**Enrolment-latency in randomised behaviour change trials: IPD meta-analysis showed association with attrition but not effect-size**

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**Abstract**

**Objective.** Non-response can bias prevalence estimates in population surveys. Effects of selective participation in behaviour change intervention trials have been little studied. We tested hypotheses that trial participants who are hard to recruit are (1) more likely to be lost-to-follow-up and (2) less responsive to intervention.

**Study Design and Setting.** We undertook a two-stage individual participant data meta-analysis of four alcohol intervention trials involving 9251 university students in Australia, New Zealand, and Sweden, comparing participants who enrolled ‘late’ (after the final invitation to participate) versus ‘early’ (before that). Outcomes were whether participants completed assessments at each trial’s primary endpoint (late/early) and number of drinks consumed per week (intervention/control) among late enrolees versus early enrolees.

**Results.** Late enrolees were more likely to be lost-to-follow-up than early enrolees (OR 2.3, 95% CI: 1.7, 2.9). Intervention effect estimates were smaller for late versus early enrolees, but not significantly so (RR=0.93; 95% CI: 0.79, 1.08).

**Conclusion.** Greater effort to recruit trial participants was associated with higher attrition, but there was no clear evidence of bias in effect estimation. The possibility that intervention effect estimates do not generalize beyond a relatively compliant minority of trial participants may warrant further study.

Key words: intervention trial; bias; non-response; selection; external validity; generalisability

**Introduction**

Attrition bias is a well-known threat to the validity of estimates of intervention effects in trials, in which there are systematic differences between treatment groups in their propensity to drop out of the study.[1](#_ENREF_1) Attrition gives grounds for concern about bias if equivalence between randomised groups is compromised.

It is common in the reporting of randomised trials of behaviour change interventions for the population from whom participants were drawn to be weakly defined.[2](#_ENREF_2),[3](#_ENREF_3) This means there may be little, if any, capacity for formal assessment of the degree to which effect estimates can be generalised to the population to whom the findings are understood to apply.

In survey research, the Continuum of Resistance Model posits that members of a population vary in their willingness to comply with efforts to recruit them. Some people volunteer readily, others require considerable encouragement, often in the form of repeated requests, and some never participate in research.[4](#_ENREF_4) A corollary of the model is that individuals who are difficult to recruit better resemble non-participants on variables of interest, than do individuals who participate more readily. This has been demonstrated in cross-sectional surveys using various methods and in a range of population groups in connection with wide-ranging subject matter, including alcohol consumption, smoking, and cardiovascular disease (e.g.,[5](#_ENREF_5),[6](#_ENREF_6)).

Non-respondents are more likely than respondents to possess characteristics of interest to health researchers (e.g., to be smokers[7](#_ENREF_7)), and have poor health (e.g., to die prematurely[8](#_ENREF_8)). In surveys, selective non-response biases estimates of prevalence and potentially also estimates of association.

In randomised trials of behavioural interventions, selective non-participation (or selection effects) may compromise generalisability by obscuring judgements about the populations to which effect estimates can be generalised. Where trial participation is based on existing cohorts in which demographic and other health-relevant data have been collected,[9](#_ENREF_9),[10](#_ENREF_10) it is possible to study selection effects i.e., differences in outcomes between those who do and do not participate in a subsequent intervention trial.[2](#_ENREF_2) Extensive efforts are often expended in recruiting participants to trials because attaining required sample sizes can be challenging.[11](#_ENREF_11)

We test the hypotheses that participants who were difficult to recruit, compared to those relatively easy to recruit, would (1) be more likely lost-to-follow-up, and (2) respond less well to intervention.

**Methods**

*Design*

We undertook a two-stage individual participant data (IPD) meta-analysis[12](#_ENREF_12) of four randomised trials, all of which were online alcohol intervention studies.

*Data*

In the THRIVE (Tertiary Health Research Intervention Via E-mail) trial,[13](#_ENREF_13) 13000 university undergraduates in Australia were invited to complete a web survey of their drinking and follow-up one and six months later. Participants were randomised without their knowledge to receive either no intervention or an intervention consisting of further assessment of their drinking followed by personalised feedback delivered electronically (see[14](#_ENREF_14) for details of the intervention).

The e-SBINZ (Electronic Screening and Brief Intervention New Zealand) trials[15](#_ENREF_15),[16](#_ENREF_16) involved a similar intervention to THRIVE but were conducted in seven New Zealand universities (see protocol for details[17](#_ENREF_17)), and the study procedures were similar to those for THRIVE.

The AMADEUS-2 trial[18](#_ENREF_18) involved an evaluation of a similar intervention with a somewhat different study design. All students in nine Swedish universities were invited to participate and those screening positive for hazardous drinking consented to be randomised to immediate or delayed access to the intervention during a two-month study period. Like the THRIVE and e-SBINZ trials, all communication with students for participation and follow-up study was by e-mail and a number of e-mails were sent for both purposes.

*Subgroups*

Subgroups were defined according to participants’ compliance with the e-mail request to participate. We operationalised compliance behaviourally, as how difficult it was to recruit participants, i.e., whether they enrolled before (‘early enrolees’) or after the final e-mail reminder (‘late enrolees’) sent to sample members who had not already participated.

*Outcomes*

We pre-specified the primary outcomes as (1) whether participants were assessed at the primary endpoint (at 6 months post intervention in THRIVE, at 5 months post intervention in the e-SBINZ trials; and at 2 months post intervention in AMADEUS-2); and (2) the number of standard drinks consumed per week.

