinical trials
- Approach requires:
    - Collecting patient data
    - Identifying patients more likely to sign up for trials
    - Reaching those patients using more targeted advertising
- Potential to improve enrollment
  - Identifies eligible patients, better than traditional approach
  - Saves time and effort
  - Helps planning, with better knowledge of target population
  - Enhances diversity in trials

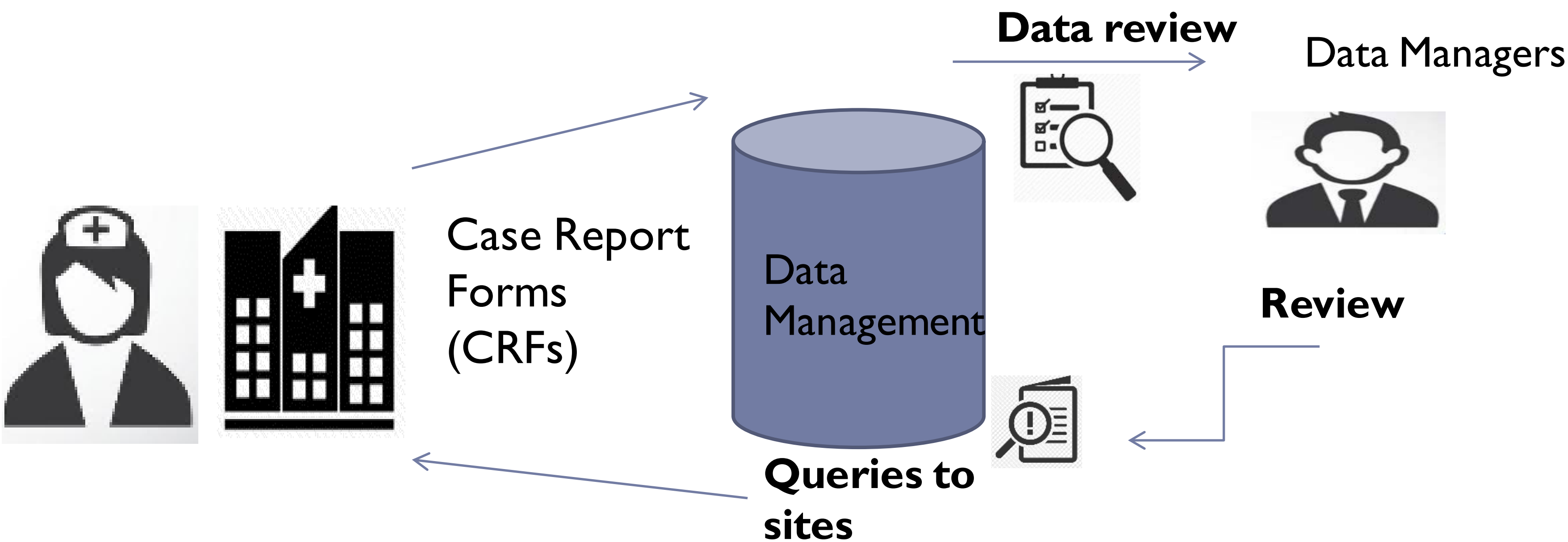
Recommender System (cont.)



Hybrid approach:

- Helps address '*cold start*' problem
  - ➢ When new user introduced but cannot be matched due to lack of information on that user.

