Understanding research

Part three: randomised controlled trials

Welcome to part three in the series 'understanding research'. This paper aims to build on the knowledge gained in parts one and two and is dedicated solely to the randomised controlled trial (RCT) (Gethin, 2008). As the RCT is the basis for understanding and testing cause and effect relationships and is widely used in health care, it is important to have a basic understanding of the components which constitute this design.

What is an experiment?

An experiment is a scientific investigation that makes observations and collects data according to explicit criteria and contains three identifying properties; randomisation, control and manipulation (LoBiondo-Wood and Haber, 2002). These studies involve a high degree of rigor, so are considered to provide the strongest evidence available on different treatment regimes (Baxter, 2001a). Experimental studies are not without limitations as many variables are not amenable to external manipulation. For example, health status varies with age and socio-economic status, so no one can randomly assign subjects by age or a certain level of income (LoBiondo-Wood and Haber, 2002). The aims of experimental studies are to examine cause-and-effect relationships between independent and dependent variables under highly controlled conditions (Burns and Grove, 2001). The RCT is a form of experimental study and is one of the simplest, most powerful and revolutionary tools of research (Jadad, 1998).

Randomised controlled trial (RCT)

The accepted current 'gold standard' in terms of properly designed evaluations is the RCT (Jadad, 1998; Johanson, 1999; Price, 1999). The RCT is defined as a quantitative, comparative, controlled experiment in which a group of investigators study two or more interventions in a series of individuals who receive them in a random order (Jadad, 1998). If properly designed, this type of trial minimises bias and allows small but clinically significant differences in benefit and harm to be detected, provided the number of subjects is large enough (Johanson, 1999). Baxter (2001a) cautions that while the idea is to make the research objective, the results will only really apply to the parameters set within the trial. Yet, as a form of research within wound healing, RCT evidence is limited both in the number of studies undertaken and in the quality of the research (Palfreyman et al, 2006).

Bias in the RCT

Bias is any factor or process that causes the results or conclusions of a trial to divert systematically from the truth (Jadad, 1998). Greenhalgh (1999) states bias may occur in RCTs if randomisation is not truly random, or if the allocation to group is not concealed and if those assessing outcome are aware of which group the patient was in. To minimise the possibility of introducing bias, four important factors must be considered; randomisation, blinding, design and reporting .

The objective of randomisation is to obtain comparable groups of certain characteristics so that known or unknown factors are evenly distributed between them (Baxter, 2001b). If properly conducted, randomisation reduces the risk of serious imbalances in unknown but important factors that could influence the clinical course of the participants (Jadad, 1998). In addition, randomisation is ethically sound as patients have a 50% chance of receiving the more effective treatment, whichever one that is, and baseline characteristics are more likely to be similar across all groups (Jadad, 1998; Johanson, 1999).

Generation of an unpredictable randomised allocation sequence represents the first crucial element of randomisation (Schulz and Grimes, 2002). Studies on the management of venous leg ulcers often fail to state the method of randomisation (Charles, 1991; Duby et al, 1993; Moffatt and Dorman, 1995). The absence within these reports of the method of randomisation means the possibility of bias having been introduced into these trials cannot be ruled out. The second element of randomisation is allocation concealment (Schulz and Grimes, 2002). Allocation concealment refers to the technique used to implement the sequence, not to generate it (Schulz and Grimes, 2002).

Methods to achieve randomisation in wound healing trials have included: alternate allocation (Sikes, 1985); medical record number (Rublin et al, 1990); and coin toss (Kikta et al, 1988). These methods can, however, be easily manipulated by the investigator if they so wish (Schultz and Grimes, 2002). In a systematic review of compression therapy the most frequently employed method of randomisation was serially numbered, sealed, opaque envelopes (Cullum et al, 2001). Schulz and Grimes (2002) suggest that if such a method is to be instituted then numbered, sealed, opaque envelopes opened sequentially after the patient's name and details are recorded could be used (Schultz and Grimes, 2002). This aims to prevent selection bias whereby potentially eligible individuals are selectively excluded from the study because of prior knowledge of the group to which they would be allocated (Jadad, 1998). Thus, proper randomisation hinges on adequate allocation concealment (Schulz and Grimes, 2002).

