



# TRANSFORMING CLINICAL PRACTICE: EVIDENCE-BASED STRATEGIES AND TOOLS

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## Objective

To provide information on the methodology of data collection.

## Comparative effectiveness research

This research often involves extensive studies to validate a hypothesis that a researcher is passionate about. An intervention is compared with either a control group or another intervention, assessing both benefits and harms. For this purpose, empirical data related to meaningful health outcomes is collected. There are various methods for this, including trials and observational studies.

## Observational studies

They can be roughly divided into:

- + **Case Studies:** Often the starting point of a research trajectory. They provide a detailed description of a specific case, detailing the circumstances without generalizing the results. There's no comparison to a control group. Such studies can lead to fresh insights, for instance, unveiling underlying biological mechanisms.
- + **Ecological Studies:** These studies focus on the characteristics of a group of individuals, often based on location. They establish a correlation or association between aggregated information on the group of individuals (e.g., location) and the group-level health state (e.g., number of symptoms or disease percentage).

- + **Cross-Sectional Studies:** Sampling data from a population at a single point in time to understand associations between health-related variables. Challenges often include a low response rate and bias in collecting retrospective data, which may reduce representativeness. However, it's possible to examine multiple variables at a low cost.
- + **Case-Control Studies:** Similar to cross-sectional studies but sampling is done from two distinct groups: one group has a specific characteristic (i.e., the cases), like having a disease, and one group lacks this characteristic (i.e., the controls) but is very similar to the cases. A drawback is the potential ambiguity in selecting controls, which can cast doubt on how representative the study is.
- + **Cohort Studies:** Collecting data from a well-defined group that is being monitored over a specific duration, like a birth cohort. Challenges include high costs, difficulties in estimating prevalence accurately if sampling is not involved, and the need for large samples and extended follow-ups, especially with rare conditions. However, being prospective in nature, cohort studies facilitate comprehensive data collection and allow for the tracking of changes over time (estimation of incidence rates).

Each study design has its advantages and drawbacks, as detailed in the table.

| COMPARATIVE EFFECTIVENESS RESEARCH<br>Epidemiological Study Designs |                   |                 |                        |
|---|-------------------|-----------------|------------------------|
| Estimation of association measures:                                 |                   |                 |                        |
| Association Measure   | Case Control      | Cross-Sectional | Cohort                 |
| Prevalence  | No                | yes             | population sample only |
| Incidence   | no                | no              | yes                    |
| Relative risk   | rare disease only | yes             | yes                    |
| Odds ratio  | yes               | yes             | yes                    |
| Excess risk   | rare disease only | yes             | yes                    |
| Attributable risk   | rare disease only | yes             | population sample only |

## Experimental studies

They typically compare a new treatment or intervention with an existing treatment or control on human beings. The control can be no intervention, a placebo, and care-as-usual. Experimental studies can be roughly divided into:

- + **Clinical Trials:** Their objectives include the determination of efficacy (treatment works) and safety (treatment does not harm). Efficacy does not mean that the treatment is effective across a broader population and on each patient. Safety is often determined in a trade-off of benefit and harms. The most common clinical trial is randomized controlled trials where the treatments involved are randomized to (groups of) patients.
- + **Pragmatic Trials:** The goal of pragmatic trial is to demonstrate effectiveness (treatment works under routine conditions). A subset of pragmatic trials that make use of cluster randomization (groups of patients are allocated to the treatments) are sometimes referred to as community trials.
- + **Field Trials:** Experiments on healthy people grouped by different interventions to determine which keeps them healthiest.

## Stages in experimental studies

There are often different stages in experimental studies to obtain specific evidence of the new treatment. These stages are common practice in the pharmaceutical industry.

- + **Preclinical:** Animal testing for efficacy and safety.
- + **Phase I:** Conducted on healthy volunteers or sometimes on patients who have no other treatment options left in order to determine relevant doses of the new treatment.

- + **Phase II:** Focuses on evaluating biological activity. It usually doesn't study clinical events but instead observes proxies due to keeping the study size limited.
- + **Phase III:** Comparative trials assessing clinical effects.
- + **Phase IV:** Examines long-term adverse consequences.