Data Capture and Processing: Traditional Approach

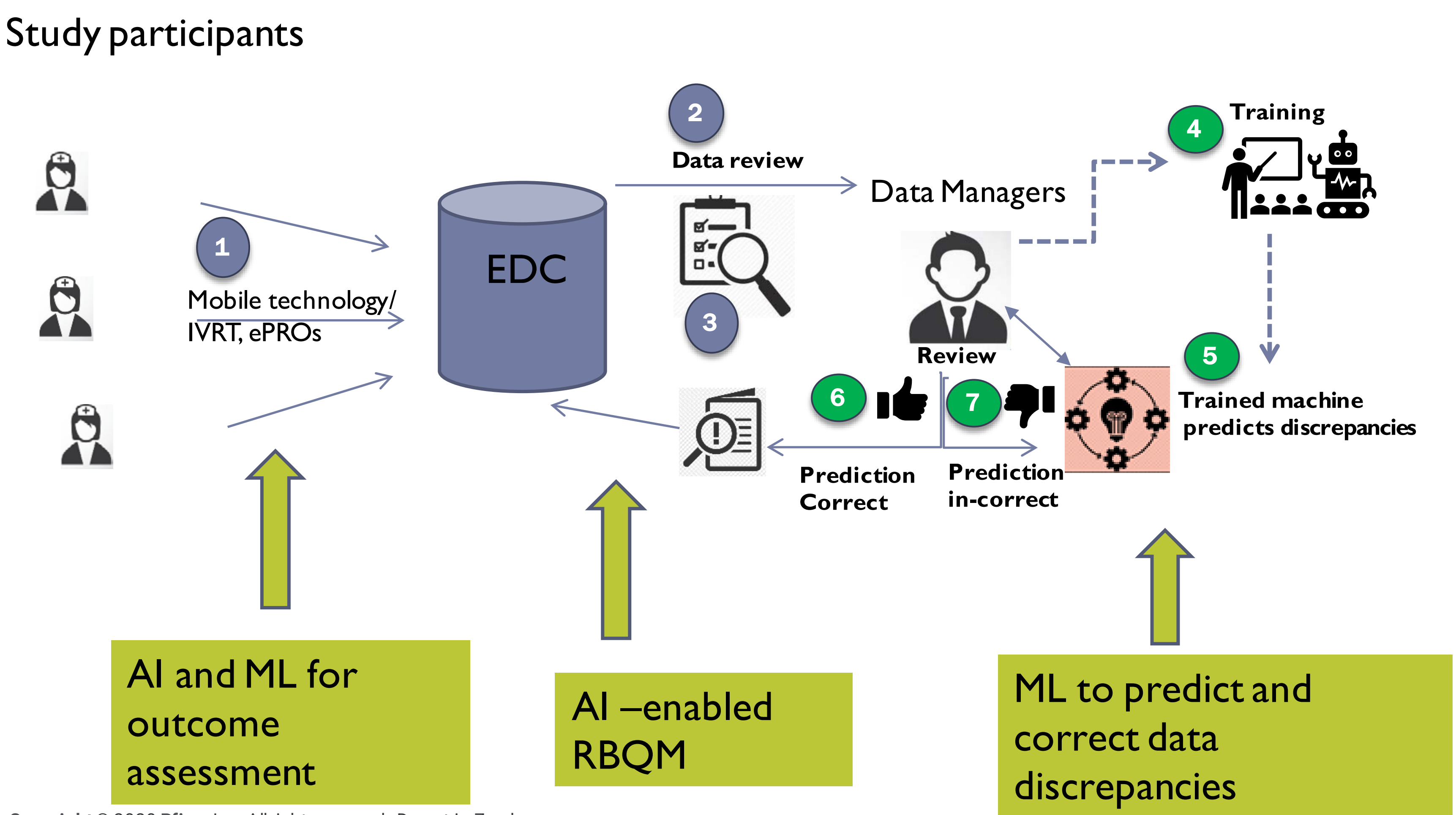


Site Investigators

On-site monitoring coupled with 100% source data verification (SDV)

Labor-intensive DM activities

Digital Solutions: Data Capture and Processing



Digital Solutions: Outcome Assessment

Examples from the literature:

- CNN: Predict depression severity from speech patterns (He et al. 2018)
- SVM: Classify/predict Alzheimer's disease (Collij et al. 2017)
- CNN: Physiological signals anomaly detection (Wang et al 2016)
- Deep Belief Network: Human activity recognition (Yalcin 2016)
- Restricted Boltzmann Machine (RBM): ECG classification (Yan et al 2015)

FDA framework for Software as a Medical Device (SaMD)

https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-and-Machine-Learning-Discussion-Paper.pdf

Digital Solutions: Risk-Based Quality Management

- RBQM:
  - o Ensures early risk detection and prevention
  - o Permits continual risk monitoring
  - o Can help identify issues that might not otherwise have been detected

- Commonly used techniques:
  - o Predictive analytics: ML models and data visualization tools
    - ➢ Identify key risk indicators
  - o Anomaly detection: branch of ML to identify cases for scrutiny
    - ➢ Regularized logistic reg, SVM, kNNS, etc.

