Column: Research methods in Psychiatry

EXPERIMENTAL STUDIES: RANDOMIZED CONTROLLED TRIALS – Part I

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Abstract

Experimental research design involves experiments where experimental groups are created, exposed to specific interventions and specific outcomes studied. Randomized controlled trials (RCTs) are true-experimental studies and the most accurate and powerful among experimental study designs. In RCTs, participants are randomly allocated to receive one of several interventions, and the effects of these interventions are studied regarding particular outcomes. The different types of RCTs are discussed.

Keywords: Experimental research design, randomized controlled trials, types of RCTs

Experimental Studies

Experimental research design is defined as "the process of carrying out research in an objective and controlled fashion so that precision is maximised and specific conclusions can be drawn regarding a hypothesis statement."[1] It involves typical experiments where experimental groups are created and are exposed to specific treatments, agents or therapeutic programmes. It is the investigator who assigns the exposure status of each participant and attempts to control all factors that can affect the outcome of the experiment.[2] Experimental studies can be of three main types – pre-experimental, true-experimental and quasi-experimental. In pre-experimental studies, one or more dependent groups are compared for the effect of an independent variable. This is the most basic type of experimental design and there is no control group. They are also called uncontrolled trials.[1,3] In quasi-experimental studies, there is a control group, but the groups are not randomly assigned and hence a cause-effect conclusion cannot be reached. These are called non-randomized controlled trials. It is done in situations where randomisation is difficult or not possible. In true-experimental studies, the comparison is made between two randomly assigned groups, where there is a control group and an independent variable which can be controlled by the investigator. This includes randomized controlled trials (RCTs).[1,3]

Randomized Controlled Trials

True-experimental design is the most accurate and powerful among experimental study designs and they encompass RCTs – one of the most revolutionary research tools. In RCTs, participants are randomly allocated to receive one of several interventions, and the effects of these interventions are studied regarding

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particular outcomes. Although the "intervention" refers to treatment, it can be any clinical manoeuvres that can impact the health status of the participants – like preventive strategies, surgical interventions, diagnostic tests, screening programmes, or health education models. The outcomes studied can range from the remission of symptoms to recovery or recurrence of disease or even death.[3]

Types of RCTs

RCTs can be classified in different ways – according to the different aspects of interventions that they evaluate, the manner in which the participants are exposed to the interventions, the number of participants studied and whether the participants and investigators are aware of which intervention they are receiving or are being evaluated.

According to the different aspects of the interventions being evaluated

Explanatory and pragmatic trials: Explanatory trials seek to assess whether an intervention works and, if so, how. Pragmatic trials evaluate whether the intervention works and its consequences, under ordinary clinical circumstances. Although these trials are at the extremes of a spectrum, most RCTs incorporate elements of both.[4,5]

Efficacy and effectiveness trials: 'Efficacy' refers to whether an intervention works in people who actually receive them and efficacy trials evaluate the efficacy of interventions in ideal or optimal circumstances. 'Effectiveness' refers to whether an intervention 'does' work rather than 'whether' it works and effectiveness trials evaluate the effectiveness of interventions in routine clinical circumstances. They are also called pragmatic trials.[4,5]

Phase I, II, III and IV trials: These refer to different trials conducted during the evaluation of a new drug. Out of these, only phase III trials are RCTS; the others are actually not randomized. After the safety of a new drug or intervention is confirmed from animal studies, Phase I studies are conducted, usually in healthy volunteers, to assess the safety of the intervention in humans. These trials are generally neither randomized nor controlled. After the Phase I trial is completed successfully, Phase II trials are conducted in patients to study the efficacy of the drug at different doses and the dosing schedule. These studies also provide additional information regarding the safety of the drug. Generally, these trials are not randomized. Once the safety and efficacy of the intervention are proven in Phase I and II trials, Phase III trials are conducted. They are typical RCTs conducted on patients to compare the effectiveness of a new intervention with an existing one. Phase IV trials are large studies to assess the adverse effects of a new drug or intervention after it has been approved for marketing. So, these are post-marketing surveillance studies.[4,5]

Superiority, non-inferiority and equivalence trials: Superiority trials assess whether the new intervention is better than or superior to the existing one. In a non-inferiority trial, the objective is to show that the new intervention is not worse than or inferior to the existing one. The new intervention may have advantages over the existing one like being less expensive, non-invasive or having a better side effect profile. Equivalence trials attempt to show that the new intervention is as effective or efficacious as the existing one within certain narrow limits. The limits to show that the two interventions are equally effective are specified in advance.[5,6]

According to the exposure of participants to the interventions

Parallel, cross-over and factorial designs: Parallel designs are RCTs in which each group of participants are exposed to only one of the interventions in the study. Crossover designs are those in which each group of participants are exposed to all the interventions used in the study in successive periods. The sequence in which the participants receive each of these

interventions is determined randomly. Each participant becomes their own control and comparisons are made 'within participants' rather than 'between participants,' as occurs in parallel designs. This design is employed in chronic conditions where the course is generally stable over time. In factorial design, two or more interventions are compared individually, in combination and against a control. In a 2X2 factorial design, there will be data from four groups – those receiving treatment A, treatment B, those receiving both treatments A and B as well as no treatment or placebo. The interaction between two treatments can also be studied in this design. Moreover, it is more cost-effective.[4,5]

According to the number of participants

N-of-1 and megatrials: 'N-of-1 trials' or 'individual patient trials' are conducted on a single patient. They are usually randomized, often blinded, and involve multiple cross-overs. The participant can receive the experimental and control interventions in sequence or in pairs at random. The results apply to that individual and are not generalisable. Megatrials are conducted with thousands of participants, generally from multiple centres from different countries, and involve limited data collection.[4,5]

Sequential and fixed trials: Sequential trials are RCTs with parallel designs where the number of participants is not specified at the outset. Participants are recruited either until a significant benefit is observed or until the lack of difference is brought out convincingly. In fixed trials or fixed-size trials, the number of participants or the sample size is established *a priori.* The number can be calculated utilising statistical methods or can be fixed arbitrarily.[4,5]

According to blinding or the awareness of participants and investigators regarding the intervention studied

Open, single-blind, and double-blind RCTs: Blinding or masking is a strategy used by researchers to keep one or more of the people involved in a trial – i.e., the participant or the investigator – unaware of the intervention being given or evaluated. This helps in reducing observation or ascertainment bias. Based on the level of blinding, RCTs can be open, single-blind, double-blind, triple-blind, quadruple-blind and so on. In open RCTs, the participants and investigators know which intervention each participant is receiving. In single-blind RCTs, one group, usually the participants, is blinded to the intervention received. In double-blind trials, the participants and treating doctors or investigators are blinded to the intervention given. In triple-blinded studies, the participants, treating doctors and the investigators or evaluators are unaware of the intervention received. In quadruple-blinded studies, the statistician is also blinded to the intervention given.[4,5]

RCTs can further be classified according to non-randomized participant preferences. Those who are eligible may refuse to participate in an RCT, while some may decide to participate with a preference for one intervention. Such trials that include a group in which the participants are allowed to choose their preferred intervention from the options available are called preference trials. Zelen design, Wennberg's design and comprehensive cohort designs are some of them.[4,5]

These are the different types of RCTs. Various steps are involved in the designing of RCTs. They shall be discussed in Part II of the discussion on RCTs.

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