## Hierarchy of epidemiological studies

Several medical journals use a specific hierarchy of study designs to quantify the importance of evidence on treatment effects. The most trustworthy evidence of treatment effects is determined with a systematic review, preferably using randomized controlled trials. This type of evidence combines multiple studies and therefore is most reliable. Second in rank is clinical trials, since they have more control over possible biases than observational study, particularly when randomization is applied. The next type of studies is cohort studies, since they are mostly prospective and therefore provide real-time evidence of certain effects. Case-control studies are then often considered the most reliable evidence, since they sample from both the cases and controls. When controls can be matched with cases using certain relevant characteristics of the patients, this provides a more reliable piece of evidence than cross-sectional studies. The lowest levels of evidence are determined by case-report studies and ecological studies. Case-report studies have no generalizability at all, while ecological studies only have generalizability at a helicopter or aggregated level.

## Biases

There are many different biases that could creep into a study and that would cause a disturbance in the estimation of the benefit and harm

of new treatments. Here, we mention just four of them, often being the most important biases that can occur in studies:

- + **Selection Bias:** The difference between participants and non-participants in terms of exposure and outcome. This would occur when the process of collecting participants is affected by factors that also influence the outcome and it is usually irreparable due to insufficient data.
- + **Recall Bias:** People with different outcomes might recall and report information differently. This type of bias is relevant when retrospective information is being collected.
- + **Observer Bias:** Judgment can be swayed by the observer's information. This bias may be eliminated when the observer is blinded from the treatment.
- + **Confounding Bias:** The relationship between exposure and outcome can be disturbed by another variable, making it challenging to observe the true effect. Typically present in observational studies.

## Blinding

In clinical trials, it is often recommended to make use of blinding. First-level blinding is making participants unaware of the treatment they receive. This would eliminate the placebo effect. There is quite some research on placebo effects through which it has been demonstrated that some participants are more susceptible to placebo than others. Second-level blinding means that the researchers and doctors are also unaware of who received which treatment. As we just stated, this is to prevent observer bias. It is preferable to include second-level blinding, but not all clinical trials can implement this since the treatment cannot be disguised.

## Foundation of randomized controlled trials

The most important element in clinical trial is randomization, i.e., the process of randomly assigning interventions to individuals. Randomization is crucial to eliminating confounding bias. Typical randomization techniques are complete randomization, random allocation rule, and permuted block randomization. Randomization is also the foundation for demonstrating that there is a benefit to the treatment.

A randomized controlled trial is, in essence, a statistical hypothesis testing study. The fundamental test statistic to demonstrate that there is a benefit beyond reasonable doubt is called the permutation test. Based on a measure of effect (e.g., a mean difference or odds ratio), the permutation tests calculate all values of the measure of effect for all possible permuted allocations of treatments that could also have been the outcome for the randomized controlled trial. The outcomes of the participants are considered given, but the treatments are permuted among the participants. This leads to a large set of values of the measure of effect and, when the observed value of the measure of

effect from the trial is away from this set, it is unlikely that the treatment does not contribute.

## Issues with randomized controlled trials

Although there is a high level of trust in randomized clinical trials, they do pose several huge challenges. One issue is that there is the vast variability among people, affecting generalizability. Other issues include participants dropping out, non-compliance, and other factors that might compromise the reliability of randomized controlled trials. These effects aren't always considered in the analyses. Ultimately, the representativeness of a trial is a question of utmost importance. There's often a significant discrepancy between the research question, aimed at a population, and the data resulting from the actual included population sample.

One study is often not enough. By pooling data from multiple studies, you can achieve consistent results, regardless of whether it's an RCT or observational study. In essence, comprehensive research requires multiple studies conducted in diverse settings, and pooling this data offers

more reliable conclusions. However, this doesn't mandate the exclusive use of RCTs; observational studies can also contribute to this pool. Thus, we may be much more flexible in the type of studies that we can use to demonstrate the benefit and harm of new treatments. This is also because causal inference can be conducted from observational studies.