Digital Solutions: Foster Innovative Designs

- Adaptive designs:
  - Provide flexibility to adjust parameters of a trial midstream
    - Shifting patients and resources to promising treatment arms
    - Sample size re-estimation
    - Early stopping for futility or efficacy
- Major obstacles:
  - Statistical challenges
  - Operational challenges

Digital Solutions: Foster Innovative Designs (cont.)

Multi-armed Bandit Designs

- Ranking and selection designs: Identify drug with best response (Gibbons, et al. 1979)
- Decision analysis-based design
  - Action wrt expected utility
- Adaptive designs: Play-the-winner

Risk Sensitive MABP (Lin, Pang and Alemayehu 2020)

A flexible approach:

- Based on a Bayesian ranking algorithm to maximize expected total rewards
- Permits:
  - o Exploration: Correct ranking of treatments
  - o Exploitation: Most patients to most effective drug

“Despite … near-perfect fit between a real-world problem and a mathematical theory, MABP has yet to be applied to an actual clinical trial” (Villar et al. 2015).

- The operational convenience offered by VTs can foster implementation of innovative designs such as MABP

Measurement Validity in Virtual Trials

Establishment of validity and reliability

- Assess ability to quantify clinical and pathological condition of interest
- Comparability to measurements obtained by established techniques
- Accuracy and precision (i.e., intra- and inter-device variability)

Approaches

- Traditional psychometric techniques to assess validity and reliability (see, e.g., Cappelleri et al 2014)
  - ➢ Factor analysis, structural equation modeling (SEM), etc.

- Modern ML tools to establish sensitivity & specificity for high dim data

Measurement Validity (cont.)

Reliability: Extent to which an instrument provides consistent results

- Intraclass correlation coefficient (ICC): Proportion of total variability (σ_T^2) in observed scores attributable to measurement error (σ_e^2):

$$\rho = \frac{\sigma_T^2 - \sigma_e^2}{\sigma_T^2}$$

- Wearable device data: Spearman-Brown prophecy formula:

$$\rho_m = \frac{m\rho}{1 + (m-1)\rho}$$

where ρ, reliability of a single daily measurement; *m,* number of daily measurements averaged

- ICC for agreement between remote vs. traditional trials
    - Lower bound of 95% C.I. > 0.7 indicate comparability (Byrom et al. 2019).

- Cohen's kappa coefficient (κ), agreement for categorical outcomes (McHugh 2021).
    - κ ≤ 0 indicate no agreement, 0.61–0.80 and 0.81–1.00, are taken as substantial and almost perfect agreement, respectively.

Other Statistical Challenges and Opportunities in DCTs

Generally, statistical issues similar in DCTs and traditional RCTs

Certain aspects of DTs that may require special attention

- ***Power and Sample Size Determination***
- ***Homogeneity/Poolability of Data***
- ***Missing Values/I***ntercurrent events
- ***Analysis of Nonstandard Data***

Other Statistical Challenges & Opportunities (cont.)

Sample Size Determination

- Estimates of variability
  - Impact of technology use on variability of outcome measures
  - Inter-rater variability vs. variability induced by technology

- Effect Size
  - Effect sizes based on traditional vs. digitally-generated outcome measures
  - Use of historical data to inform effect size determination

Other Statistical Challenges & Opportunities (cont.)

Homogeneity/Poolability of Data

- Consideration for heterogeneity in data collection
- Use of model-based methods: Bayesian hierarchical model with robust pooling, incorporating change in practice over time
- Power and *post hoc* analyses implications (Eremenco et al. 2014).

Other Statistical Challenges & Opportunities (cont.)

Estimands in Virtual Trials

- **Intercurrent events (ICEs)**associated with technology use: Implications for future clinical practice
  - o Treatment policy: ICEs irrelevant?
  - o Composite strategies: ICEs part of definition of outcome variable?
  - o While-on-treatment strategy: Loss to follow-up vs. missing data due to device malfunction?
  - o Hypothetical strategy: Treatment effect if ICEs did not occur?

