Randomized controlled trial

Systematic reviews of randomized controlled trials (RCTs) are generally considered the highest level of evidence for the relative effectiveness of interventions

Randomized controlled trial (or randomized control trial; RCT) is a type of scientific (often medical) experiment, where the people being studied are randomly allocated one or other of the different treatments under study.

They form the basis of today's evidence-based approach to medicine, and play a critical role in guidelines and the drug and device approval process. Conflicts of interest (COIs) are commonplace in medical research, but little is known about their influence.

Furthermore, even RCTs in surgery come with several limitations; most notably, interventions are often insufficiently standardized and assume a homogeneous patient population, which is not always applicable to neurosurgery. Lastly, guidelines are often outdated by the time they are published and smaller fields such as neurosurgery may lack a sufficient workforce to provide regular updates. These limitations raise the question of whether it is ethical to use low-level evidence for guideline recommendations, and if so, how strictly guidelines should be adhered to from an ethical and legal perspective.

Tewarie et al. aims to offer a critical approach to the ethical and legal status of guidelines in neurosurgery. To this aim, the authors discuss: 1) the current state of neurosurgical guidelines and the evidence they are based on; 2) the degree of implementation of these guidelines; 3) the legal status of guidelines in medical disciplinary cases; and 4) the ethical balance between confident and critical use of guidelines. Ultimately, guidelines are neither laws that should always be followed nor purely academic efforts with little practical use. Every patient is unique, and tailored treatment defined by the surgeon will ensure optimal care; guidelines play an important role in creating a solid base that can be adhered to or deviated from, depending on the situation. From a research perspective, it is inevitable to rely on weaker evidence initially in order to generate more robust evidence later, and clinician-researchers have an ethical duty to contribute to generating and improving neurosurgical guidelines [1)]

Clinicians' trust level of evidence 1 recommendations, issued on preponderantly solid randomized clinical trials (RCTs), to guide best practice decision-making. However, sometimes physicians following one clinical practice guidelines (CPG) find themselves in a situation in which they do not follow another, issued on the same strong evidence base. The aim of Volovici et al. is to reflect on the consistency of recommendations in different guidelines (between-guideline consistency). They also consider within-guideline consistency (or durability), defined as the number of recommendations carried over from one edition to another in consecutive editions of the same CPG. For illustration purposes, they use two examples: hypertension guidelines and traumatic brain injury (TBI) guidelines. They conclude that just like research, CPGs also need to have between-guideline and within-guideline consistency (akin to the reproducibility of studies). Clinicians and researchers should take into account the lower consistency of guidelines that are not based on at least one strong RCT [2)].

see also Neurosurgical Randomized Controlled Trial.

Usually, the randomized trial is the appropriate study to verify efficacy because it provides greater control of the possible confounding variables. Effectiveness is the capacity to reproduce and obtain the same results within the medical community, using different centers and with professionals who have distinct degrees of experience. The observational study is generally used, because it selects patients with more heterogeneous characteristics and centers with different expertise.

(or randomised control trial; RCT) is a type of scientific (often medical) experiment, where the people being studied are randomly allocated one or other of the different treatments under study. The RCT is the gold standard for a clinical trial. RCTs are often used to test the efficacy or effectiveness of various types of medical intervention and may provide information about adverse effects, such as drug reactions. Random assignment of intervention is done after subjects have been assessed for eligibility and recruited, but before the intervention to be studied begins.

Experimental study designs can provide the evidence needed to answer pertinent clinical questions. To study the efficacy of a treatment, there needs to be a control group, ideally in the context of a randomized controlled trial (RCT).

Although the call for evidence based practice in surgery is increasingly high on the agenda, most surgeons feel that the format of the randomized controlled trial is not suitable for surgery [3) 4)].

Random allocation in real trials is complex, but conceptually, the process is like tossing a coin. After randomization, the two (or more) groups of subjects are followed in exactly the same way, and the only differences between the care they receive, for example, in terms of procedures, tests, outpatient visits, and follow-up calls, should be those intrinsic to the treatments being compared. The most important advantage of proper randomization is that it minimizes allocation bias, balancing both known and unknown prognostic factors, in the assignment of treatments.