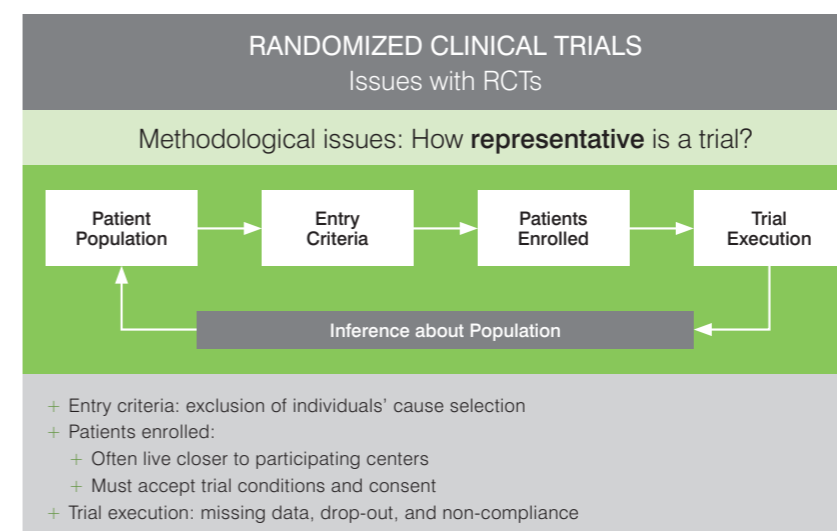
## From efficacy to implementation

There is often a gap in comparative effectiveness research (CER) where the focus on process thinking is missing. Implementing findings into practice necessitates a process-oriented approach. This means:

- + Clearly defining the intended outcomes of each activity.
- + Identifying and following steps that facilitate practical implementation.
- + Adopting a phased approach.
- + Making adjustments based on accumulated knowledge.
- + Continuously monitoring and overseeing all activities.

The overarching idea is that while efficacy research can highlight what works in a controlled environment, the journey to actual implementation in the real world requires a comprehensive, phased, and adaptive strategy that takes various factors into account.

When adopting a process-oriented approach, the likelihood of a type I error might exceed the conventional 5% threshold defined in typical studies. This risk should be mitigated through methods such as intensive simulation studies and the use of digital twins. There's a pressing need for new evidence-based methodological studies. The emphasis on randomization might decrease and study designs could be seamlessly integrated into daily routines. However, this inte-



gration complicates statistical analyses, necessitating sophisticated bias correction methods. Frequent interim evaluations become crucial, as does the application of AI and the need to estimate individual causal effects due to population heterogeneity. Future studies should be pragmatic, eliminating exclusive criteria. Moreover, these novel study designs should also provide insights into:

1. **Details of Effectiveness:** This should encompass both a general overview and an understanding of individual outcomes.
2. **Understanding of Causal Effects:** Specifically, understanding the impact of the new intervention in relation to other factors and conditions.
3. **Practical Application:** This would involve insights into how the clinical setting can accommodate or adapt to the new intervention.

Currently, there's scarcely a trial design that meets all these criteria. Therefore, there's a compelling case for transitioning to adaptive trial designs. An adaptive trial design is one that allows for modifications to the trial procedures (like dose adjustments) based on interim results. The main advantage of adaptive designs is their flexibility. They can provide a more efficient and ethical approach

to determining the clinical benefits of an intervention, especially when there's uncertainty about the best treatment approach. With the advent of sophisticated statistical software and an increasing emphasis on patient-centric research, adaptive designs are becoming more prevalent. They allow researchers to 'learn' from the data as the trial progresses, potentially reducing the number of participants exposed to an inferior treatment and potentially accelerating the clinical development timeline.

**Switch Designs** are often more effective than RCTs since they are immediately implemented in the routine clinical practices. By the end of these studies, evidence is presented to determine whether a particular intervention has worked or not. Data analytic methodology has been worked out in the last decade to effectively make use of these designs compared to more traditional randomized controlled trials. Switch designs can also be more powerful than traditional randomized controlled trials.

**Single Patient Trials:** This approach involves testing multiple treatments within a single patient, searching for the most effective treatment for one person, which can be particularly applicable in fields like psychology. The results of

these individual trials can then be aggregated for broader analysis.

**Space RCTs:** Experiments are conducted within a cohort, with every member of the cohort participating in the study. A major advantage of this method is the abundance of control subjects available. A random sample of participants is taken from within the cohort (note: this is different from randomization). As choices are made at various points, multiple groups emerge. This design allows researchers to explore the impact of different attributes, such as an individual's intrinsic motivation to participate, on the outcomes. This strategy permits both individual matching (to determine individual effects) and comparisons between different intervention groups.

### Conclusion

The ultimate success of a study is when it culminates in full implementation at the workplace. Naturally, this encompasses all other aspects of implementation science, including understanding the contextual factors, barriers, and facilitators to implementation. It's essential to take a multi-dimensional approach involving stakeholders, adapting to local conditions, and evaluating both the process and outcomes of implementation. This holistic approach ensures that the findings of a study aren't just theoretically significant, but they also bring about change. Thus we advocate the development of process thinking in comparative effectiveness research and making use of different studies to accumulate evidence.