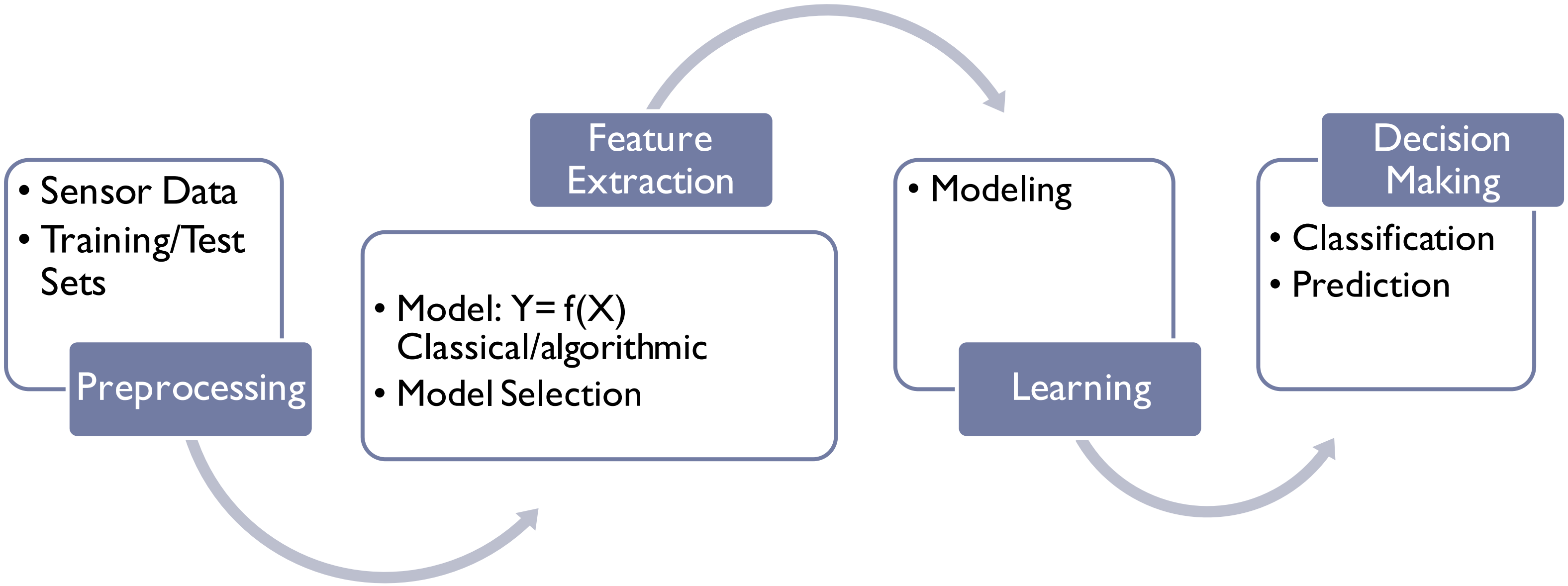
- **Definition of outcomes**: Nonstandard mode and frequency of measurements, e.g., wearables, sensors, etc.

Example: Analysis of Wearable Device Data

Activity patterns over time

Other Statistical Challenges & Opportunities (cont.)

Analyzing high-dimensional, non-standard data



Other Statistical Challenges & Opportunities (Cont.)

A simple model:

Time varying effect of covariates X(t) and Z(t) on

$Y_{ij}(t)$ = Measurement for subject i, on day j, at time t

$$Y_{ij}(t) = X_i\,\beta(t) + Z_i(t)\,\gamma(t) + e_{ij}(t)$$

Approaches:

- Penalized splines to fit β(t), γ(t)
- Need to account for functional correlation within subjects
- Inference: Bootstrap

Other Statistical Challenges & Opportunities (Cont.)

