University of Glasgow

Institute of Health & Wellbeing

Week 2 – exercises

1) A small, non-randomised intervention study produces the following result for all-cause mortality outcome in a stroke population – (Technology B vs. Technology A) unadjusted relative risk (RR) = 5.23, 95% CI (1.67, 11.62), p<0.001
   a) How good is the evidence that Technology A is more effective than Technology B?
   b) What further information would you like to be better informed to answer part a)?

a) The evidence that Technology A is more effective than Technology B is not very good at all. Firstly, its evidence from a non-randomised study and we know such studies are prone to bias and cannot control against unmeasured confounding. Second, the effect size is presented as 'unadjusted' therefore not even potentially confounding variables that have been measured are adjusted for. Third, it's a 'small' study and this is reflected by the wide 95% CI for the effect size (RR) – a lot of uncertainty about the size of effect. Fourth, is all-cause mortality the most appropriate outcome to compare technologies with for this stroke population? What about quality of life? Functional status?

b) In broad terms, we need more information to assess how well this study has been carried out. With more information we can assess the potential for bias (threats to internal validity). Further information about the study setting, definition of the cohort, inclusion/exclusion criteria would help assess the generalisability of the findings (external validity).

2) These questions should be attempted after reading McKee *et al* [1] and Sox *et al* [2].
   a) It is often said that for evaluating interventions randomised studies have better internal validity than external validity, whereas non-randomised studies have better external validity than internal validity. Can you explain what is meant by this?
   b) In [1] there is a summary of a review of threats to internal and external validity in randomised and non-randomised studies. What point(s) is Figure 1 trying to convey? Provide a summary and critique the figure – is it successful at getting the message it wants to convey across?
   c) From [2], we learn that randomisation is the 'perfect instrument'. Can you explain this? In answering, you might find it helpful to consider the randomisation process being a coin toss.

d) Given instrumental variable (IV) analyses deal with unmeasured confounding, they seem perfect for evaluating interventions from non-randomised studies. However, there are difficulties. Summarise and discuss the difficulties associated with the IV method.

a) Internal validity in this context is essentially about whether a study provides a 'true' (unbiased) estimate of the intervention effect. Whereas, external validity refers to the extent to which study results can be generalised to a wider population. On average, a randomised study will have better internal validity than a non-randomised study because their experimental nature makes them less susceptible to bias and the power of randomisation is that it limits the influence of confounding. On the other hand, it could be said that non-randomised studies have, on average, better external validity because they are often based on samples of data that better represent the population at large than randomised studies with strict eligibility criteria.

b) The point that Figure 1 is trying to convey is that a study (i.e. trial) population is a subset of the wider, reference population and therefore can we apply the trial results to the wider population (how generalisable are the results?). In my opinion, the figure is good but does not "stand alone" in the sense that you need to read the accompanying text to fully understand it. Some things are left unexplained – more explanation of the 'potential to benefit' axis should have been given – is it saying that because those excluded from RCTs have worse prognosis they have less potential to benefit?

c) We learn from [2] that an 'instrument' "…is something that is an external cause of the intervention…but is by itself unrelated to the outcome." I think Figure 3 in [2] provides a very clear graphical representation of what an instrumental variable is and what assumptions are made in instrumental variable analyses. If we represent the randomisation process as a coin toss, it is a 'perfect instrument' as we know the result of tossing a coin (a 'head' or a 'tail') is not associated with outcome. It only becomes indirectly associated with the outcome because the result of the coin toss determines which intervention/technology is received. Moreover, we know that the result of tossing a coin will be completely unrelated to any potential confounding variable (whether measured or unmeasured).

d) Main Difficulties: 1) finding 'good instruments' that are strongly associated with intervention/technology allocation but also meet all assumptions; 2) sometimes we can't measure the instrument itself but rely on proxies (e.g. if the instrument is a physician's preference to prescribe drug A over drug B, then that cannot be directly measured…but we can calculate the proportion of times a physician prescribed drug A instead of drug B to their last patient(s)); then the question is, what is the 'best' proxy and how well do the proxies represent that we cannot measure directly (a physician's preference in this case).

[1] McKee M *et al*. Interpreting the evidence: choosing between randomised and non-randomised studies. *BMJ* 1999;319:312. http://www.bmj.com/content/319/7205/312.1; [2] Sox HC *et al*. The Methods of Comparative Effectiveness Research. *Annual Review of Public Health* 2011;33:424-445. https://www.annualreviews.org/doi/pdf/10.1146/annurev-publhealth-031811-124610