What is Trials Methodology Research?

Here are some great examples of how Trials Methodology Research has improved the way we design, conduct and analyse clinical trials for the benefit of participants, researchers, and others who use the evidence to make decisions about healthcare.

The examples illustrate how Trials Methodology Research is making it easier for patients to take part, helping improve patient decision making, helping measure what matters, gathering reliable evidence more quickly and making trials more acceptable especially in challenging situations. These are things that especially matter for those who volunteer to take part as well as important issues for researchers.

Trials Methodology Research is increasingly drawing upon the active involvement of patients and the public in its work.

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Making it easier for patients to take part in research

Working out how to make randomised clinical trials become part of routine patient care is a top priority for doctors and researchers[1]. The ALL-HEART study[2] (Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease) is an example of a trial that is putting this into practice.

The research team have made taking part in the trial easier for patients, which also means that the trial is much more cost-efficient. Instead of having to attend multiple visits in hospital settings, patients attend only one or two times at their local GP practice, and then the remainder of the study follow-up over the next few years is conducted remotely.

Between 2014 and 2017, 5,937 participants were recruited and randomised from 424 GP practices across England and Scotland. Records of hospitalisations and deaths are collected from national NHS databases (ISD Scotland and NHS Digital) to allow identification of study endpoints such as myocardial infarction or stroke in a reliable and efficient manner. Annual follow-up contact is made with participants either by email, post or telephone to collect participant reported outcomes and record continuing adherence with randomised treatment.

Results are expected in 2021. For further information see the ALL-HEART study website www.allheartstudy.org .

The ALL-HEART study is funded by NIHR HTA (11/36/41).

[1] https://priorityresearch.ie/priority-one-questions/

[2] Mackenzie IS, *et al*. Multi-centre, prospective, randomised, open-label, blinded endpoint trial of the efficacy of allopurinol therapy in improving cardiovascular outcomes in patients with ischaemic heart disease: protocol of the ALL-HEART study. *BMJ Open* 2016; 6(9): e013774. DOI: http://dx.doi.org/10.1136/bmjopen-2016-013774.

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Improving how patients decide about taking part in research

Researchers have developed a way of helping patients make a more informed decision about whether or not to take part in studies of the effects of treatments.

Studies where patients are allocated (randomised) to one of two or more treatments are needed to provide evidence about which works best. However, many randomised studies find it difficult to recruit enough participants. Poor recruitment can mean that studies are delayed, cost more, or stop without answering the important question they were funded for.

The QuinteT (qualitative research integrated in trials) research group at the University of Bristol has developed the QuinteT Recruitment Intervention (QRI)[1] to gather evidence to help overcome this problem. The QRI uses interviews with patients and recruitment staff, along with audio-recordings of clinic consultations, to understand how to improve the ways patients are found, approached and invited to take part in the treatment studies.

QRIs in over 40 randomised studies have provided better understanding of why recruitment is a difficult process for patients and clinicians. When these difficulties are acknowledged and understood, the QRI supports clinical and recruitment staff to improve their explanation of the study to patients, so that it is clear why the study is needed, what its aims are, and what will happen if someone takes part.

Recruitment has improved in many of the randomised studies using QRI, and many more patients are now able to make informed decisions about whether or not to take part in such research.

[1] Donovan JL, *et al*. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). *Trials* 2016; 1: 283

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Measuring what matters to patients

Patients are increasingly being involved in determining what aspects of their health condition should always be measured in clinical trials, helping to ensure that the findings of the research will be relevant to them and people like them in the future.

When researchers test treatments to make sure they work and are safe, they look at the effects on patients by measuring the 'outcomes' of the treatments.

A 'core outcome set' is a list of which outcomes should always be measured in treatment studies and it is important that patients and carers have a say alongside health professionals when these sets are developed. Involving patients has identified outcomes important to them as a group but which might have been overlooked if health professionals had done the work on their own.