Blinding represents any attempt by the investigator to keep one or more of the people involved in the trial unaware of the intervention that is being given or evaluated in order to reduce the risk of ascertainment or observational bias (Jadad, 1998; Johanson, 1999). This bias is present when the assessment of the outcomes of an intervention is influenced systematically by knowledge of which intervention a participant is receiving (Jadad, 1998). Within wound healing, RCTs are more difficult than in other medical problems as blinding of researchers, medical staff and patients to highly visible problems and/or interventions is very difficult. Thus, most wound care trials are open trials and

are rarely blind (Venkatraman et al, 2002; Gethin and Cowman, 2009). This difficulty is demonstrated in Ormiston et al's (1985) study comparing cadexomer iodine to a standard dressing for chronic venous leg ulcers, whereby traces of the dressing could be seen, thus allowing researchers to know which treatment the subjects were receiving.

Cochrane Library and Health Technology Assessments recommend that whenever possible an observer 'blind' to the original treatment should undertake the outcome assessment (Cullum et al, 2001; O'Meara et al, 2001). However, within pragmatic trials blinding is not always possible, particularly as placebos are not generally used (Roland and Torgerson, 1998). Schulz and Grimes (2002) argue that blinding becomes less important to reduce observer bias as the outcomes become less subjective, since objective (hard) outcomes leave little opportunity for bias. Blinding is recommended whenever possible, but studies should be assessed on overall merit rather than on one single element.

Reporting

In most cases the only information that the practitioner has to interpret a trial is the published report. To improve the quality of reports of trials and standardise information an international group of epidemiologists, biostatisticians and journal editors published a statement called CONSORT (consolidation of the standards of reporting trials) (Begg et al, 1996). This format ensures that information regarding all aspects of a trial are reported on. However, this does not overcome publication bias. Some evidence shows a propensity for investigators and sponsors to write and submit and for peer-reviewers and editors to accept manuscripts for publication, depending on the direction of the findings (Jadad, 1998). This tendency, which appears to favour trials with positive results, has been called publication bias (Jadad, 1998).

Publication bias is a major problem in professional literature, positive results being more likely to get submitted and published. Cullum et al (2001) recommend that prospective registration of research studies should be mandatory to ensure inclusion of unpublished trials in systematic reviews. The current situation results in readers drawing conclusions (often incorrect) from a skewed and incomplete database. Provided the methodology is robust, all research results offer valuable information and knowledge to the field and should be published. Furthermore, the Declaration of Helsinki (1964) states that negative as well as positive results of research should be published or otherwise publicly available.

Assessment of trial validity

Internal validity is defined as the extent to which the effects detected in the study are a true reflection of reality, rather than being the result of the effects of extraneous variables (Burns and Grove, 2001). External validity is defined as the extent to which study findings can be generalised beyond the sample used in the study (Burns and Grove, 2001). Assessment of the validity of the trial can be considered under four key areas known to affect systematic bias (Higgins and Green, 2006); selection bias, performance bias, attrition bias and detection bias.

Selection bias

It is argued that in a clinical trial the selection of patients should be representative of some future class of patient to whom the trial's findings may be applied (Pocock, 1983). In the RCT one is trying to test an intervention in order to guide the treatment of a future group of patients with the same condition.

Chang et al (2004) identified six reasons why patients participate in research, including; benefit to self, benefit to others, gratitude to the physician, positive comments by the trusted professional, the appearance, personality, manner and gender of the recruiter and monetary compensation. The first two of these reasons are supported by two online surveys involving 4,600 adults in the USA and the European Union, in which the most commonly mentioned motivation for participation was altruism (Brescia, 2005; Rochester, 2005). Sixty-eight percent of respondents were willing to participate in a clinical trial and of these, 10% had already done so, while 84% understood it to be voluntary (Brescia, 2005; Rochester, 2005). These findings are interpreted with caution, as being confined to an online poll implies a certain willingness on the part of the respondent to contribute to the research survey in the first place. However, they do highlight the willingness of patients to trial participation.

