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In *The Lancet Global Health*, Rajshree Thapa and colleagues report the extended 5-year follow-up for the Community-Based Intervention for Control of Hypertension in Nepal (COBIN) cluster trial,[1] in which health workers provided lifestyle advice and blood pressure monitoring every 4 months for 12 months. The COBIN trialists deserve congratulations for an excellently designed and executed study. At 12 months systolic blood pressure was reduced across participants who were normotensive, prehypertensive, and hypertensive (for whom systolic blood pressure [intervention *vs* control] was –4·9 mm Hg [95% CI –7·8 to –2·0]).[2]

The 5-year follow-up assessed sustainability of this blood pressure reduction, after health worker intervention ceased at 12 months. The authors from their systematic review of effectiveness of community health workers in reducing blood pressure and controlling hypertension noted that just five (15%) of 34 completed randomised trials had an intervention lasting more than 1 year, and post-intervention follow-up was usually less than 1 year. Margolis and colleagues[3] had shown early benefit (at 1 year) that disappeared by 54 months. Here, in COBIN, however, not only did the benefit disappear, it also reversed: by 5 years the 5-mm Hg reduction at 1 year had become a 5-mm Hg increase (intervention *vs* control; 95% CI 0·8–9·1). This finding was for those with hypertension; similar albeit smaller effects were seen for those with normotensives or pre-hypertensive blood pressure.

This finding is troubling, indicating potential harm. The intervention might have been doing more harm than good, judging by the net effect over 5 years. Possible mechanisms might include lowered self-efficacy, with a misplaced sense of the work having been done, for patient and clinician, returning to higher-risk behaviours. More alarming, if this finding is generalisable, there have been more than 35 randomised trials that have potentially overlooked this risk, having too short of a follow-up. This is letting patients down.

There are, however, substantial logistical and methodological challenges to extended follow-up in randomised trials. 5-year follow-up takes more than 5 years to observe, and trials are already expensive to run. The protection against bias of randomisation tends to diminish as missing data increasing over time. COBIN had remarkably good retention, with 83% of randomly assigned participants (and 92% of those with 1-year outcomes) providing 5-year data. However, there are often differences between those participants who do and do not return for follow-up. The missing data might be informative rather than missing at random.[4] In COBIN, fewer than 300 participants (and no clusters) were lost to follow-up, with most of these not found, with 23 deaths, eight migrations, and 29 refusals. No breakdown was given by randomised group; these missing data might not have strongly influenced the reported findings, although appropriate sensitivity analyses could have helped.[5] COBIN also faced the additional challenge of the COVID-19 pandemic when securing 5-year follow-up.

Long-term follow-up is usually analysed under an intention-to-treat approach (the treatment policy estimand) and intercurrent events (such as cross-over or additional treatments), missing data, and any differential effects of these across the randomly assigned groups can create substantial bias. Additionally, a harm might need to be analysed according to treatment received. This all makes for difficulty in interpreting such estimates.

So, what is needed? First, as for any estimated benefit or harm, is the effect real? Being confident the effect is real could translate into knowing when and how to reinforce the intervention to avoid waning and reversal. But this needs more studies with long-term follow-up. There are sadly too many randomised trials with sparse long-term follow-up, to the patient's disadvantage—eg, the ongoing concerns regarding pelvic mesh implantation[6] or the possible long-term neuropsychiatric effects of mefloquine for malaria prophylaxis.[7] Even when the regulators enforce post-marketing surveillance studies, such efforts can be too little, too late (eg, in the case of the withdrawn Essure birth control device [Bayer, Germany] the US Food and Drug Administration mandated a 522 post-marketing surveillance study only 14 years after approval, and the study has failed to recruit satisfactorily).[8] Ideally, long-term follow-up should be specified in the protocol, with responsibility taken by sponsor and funder to resource this, and appropriate methodology should be specified

in in the statistical analysis plan for assessing long-term efficacy and safety. There are promising developments using routine data for quantifying such long-term efficacy and safety,[9,10] but patient-reported outcomes will often also be needed.

COBIN 5-year findings suggest that we need to increase spending on long-term follow-up, otherwise risking missing important longer-term understanding of efficacy and safety. Despite many logistical and methodological challenges of assessing long-term signals, we must address robustly this often-overlooked dimension as an unfortunate evidence gap. We must deliver the best care to the greatest number of people—the hope is that since randomised trials are continually improving, then here is an opportunity not to be missed.

I declare no competing interests.

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