For example:

- When patients were included in discussions about a core outcome set for chronic pain that was initially developed with health professionals, they highlighted the importance of several additional outcomes: fatigue, sleep, home and family care, social and recreational activities, interpersonal relationships and sexual activities[1].

- Whilst developing a core outcome set of treatments to prevent pre-term birth, the research team reported that including parents of pre-term babies really made a difference. They identified the importance of including longer term problems resulting from the child's nervous system development that should always be measured[2].

Click here to watch an animated description of core outcome sets. You can find out more about core outcome set development on the COMET Initiative website.

[1] Turk D, *et al*. Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. Pain 2018; 137: 276-85

[2] van 't Hooft J, *et al*. A Core Outcome Set for evaluation of interventions to prevent preterm birth. Obstetrics & Gynecology 2016; 127(1): 49-58

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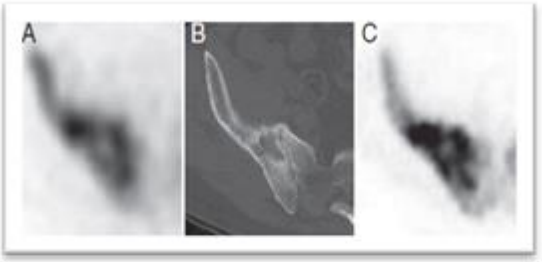
Gathering reliable evidence more quickly through better research design

A novel trial design, called an 'adaptive trial design', allowed a trial to stop earlier with the conclusion that a new technique for imaging a tumour was better than the two existing techniques.

The design included features that allowed early stopping if the new technique (^{18}Fluorine-labelled sodium fluoride) was much better or worse than the two existing comparison techniques at detecting tumour lesions. This reduced the length of the trial by at least a year and allowed high-quality evidence about the new technique to be published quickly in the journal Annals of Oncology[1].

[1] Gerety EL, *et al*. Prospective study evaluating the relative sensitivity of ^{18} F-NaF PET/CT for detecting skeletal metastases from renal cell carcinoma in comparison to ultidetector CT and ^{99m} Tc-MDP bone scintigraphy, using an adaptive trial design. Annals of Oncology 2015; 26(10): 2113-8. doi:10.1093/annonc/mdv289



Images of a lesion in the right ilium detected by the three scanning techniques.

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Developing ways of making trials more acceptable in challenging settings

Emergency medicine in children

Researchers have developed ways of doing trials of emergency treatments for critically ill children that are acceptable to children, parents and health professionals.

In most clinical trials patients give consent before the research starts. But in trials of emergency treatments for critically ill children every moment counts and there is no time to ask for consent before the research starts. Research by a team in Liverpool has found that parents and children understand that trials are essential to identify whether emergency treatments for critically ill children are safe and effective.

The research has also helped to develop ways of doing the trials that are acceptable to children, parents and health professionals. The findings have been used to develop guidance for health professionals, and resources for children and parents to explain how and why research is done in emergency situations: https://www.youtube.com/watch?v=_Fs1yUxeBFQ.

The guidance has helped in nine clinical trials involving over 1000 children, in training 2000 UK doctors and nurses in 30 hospitals, and in training ethics committees across the UK. Much needed trials to improve care for critically ill children are now happening and being carried out with the perspectives of families in mind.

Perinatal trials

Researchers have developed ways of doing trials during or shortly after childbirth that are acceptable to women and families.

Obtaining consent from women around the time of giving birth is challenging. Women who give birth prematurely are fearful about their babies' survival and seeking written informed consent is not always appropriate. Yet, it is important to offer women and families the choice to take part in research. Research by a team in Nottingham discovered that asking for verbal assent, followed by full written consent at a later date, was acceptable to women and health professionals[1,2]. While some challenges remain, this method of consent offers women the choice of participating in

research and it now features in guidance published by the Royal College of Obstetricians and Gynaecologists (RCOG): https://www.rcog.org.uk/globalassets/documents/guidelines/clinical-governance-advice/clinical-guidance-6a-2016.pdf.

[1] https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2149-3

[2] https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-1940-5.