



# Practical Considerations in Utilizing Cluster Randomized Clinical Trials in Medical Research

April 2021

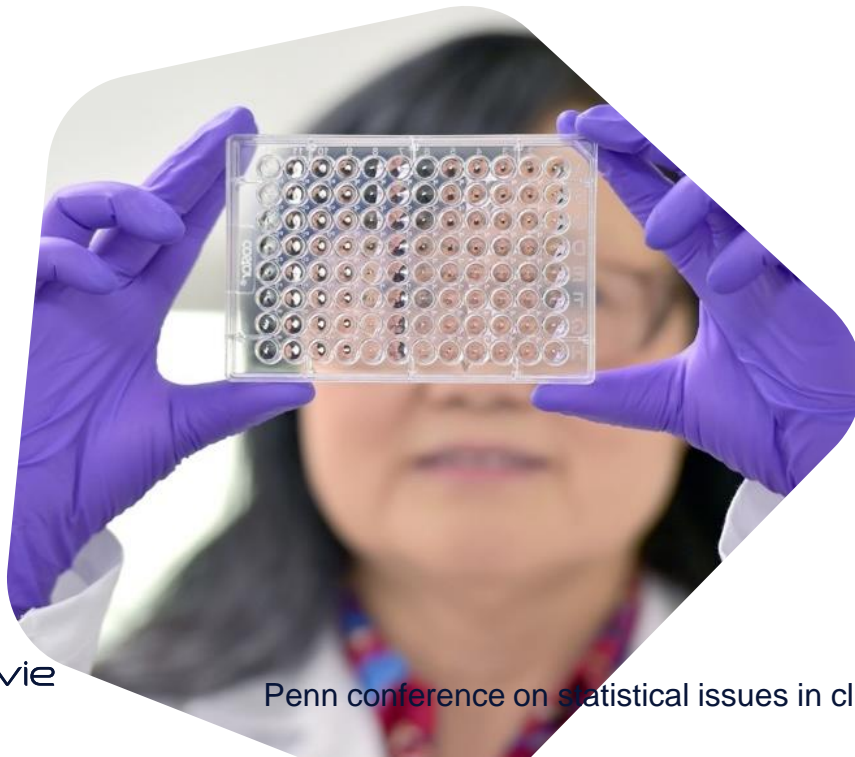
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Penn conference on statistical issues in clinical trials

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- 1. Background and rationale on the use of RWD/RWE**
2. Introduction of cluster randomized controlled trials and motivating examples
3. Design issues, operational challenges, and statistical considerations
4. Concluding remarks

# Definition of RWD/RWE in the FDA RWE Framework (Dec. 2018)

**Real World Data (RWD)** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

electronic health records (EHRs)

claims and billing data

data from product and disease registries

patient-generated data including in home-use settings

data gathered from other sources that can inform on health status, such as mobile devices