*Analysis*

We used logistic regression to estimate odds ratios for associations between late enrolment and loss-to-follow-up, and negative binomial regression to produce rate ratios for the number of drinks consumed per week, with 95% confidence intervals.[19](#_ENREF_19) For the second outcome we produced effect estimates for the subgroups in each study, and across the four studies using IPD.[12](#_ENREF_12) All analyses were conducted in Stata 15.1.

We examined effect modification of early vs late enrolment analysing IPD from each study in a negative binomial model including variables for: *intervention*, *latency*, and the interaction term *intervention\*latency*. Using the results of the interaction effects from each study we employed metan to analyse aggregated estimates in a random effects model, obtaining summary effect sizes with 95% confidence intervals, and producing forest plots.[12](#_ENREF_12)

*Ethical approval*

The THRIVE trial was approved by the ethics committee of Curtin University, the e-SBINZ trials by New Zealand’s Multi-region Ethics Committee, and AMADEUS-2 by the Regional Ethical Committee in Östergötland, Sweden.

**Results**

In the THRIVE trial, 1385 participants were classified as early enrolees and 193 as late. In the e-SBINZ Māori trial, the corresponding numbers were 1202 and 194; in the SBINZ non-Māori trial they were 2482 and 330; while in the AMADEUS-2 trial they were 785 and 147.

In the THRIVE trial, 35% of participants in the control group and 35% in the intervention group were lost-to-follow-up. In the e-SBINZ Māori trial, the corresponding proportions lost-to-follow-up were 20% and 22%; in the SBINZ non-Māori trial they were 18% and 16%; while in the AMADEUS-2 trial they were 32% and 51%.

Figure 1 shows that in each of the trials late enrolees were more likely to be lost-to-follow-up than early enrolees. This was the case in each trial, as well as when the data were combined. There was important heterogeneity across studies (I2=80.6%).



**Figure 1. Forest plot of loss-to-follow-up for late versus early enrolees in the four trials**

Intervention effect estimates (rate ratios) in the four trials were 0.87 (THRIVE; 95% CI: 0.79, 0.96), 0.78 (e-SBINZ Māori; 0.68, 0.88), 0.90 (e-SBINZ non-Māori; 0.82, 0.99), and 0.91 (AMADEUS2 0.82, 1.01), while the overall estimate was 0.87 (0.81, 0.92; I2=34.9%, p=0.21). Figure 2 presents estimates of model interaction terms representing intervention effects ratios for early versus late enrolees. In the first two trials late enrolees responded less well to intervention (ratios <1) than early enrolees (i.e., in the hypothesised direction), however, this was not the case for studies 3 and 4, and the combined ratio of effects, while in the hypothesised direction, was small (RR=0.93; 95% CI: 0.79, 1.08) and not statistically significant. A fixed effect model yielded similar results (RR=0.92; 95% CI: 0.78, 1.10).



**Figure 2. Forest plot of interaction terms (meta-analysis of ratio of effects for late versus early enrolees) in each of the four trials and overall**

**Discussion**

Late enrolees were more likely than early enrolees to be lost to follow-up in each trial. The I2 statistic suggests important heterogeneity, though not which could alter this main finding. There was not consistent evidence across trials that late enrolees benefitted less from intervention than early enrolees.

Strengths of the study include objective measurements of exposure (timing of participant enrolment) and the loss-to-follow-up outcome, both of which were recorded by the web server. Further strengths are the similarity of the intervention and study populations, and cultural differences across the trial populations.

Self-report of drinking outcomes, differences between AMADEUS-2 and the other study designs, and small numbers of late enrolees are limitations. For errors in reporting of alcohol consumption to have biased these study findings, late enrolees allocated to intervention would have to have been more or less inclined to report their consumption accurately than late enrolees allocated to the control group. We have no reason to expect such a three-way interaction but the possibility cannot be excluded given that participants could not be randomised to how compliant they would be with the request to participate.

Our findings on study withdrawal may have implications for the conduct of behaviour change intervention trials. Because these data were collected in the context of online studies of university student drinking, replication studies in other settings, behaviours, and populations are needed. If these findings are replicated it appears possible that trial recruitment methods will be enhanced by the recognition that extensive effort to recruit more reluctant participants may need to be balanced against an increased likelihood of loss-to-follow-up.

The findings are consistent with the survey research literature on selective non-response,[5](#_ENREF_5),[6](#_ENREF_6) late enrolees being more likely to be lost-to-follow-up. Further research could test the hypotheses that attrition bias is introduced by late participants, and by extension, that non-participants would respond less well to behavioural interventions. If less effort had been made to recruit participants in these trials, attrition would have been lower and effect estimates may have been a little larger. Date-stamping of participation data, achieved through the design of web-based questionnaires, facilitated the present study. In non-web contexts, data on the effort required to recruit participants should be collected to enable research of this kind, perhaps with pooling across trials to achieve the number of less compliant participants necessary to estimate associations.

One possibility raised by these findings is that behavioural intervention estimates do not generalize beyond a relatively compliant minority. This deserves further investigation in relation to other population groups, interventions, and settings. Research on the psychology and effects of research participation is needed,[20](#_ENREF_20) as are studies that examine mechanisms by which bias may be introduced and managed in trials.[21](#_ENREF_21) [10](#_ENREF_10) This could illuminate the determinants and sequelae of compliance versus apathy or resistance, in order to properly appreciate connections between different forms of bias and the validity of inferences commonly drawn in health research.[22](#_ENREF_22)

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