General framework: Penalized likelihood estimation: $L(\eta) + \lambda\ J(\eta)$,

$L(\eta)$, -log likelihood;
$J(\eta)$, quadratic "roughness" functional
Minimization in space H = { *f: J(f)* < ∞ }

Typically, H Reproducing Kernel Hilbert Space

- Framework for many ML models, including SVM, LASSO, etc.
- A special case: **Smoothing Spline ANOVA (SSANOVA):**

Example: Cubic smoothing splines:

$$\frac{1}{n}\sum_{k=1}^{n}(Y_k - \eta(x_k))^2 + \lambda \int_0^1 (\eta''(x))2dx, \text{ where}$$

$$\{f: \int_0^1 (f''(x))2dx < \infty\}$$

Inference relating to SSANOVA: Bayesian confidence/credible intervals

Statistical Challenges & Opportunities (Cont.)

- Other commonly used techniques for **wearable device** data:

  Examples from the literature

  - **SVM, kNN, CART**: Detect various activities (Guiry et al. 2014)
  - **Random forests, decision Trees, SVM and Naive Bayes**: Muscle movements (Mortazavi et al. 2014)
  - **Hidden Markov Models**: Categorize epochs into sleep/wake states (Li 2019; detect arm posture Shen et al. 2016)

Statistical Challenges & Opportunities (Cont.)

Inference Involving ML Techniques

- Primary objectives of ML models
  - ➢ Prediction, classification, dimensionality reduction, etc.
  - ➢ Most applications not concerned with classical inference: Estimation, testing, confidence interval construction

- Recent developments relating to inference with ML
  - ➢ Causal inference in observational studies (Wager 2021; Ratkovic 2019)
  - ➢ High dimensional covariate adjustment in RCTs to improve efficiency (Wager et el. 2016)
  - ➢ Confidence intervals and related inference with random forest (Mentch and Hooker 2016; Wager et al. 2014)

- Enhancing validity of inference involving high dimensional data
  - ➢ Post-selection inference (Tibshirani et al. 2014)
  - ➢ Targeted learning (van der Laan, 2011)
  - ➢ Consider testing as a classification problem (Zhan and Kang, 2019)

Privacy and Confidentiality: Statistical Considerations

Privacy and confidentiality

- Online recruitment may not reliably protect patient against harm
  - ➢ Use of sensitive personal information, unintentionally revealed by Internet users
- Measures by data aggregators to protect privacy may be inadequate

Recent trends:

- Incorporate privacy constraints in a decision theoretic setting
- Optimality results assessed under local differential privacy: Modelling with privacy data remaining private from statistician or learner

Duchi, Jordan, Martin and Wainwright, 2013. [1302.3203] Local Privacy, Data Processing Inequalities, and Statistical Minimax Rates (arxiv.

Data and System Integrity & Other Ethical Issues

- Implementation of a robust security system
  - Ensure authorized use, identification of authors of records, and availability of audit trails
  - Authentication of patient identity: AI for biometric authentication
- Best practices to minimize unintentional data corruption during transmission or intentional modification by malicious users.

- Ensure equitable selection of subjects”
  - VTs may exclude those who do not use Internet or own computer/smartphone
  - Bias against the poor, old, or those who live in rural areas.

DCTs in Pandemic Settings

- Pandemic disruptions of traditional trials
  - Quarantines, site closures, travel limitations, interruptions to drug supply
  - Covid-19 infections of patients and/or site personnel
- Impacts
  - Informed consent, study visits and procedures, data collection, study monitoring, AE reporting, and changes in site operations
  - Several clinical trials closed at height of pandelic (Bernstein Research, 2020)
- Mitigating measures
  - Changes in protocol and other operational processes
  - Leverage technology for outcome assessment:
  - Assess analytical approaches: Estimand definitions, combinability of data, etc. (Meyer et al 2020)

Concluding Remarks

- Major issues with current paradigm for drug development
- DCTs can enhance drug development
  - o Enhance operational efficiency: Patient recruitment, data capture and processing
- DCTs offer considerable statistical opportunities
  - o Facilitate implementation of complex and innovative designs
  - o Use of modern analytics to analyze high dimensional data
- Success factors
  - o Effective use of technology, and modern analytics
  - o Best practices for data and system integrity; and protection of patient privacy and confidentiality
  - o Availability of transparent regulatory framework for technology use.

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