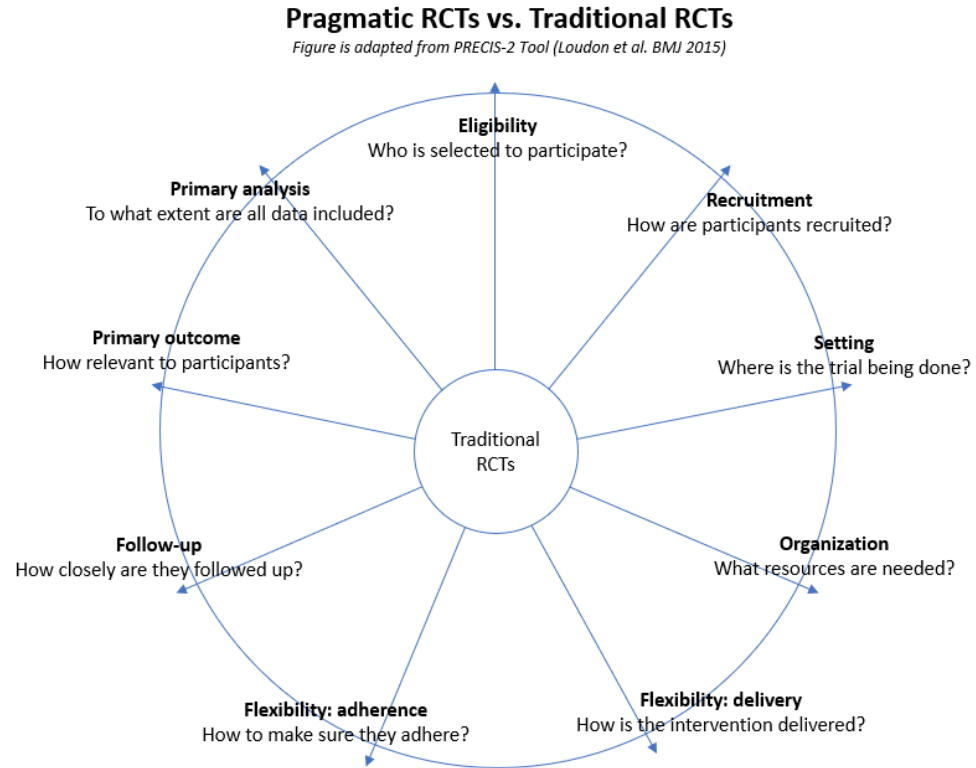
**Real World Evidence (RWE)** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

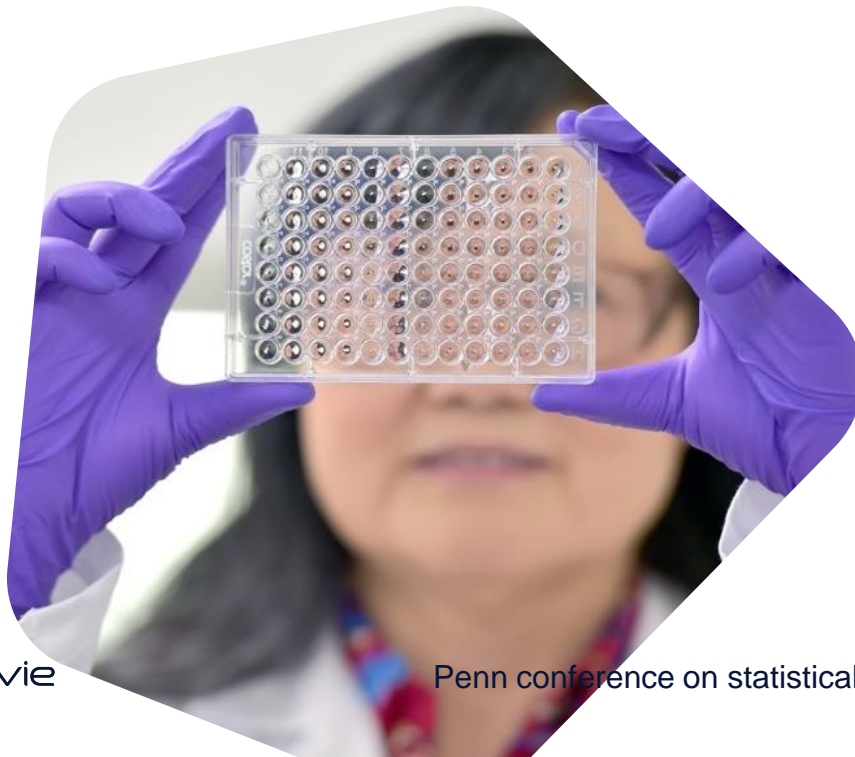
Generated using many different study designs; including but not limited to

- \* large simple trials
- \* observational studies
- \* pragmatic clinical trials; e.g.,
  - pragmatic RCTs
  - cluster RCTs
  - stepped-wedge trials

# Use of Pragmatic Elements in RCT setting

- Traditional RCTs
  - Investigating efficacy
  - Answering “Can it work?”
- Pragmatic RCTs
  - Investigating effectiveness
  - Answering “Does it work”
  - Generalizability for evidence-based decision making





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# Introduction of cluster RCTs

## What are cluster RCTs

- ❖ Cluster RCTs are pragmatic RCTs that have experiments as intact social units or clusters of individuals rather than independent individuals being randomly allocated to intervention groups
- ❖ Clusters could be families, communities, health professionals, clinics, hospitals, etc.

