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# Appendix

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**On-line appendix. Examples of CER study designs**

| Study design | Description | Example | Advantages | Disadvantages |
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| Pragmatic RCT[1] | Assesses effectiveness in typical real-world setting by having relaxed patient selection criteria, relaxed protocols which allow patient/provider discretion, active comparators, longer term follow-up, outcome measures relevant to patients, doctors and funders | The ALLHAT trial assessed whether newer, more costly antihypertensive agents (ACE inhibitors, calcium antagonists) were as good or better than thiazide-based diuretics in preventing cardiovascular events. It had broad inclusion criteria, allowed flexibility in dosing of therapies, involved multiple clinical settings, and used patient-relevant outcomes. It showed that coronary heart disease risk was not reduced for any of the newer drug classes compared with older and cheaper thiazide based | Results are more generalisable. Outcome measures are more useful to patients and physicians making choices. Maintains all or much of the scientific rigor of explanatory RCTs | May mask small true differences between treatments. |

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| | | diuretics. | | |
| Cluster RCT[2] | Groups (or clusters) of people, rather than individuals, are randomised to an intervention. These groups may include communities, clinics, hospitals, or different jurisdictions. Individuals within a cluster will tend to resemble each other which needs to be accounted for in the statistical analysis. | The Quality in Acute Stroke Care (QASC) study randomised 19 acute stroke units (ASUs) to a multidisciplinary intervention targeting evidence-based management of fever, hyperglycaemia, and swallowing dysfunction (with multidisciplinary team building workshops to address implementation barriers) or to an abridged version of existing guidelines. Results showed an improvement in 90-day death or dependency and better physical function in patients of intervention ASUs compared to controls. | Ideal approach for comparing alternative interventions delivered within natural groupings of patients and/or providers.<br>Avoids contamination between different intervention groups. | Analysis of results requires sophisticated statistical techniques that account for clustering effects when individual patients/providers are the unit of analysis. |

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| Adaptive RCT[3] | Trial designed to change or adapt in response to information generated during the trial. | In a trial involving patients with acute myeloid leukaemia, a new drug, troxacitabine (T), was combined in turn with standard therapies idarubicin (I) and cytarabine (A) and compared with the two standard therapies in combination: TI versus TA versus IA. Bayesian probabilities of treatment comparisons were calculated continually. Patients entering the trial were assigned to therapy randomly, but imbalanced so as to favour therapies with higher probabilities of being better. As the trial progressed, on the basis of low assignment probabilities | Allows trial design to be changed during the course of the study based on new data.<br>May reduce sample size, time, or cost of studies (as the example shows).<br>Ability to include or exclude relevant comparators to enhance clinical relevance of trial results.<br>Can incorporate Bayesian designs whereby prior probabilities of intervention effectiveness based on all pre-existing clinical data can be calculated and then revised as trial proceeds which in turn informs change in trial design to yield maximum information | Adaptations may result in difficulty addressing original research questions.<br>Changes in patient population may deviate from original target population. |

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| | | of complete remission (CR), TI was withdrawn first, followed by TA, with IA ending up as having the highest CR rate of 56% out of 18 patients. | value. | |
| Stepped wedge RCT[4] | Studies which involve sequential roll-out of an intervention to participants (individuals or clusters) over pre-specified time periods. By the end of the study, all participants will have received the intervention, although the order in which participants receive the intervention is determined at random and those yet to receive the intervention act as controls. | The effects of introducing a critical care outreach service on in-hospital mortality and length of stay were assessed in an 800 bed general acute hospital. The intervention comprising a nurse-led team of nurses and doctors experienced in critical care, a 24-h service, emphasis on education and practical help for ward staff was introduced to 16 wards in random sequence during a 32-week study period. Outreach intervention reduced | Useful for interventions predicted to do more good than harm (making a parallel design in which certain participants do not receive the intervention for a prolonged period of time potentially unethical) and/or where, for logistical, practical or financial reasons, it is impossible to deliver the intervention simultaneously to all participants.<br>Provide opportunities to evaluate and refine | Intervention and its implementation may change over time which compromises trial integrity.<br>Groups receiving intervention in early stages may be systematically different to those in later stages and possibly contaminate those which are yet to receive intervention. |

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| | | in-hospital mortality by 48% compared with control but also possibly increased length of stay. | intervention implementation. | |
| Network meta-analysis[5] | Form of meta-analysis comparing multiple treatments using data from direct (head to head) trials and indirect comparisons | Several treatments are available to treat relapsing-remitting multiple sclerosis: interferon, glatiramer, natalizumab and fingolimod. A network meta-analysis used data from 10 randomised trials for direct and indirect comparisons. It found that fingolimod had the most favourable profile in terms of relapse-free rates at 12 months follow-up. | Multiple drugs can be simultaneously compared in an internally coherent analysis which combines evidence from head to head trials and indirect comparisons.<br>Maintains randomisation within individual trials. | Indirect evidence may not be consistent with direct evidence.<br>Clinical and statistical comparability of trials (homogeneity, similarity and consistency of evidence) may not be guaranteed.<br>Differences in patient characteristics may not be identical or evenly distributed across trials. |
| Observational[6] | Studies where patients | A national US cohort study of | Representative of routine | Prone to confounding due to |

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| studies | receiving a particular treatment are observed rather than being assigned to treatment randomly. Data may be obtained from several sources such as administrative databases, clinical registries, census statistics, and cohort studies. Include before-after studies or parallel cohort studies. | 158,831 elderly patients hospitalized with first episode of AMI and followed up for 7 years. The study found that patients in geographical regions characterised by more invasive management strategies (performance of cardiac catheterization within 30 days) did not demonstrate better long-term survival than those residing in regions with more intensive medical management strategies (prescription of beta-blockers to appropriate patients at discharge). Sophisticated statistical analysis was performed to minimise confounding. | practice by observing actual patient and prescriber practices.<br>Possibility of evaluating a large number of comparators at relatively low cost and high speed. | known or unknown differences in patient groups before treatment, differences in patient selection (confounding by treatment indication) and adherence in treatment.<br>Methodological tools to minimise confounding cannot generally remove all bias. |

## References


1. The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker *vs* diuretic. The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288: 2981–97.
2. Middleton S, McElduff P, Ward J, et al. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. Lancet 2011; 378 (9804):1699-706.
3. Giles FJ, Kantarjian HM, Cortes JE, et al. Adaptive randomized study of idarubicin and cytarabine versus troxacitabine and cytarabine versus troxacitabine and idarubicin in untreated patients 50 years or older with adverse karyotype acute myeloid leukemia. J Clin Oncol 2003; 21: 1722–1727.
4. Priestley G, Watson W, Rashidian A, et al. Introducing critical care outreach: A ward-randomised trial of phased introduction in a general hospital. Intens Care Med 2004; 30:1398-1404.
5. Del Santo F, Maratea D, Fadda V, et al. Treatments for relapsing-remitting multiple sclerosis: summarising current information by network meta-analysis. Eur J Clin Pharmacol 2012; 68: 441-8.
6. Stukel TA, Lucas FL, Wennberg DE. Long-term outcomes of regional variations in intensity of invasive vs medical management of Medicare patients with acute myocardial infarction. JAMA 2005; 293: 1329-1337.