Performance bias

Performance bias refers to systematic differences in the care provided to the participant in the comparison groups other than the intervention under investigation (Higgins and Green, 2006). To protect against performance bias, it is recommended that those providing and receiving care be 'blinded', so that they do not know the group to which the recipients of care have been allocated (Higgins and Green, 2006). Blinding refers to keeping trial participants, investigator and/or assessors unaware of an assigned intervention so that they are not influenced by that knowledge (Schultz and Grimes, 2002).

Attrition bias

Attrition [withdrawal] bias refers to systematic difference between the comparison groups in the loss of participants from the study (Higgins and Green, 2006). Poor compliance with the protocol may contribute to attrition bias. It is proposed that poor compliance with a study protocol may suggest that the treatment as used in the RCT is not practical (Prescott et al, 1999). It could also reflect poor trial design. To a great extent, compliance with the intervention is one of the most important outcomes of pragmatic trials (Godwin et al, 2003). If the physician or the patient does not comply with the intervention, then, according to Godwin et al (2003), it

does not matter that it can work in a perfect or ideal environment because if it does not work in the real world, it is of no use.

Detection bias

Detection bias, also called ascertainment bias, refers to systematic differences between the comparison groups in outcome assessment (Higgins and Green, 2006). Ascertainment bias can be introduced by the person administering the intervention, the person receiving the intervention, the investigator assessing or analysing the outcomes and even by the person who writes up the report (Jadad, 1998). Trials that blind outcome assessors should be less likely to be biased than those trials that do not. Studies in which the outcomes are more objective reduce the risk of ascertainment bias.

Conclusion

The RCT is a powerful research methodology which aims to determine cause and effect relationships. It is highly organised methodology that bases its design on three key features; randomisation, control and manipulation. As a quantitative methodology, assessment of outcomes should be objective and have a high degree of internal and external validity. Trials should be assessed for levels of bias. In the RCT, bias is anything that deviates from the truth. The greatest sources of bias are: selection bias, performance bias, attrition bias and detection bias. WUK

Next article

The next and fourth article in the series will explore qualitative research studies.

Georgina Gethin is Lecturer, Research Centre, Faculty of Nursing and Midwifery, Royal College of Surgeons in Ireland, Dublin

References

Baxter, H. (2001a) Understanding research: 1 Methodologies used to answer research questions. *J Wound Care* **10(7)**: 269–72

Baxter H (2001b) Understanding research: 2 Ensuring reliability and validity. *J Wound Care* **10(8)**: 329–31

Begg C, Cho M, Eastwood S (1996) Improving the quality of reporting of randomised controlled trials. *J Am Med Assoc* **276**: 637–9

Brescia B (2005) Europeans Weigh-in on Clinical Study Participation. Applied Clinical Trials online. Available online at: www.actmagazine.com, 46–52

Burns N, Grove S (2001) *Nursing Research, conduct, critique and utilization*. Saunders, Pennsylvania.

Chang B, Hendricks A, Slawsky M, LoCastro J (2004) Patient recruitment to a randomised clinical trial of behavioural therapy for chronic heart failure. *BMC Med Res Methodol* **4**: 8

Charles H (1991) Compression healing of ulcers. *J Distr Nurs* **4**: 6–7

Cullum N, Nelson EA, Fletcher AW, Sheldon TA (2001) Compression for venous leg ulcers. Cochrane Database of Systematic Reviews, Issue 2. Art. No: CD000265. DOI: 10.1002/14651858.CD000265