The terms “RCT” and randomized trial are sometimes used synonymously, but the methodologically sound practice is to reserve the “RCT” name only for trials that contain control groups, in which groups receiving the experimental treatment are compared with control groups receiving no treatment (a placebo-controlled study) or a previously tested treatment (a positive-control study). The term “randomized trials” omits mention of controls and can describe studies that compare multiple treatment groups with each other (in the absence of a control group).

Similarly, although the “RCT” name is sometimes expanded as “randomized clinical trial” or “randomized comparative trial”, the methodologically sound practice, to avoid ambiguity in the scientific literature, is to retain “control” in the definition of “RCT” and thus reserve that name only for trials that contain controls. Not all randomized clinical trials are randomized controlled trials (and some of them could never be, in cases where controls would be impractical or unethical to institute). The term randomized controlled clinical trials is a methodologically sound alternate expansion for “RCT” in RCTs that concern clinical research; however, RCTs are also employed in other research areas, including many of the social sciences.

Phases

Phase 1 randomized controlled trial

Phase 2 randomized controlled trial

Phase 3 randomized controlled trial

Phase IV: Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.

A study aimed to determine the trial discontinuation and publication rate of randomized controlled trials (RCTs) in neurosurgery.

Trials registered from 2000 to 2012 were identified on the website clinicaltrials.gov using a range of key words related to neurosurgery. Any trials that were actively recruiting or had unknown status were excluded. Included trials were assessed for whether they were discontinued early on the clinicaltrials.gov database; this included trials identified as withdrawn, suspended, or terminated in the database. For included trials, a range of parameters was identified including the subspecialty, primary country, study start date, type of intervention, number of centers, and funding status. Subsequently, a systematic search for published peer-reviewed articles was undertaken. For trials that were discontinued early or were found to be unpublished, principal investigators were sent a querying email.

Sixty-four neurosurgical trials fulfilled our inclusion criteria. Of these 64, 26.6% were discontinued early, with slow or insufficient recruitment cited as the major reason (57%). Of the 47 completed trials, 14 (30%) remained unpublished. Discontinued trials showed a statistically significant higher chance of remaining unpublished (88%) compared with completed trials (p = 0.0002). Industry-funded trials had a higher discontinuation rate (31%) compared with non-industry-funded trials (23%), but this result did not reach significance (p = 0.57). Reporting of primary outcome measures was complete in 20 (61%) of 33 trials. For secondary outcome measures, complete reporting occurred in only 11 (33.3%) of 33.

More than a fifth (26.6%) of neurosurgical RCTs are discontinued early and almost a third of those that are completed remain unpublished. This result highlights significant waste of financial resources and clinical data [5].

1)
Tewarie IA, Hulsbergen AFC, Volovici V, Broekman MLD. The ethical and legal status of neurosurgical guidelines: the neurosurgeon's golden fleece or Achilles' heel? Neurosurg Focus. 2020 Nov;49(5):E14. doi: 10.3171/2020.8.FOCUS20597. PMID: 33130626.
2)
Volovici V, Steyerberg EW. Lost in translation between evidence and recommendations: Expert opinion is needed to define “level I”. World Neurosurg. 2021 Mar 25:S1878-8750(21)00465-4. doi: 10.1016/j.wneu.2021.03.095. Epub ahead of print. PMID: 33775869.
3)
Unger CA, Barber MD. Studying surgical innovations: challenges of the randomized controlled trial. J Minim Invasive Gynecol 2015;22:573–82.
4)
Ceelen WP. Clinical research in surgery: threats and opportunities. Eur Surg Res 2014;53:95–107.

5)
Jamjoom AAB, Gane AB, Demetriades AK. Randomized controlled trials in neurosurgery: an observational analysis of trial discontinuation and publication outcome. J Neurosurg. 2017 Oct;127(4):857-866. doi: 10.3171/2016.8.JNS16765. Epub 2016 Nov 25. PubMed PMID: 27885950.