## Some examples

- Medical practices selected as the randomization unit in trials evaluating the effectiveness of disease screening programs
- Villages selected as the randomization unit in trials evaluating the effectiveness of new vaccines in developing countries
- Hospitals selected as the randomization unit in trials evaluating the effectiveness of education guidelines directed at physicians

# Motivating example – The REACH study (posted on clinicaltrials.gov 2019)

## HCV epidemic

- ❖ Hepatitis C Virus (HCV) is a blood-borne virus that damages the liver and is a major public health concern. HCV risk is substantially high in special patient population such as drug user. The clinical challenge is to identify those infected and bring them into treatment before the disease advances
- ❖ The traditional pathway to diagnosis and treatment in drug users is through GPs, drugs workers, drug agencies, social workers, community pharmacies, etc.

## Rationale for the study

- Highly effective Directly Acting Antiviral (DAA) treatment combinations are now available and achieve HCV cure rates in excess of 95%, with once or twice daily tablets for 8-24 weeks



## Motivating example – The REACH study (Cont'd)

### REACH study design

- ❖ The REACH HCV study is an international, cluster-randomized non-clinical trial with two arms.

1. REACH pathway: Education of HCV risk plus outreach nurse offering point-of-care Hepatitis C (HCV) testing to opiate substitution therapy patients in community pharmacies and subsequent follow-up with the outreach nurse
2. Education only pathway: Education of HCV risk plus community pharmacists advising opiate substitution therapy patients getting tested for HCV at local clinic by a specialist nurse and subsequent follow-up with local clinic nurse

### Study features

- The primary outcome measure is the proportion of patients in a population of stable opiate substitution therapy patients achieving Sustained Viral Response at 12 weeks post-treatment in the REACH pathway versus education-only pathway (Intention to Treat analysis).
- A key feature is that the units of randomization are pharmacies