Duby T, Cherry G, Hoffman D, Cameron, J, Dobloff-Brown D, Ryan T (1993) A randomised trial in the treatment of venous leg ulcers comparing short-stretch bandages, four layer bandage system and a long stretch-paste bandage system. *Wounds — a compendium of clinical research and practice* **5(6)**: 276–9

Gethin G (2008) Understanding research: part 1. *Wounds UK* **4(4)**: 140–1

Gethin G, Cowman S (2009) Manuka honey vs hydrogel, a prospective, open label, multicentre randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. *J Clin Nurs* **18(3)**: 466–74

Godwin M, Ruhland L, Casson I, et al (2003) Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC Med Res Methodol* **3**: 28

Greenhalgh T (1999) Critical appraisal of the research literature. In: O'Brien I, Pipkin B, eds. I*ntroduction to Research Methodology*. Royal College of Obstetricians and Gynaecologists, London

Higgins J, Green S (2006) Assessment of study quality. In: Higgins CS, Green S, eds.*Cochrane Handbook for Systematic Review of Interventions* 4.2.6 [updated September 2006], Vol. issue 4. John Wiley & Son Ltd, Chichester

Jadad A (1998) *Randomised Controlled Trials*. British Medical Journal Books, London

Johanson R (1999) Clinical trials. In: O'Brien I, Pipkin B, eds. I*ntroduction to Research Methodology*. Royal College of Obstetricians and Gynaecologists, London

Kikta MJ, Schuler JJ, Meyer JP, et al (1988) A prospective, randomized trial of Unna's boot versus hydroactive dressing in the treatment of venous stasis ulcers. *J Vasc Surg* **7**: 478–83

LoBiondo-Wood G, Haber J (2002) *Nursing research methods critical appraisal and utilization*. Mosby, Missouri.

Moffatt C, Dorman M (1995) Recurrence of leg ulcers within a community ulcer service. *J Wound Care* **4(2)**: 57–61

O'Meara SM, Cullum N, Majid M, Sheldon TA (2001) Systematic review of antimicrobial agents used for chronic wounds. *Br J Surg* **88**: 4–21

Ormiston MC, Seymour MT, Venn GE, Cohen RI, Fox JA (1985) Controlled trial of iodosorb in chronic venous ulcers. *Br Med J* **291**: 308–10

Palfreyman SSJ, Nelson EA, Lochiel R, Michaels JA (2006) Dressings for healing venous leg ulcers. Cochrane Database of Systematic Reviews 2006, Issue 3. Art No: CD001103. DOI: 10.1002/14651858.CD001103.pub2

Pocock SJ (1983) *Clinical Trials: a practical approach*. John Wiley & Sons, London

Prescott RJ, Counsell CE, Gillespie WJ, et al (1999) Factors that limit the quality, number and progress of randomised controlled trials. *Health Technol Assess* **3(20)**: 1–143

Price P (1999) The challenge of outcome measures in chronic wounds. *J Wound Care* **8(6)**: 306–8

Rochester (2005) Public perception of clinical research studies. Applied Clinical Trials online. Available online at: www.actmagazine.com/appliedclinicaltrials

Roland M, Torgerson D (1998) Understanding controlled trials; What are pragmatic trials? *Br Med J* **316**: 285

Rublin J, Alexander J, Plecha E, Marman C (1990) Unna's boot versus polyurethane foam dressings for the treatment of venous ulceration, a randomised prospective study. *Arch Surg* **125(4)**: 489–90

Schultz K, Grimes D (2002) Blinding in randomised trials: hiding who got what. *Lancet* **359**: 696–700

Schulz K, Grimes D (2002) Allocation concealment in randomised trials: defending against deciphering. *Lancet* **359**: 614–18

Sikes E (1985) Evaluation of a transparent dressing in the treatment of stasis ulcers of the lower limb. *J Enterostomal Ther* 12: 116–20

Venkatraman P, Anand S, Dean C, Nettleton R (2002) Clinical trials in wound care 1: the advantages and limitations of different clinical trial designs. *J Wound Care* **11(3)**: 91–4