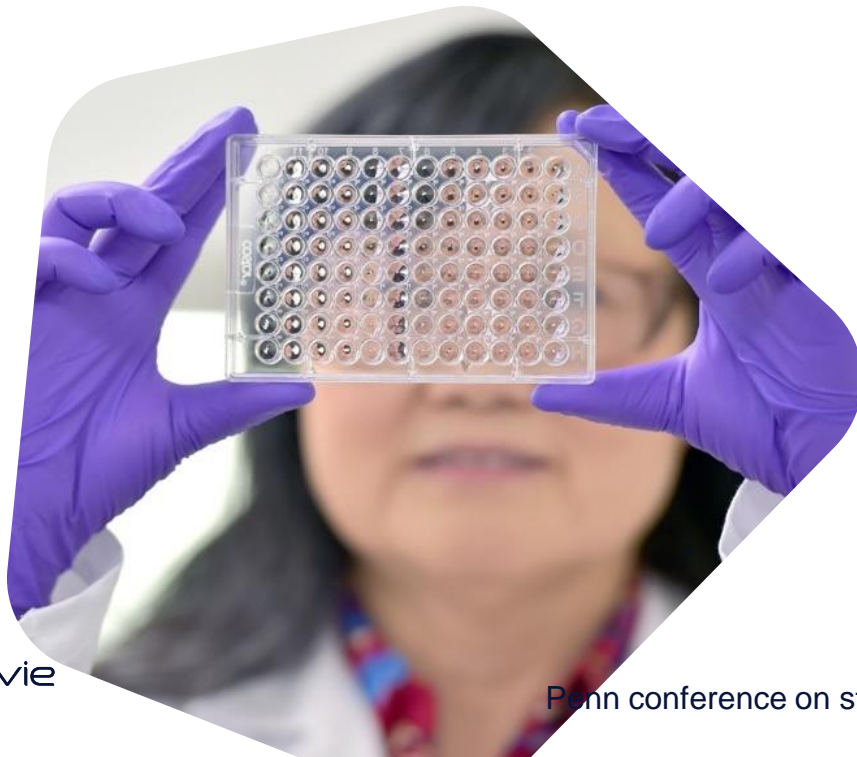
## Other motivating examples

### The REACT Study

- ❖ Khanna et al. (2015) conducted a cluster randomized trial, comparing two disease management strategies:
  1. conventional management of Crohn's disease
  2. early combined immunosuppression strategies (ECI)
- ❖ Randomization units: community gastroenterology practices

### Treat-to-target care

- ❖ Several investigator-initiated-study (IIS) proposals sponsored by AbbVie, proposing to conduct cluster randomized trial to compare the following two approaches to improve patient care and outcomes
  1. treat-to-target care approach
  2. Best usual care
- ❖ Randomization units: health care providers



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# Design considerations

## Design considerations

- ❖ Compared with traditional RCTs, cluster RCTs are more diverse and may be more complex in the following aspects
  - Study population (more general in real-world setting)
  - Sampling units (sampling units are clusters)
  - Treatments/interventions (change in clinical practice or disease management)
  - Outcomes (may not be well-defined)
  - Covariates (can be cluster-specific or individual-specific)

# Considerations of using cluster randomized trials

## Advantages

- Administrative convenience; intervention naturally applied at the cluster level
  - Evaluate a new standard of care, guideline recommendation, or other practice-wide, hospital-wide, or system-wide change on patient outcomes
- Simplified data collection and lower cost
- Ethical considerations
  - Ethics of testing social interventions vs. ethics of treating individual patients
- Avoidance of treatment group contamination
  - May dilute the observed differences between comparators and can affect the reliability and validity of the study with patient as randomized unit
- Enhancement of subject compliance

# Challenges of cluster randomized trials

## Consent

- Two levels of consent
  - Group level - Often challenging requesting consensus at community level
  - Individual level consent - Despite consent at the representative level, an individual's right to refuse to participate should be respected

## Recruitment Bias

- Recruitment bias (Giraudeau et al., 2009)
  - The comparability of groups is challenged because randomization units are groups instead of individual level
  - Blinding is usually not possible, which may induce differential recruitment and thus imbalance between groups
  - The principle of intention to treat is challenged, due to the lack of any statistical method to handle non-recruited participants
  - Empty clusters (i.e., clusters with no data for participants) are discarded, violating the very principle of intention to treat

## Challenges of cluster randomized trials (Cont'd)

### Selection Bias

- Individuals are often recruited into the study after the cluster allocation, leaving the potential for knowledge of the cluster's intervention allocation to influence whether individuals are recruited or selected into the analysis

### Other Challenges

- The ultimate goal of most studies is at the individual level; analyzing multi-level data is challenging
- The dependence between individuals within clusters (i.e., intra-cluster correlation) is challenging for both power analysis and data analysis
- Missing data at cluster or individual level and non-compliance problems are challenging for data analysis
- Objective outcome ascertainment and intercurrent events are challenging in both design and analysis stages

# Statistical considerations

## Sample size calculation

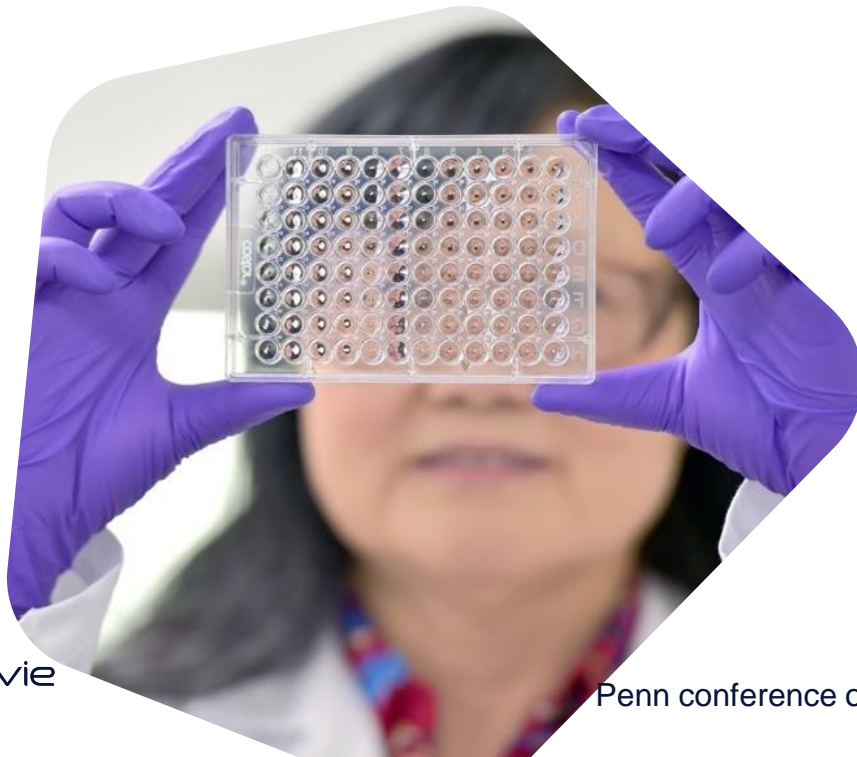
- Need to take the dependence among subjects within clusters into consideration and adjust for it in sample size calculation accordingly
- The dependence among subjects is known as *Intra-cluster Correlation Coefficient* (ICC)
- Sample size calculation and power analysis that take ICC into account are well studied; but **further research is in need** for two scenarios
  - Clusters sizes vary - some clusters are small while some clusters are large
  - Multiple levels in cluster - for example, a three-level cluster RCT is randomized over clinic site levels, within each site, there are health care providers, and within each provider, there are patients



## Statistical considerations (Cont'd)

### Statistical analysis

- Similarly, we need to take the dependence among subjects within clusters (ICC) into consideration and adjust for it in statistical analysis
- Mixed-effects model and generalized linear mixed models are popular tools for analyzing data from cluster RCTs
- When there are multiple levels (e.g., sites-providers-patients), Bayesian hierarchical models are popular tools
- Statistical analysis that takes ICC into account are well studied; but **further research is in need** for the following two scenarios
  - Missing data: If we are using multiple imputations approach for handling missing data, then the multiple imputations need to take ICC into account as well
  - Confounding bias: If we are using causal inference methods (say G-methods) to adjusting for confounding bias, then the G-methods need to take ICC into account as well



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## Concluding Remarks

- RWD/RWE research is evolving rapidly and is playing an increasingly important role in clinical development
- Cluster RCTs, as pragmatic clinical trials, coupled with effective treatment, are useful and could play an important role in studying and optimizing behavior interventions, disease management, and social policies at cluster level
- Challenges in study design, operational implementation, and statistical analysis of such trials need to be carefully thought out

## References

FDA RWE Framework. <https://www.fda.gov/media/120060/download>

Giraudeau B, Ravaud P. Preventing Bias in Cluster Randomised Trials. PLoS Medicine 2009, Vol 6, Issue 5

Khanna R, Bressler B, Zou G, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomized controlled trial. Lancet 2015, Vol 386, 2815-34

Loudon K, Treweek S, Sullivan F, et al. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015, 350 doi: <https://doi.org/10.1136/bmj.h2147>

REACH study protocol

<https://www.clinicaltrials.gov/ct2/show/NCT03935906?term=Dillon&cond=HCV&draw=2&rank=4>



**Thank You**