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Supporting Information

Supplementary methods and results

This appendix was part of the submitted manuscript and has been peer reviewed.
It is posted as supplied by the authors.

Appendix to: Coskinas X, Simes RJ, Martin AJ. Changes to design and analysis elements of research plans during randomised controlled trials in Australia. *Med J Aust* 2022; doi: 10.5694/mja2.51715.

1. Sample size calculation

The planned sample size was 100 RCTs to provide a suitably precise estimate to be made of the pervasiveness of changes to RCT research plans, i.e., where the limits of the corresponding 95% confidence interval for the proportion were within +/- 10% of the point estimate. For a given sample size, the width of a 95% confidence interval for a proportion, p, will be greatest when p=0.5. With n=100, the 95% confidence interval given p=0.5 is 0.4 to 0.6, i.e., the limits of the interval are within +/- 10% of the point estimate. For any other value of p, the confidence interval will be narrower. A sample size of N=100 is thus sufficient to yield a 95% confidence interval with limits that are within +/- 10% of the point estimate.

Table 1. Changes to 124 trials with available protocols: univariate and logistic regression analyses

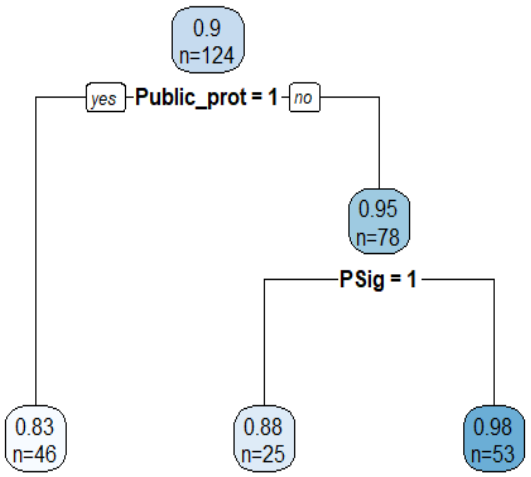
Type of change/variable	Univariate analysis: odds ratio (95% CI)	Relaxed LASSO odds ratio	Logistic regression: odds ratio (95% CI)
Any			
Statistical significant finding*	0.95 (0.27–3.31)	NA	NA
Drug trial (*v* other trial type)	0.63 (0.18–2.16)	NA	NA
Planned sample size (per participant)	1.00 (1.00–1.00)	NA	NA
Publication year (per year)	0.96 (0.79–1.18)	NA	NA
Publicly available protocol	0.22 (0.06–0.77)	NA	0.22 (0.06–0.77)
Primary outcome			
Statistical significant finding*	0.67 (0.30–1.48)	NA	NA
Drug trial (*v* other trial type)	0.66 (0.32–1.36)	NA	NA
Planned sample size (per participant)	1.00 (1.00–1.00)	NA	NA
Publication year (per year)	1.08 (0.95–1.22)	NA	NA
Publicly available protocol	0.72 (0.34–1.52)	NA	NA
Eligibility criteria			
Statistical significant finding*	0.78 (0.36–1.69)	0.63	0.63 (0.28–1.47)
Drug trial (*v* other trial type)	1.11 (0.54–2.28)	NA	NA
Planned sample size (per participant)	1.00 (1.00–1.00)	1.00	1.00 (1.00–1.00)
Publication year (per year)	0.96 (0.85–1.09]	NA	NA
Publicly available protocol	0.37 (0.17–0.80)	0.31	0.31 (0.14–0.70)
Sample size			
Statistical significant finding*	0.74 (0.34–1.62)	0.73	0.69 (0.31–1.54)
Drug trial (*v* other trial type)	1.02 (0.50–2.10)	NA	NA
Planned sample size (per participant)	1.00 (1.00–1.00)	1.00	1.00 (1.00–1.00)
Publication year (per year)	1.01 (0.90–1.15)	NA	1.02 (0.90–1.16)
Publicly available protocol	1.10 (0.53–2.30)	1.01	NA
Analysis set population			
Statistical significant finding*	0.69 (0.27–1.79)	NA	NA
Drug trial (*v* other trial type)	1.38 (0.58–3.29)	NA	NA
Planned sample size (per participant)	1.00 (1.00–1.00)	NA	NA
Publication year (per year)	1.05 (0.91–1.21)	NA	NA
Publicly available protocol	0.86 (0.36–2.06)	NA	NA
Primary analysis method			
Statistical significant finding*	1.24 (0.54–2.86)	NA	NA
Drug trial (*v* other trial type)	0.35 (0.15–0.80)	0.51	0.36 (0.16–0.83)
Planned sample size (per participant)	1.00 (1.00–1.00)	1.00	1.00 (1.00–1.00)
Publication year (per year)	1.07 (0.94–1.22)	NA	NA
Publicly available protocol	0.76 (0.35–1.63)	NA	NA

CI=confidence interval, LASSO=least shrinkage and selection operator, NA=not applicable (ie, LASSO procedure penalised the coefficients for the covariate to 0).

* That is, $P < 0.05$.

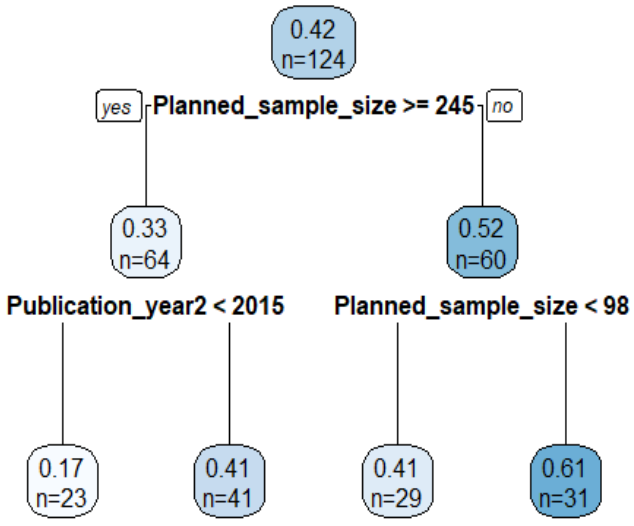
Figure 1. Recursive partitioning for 124 trials with available protocols

A. Any change



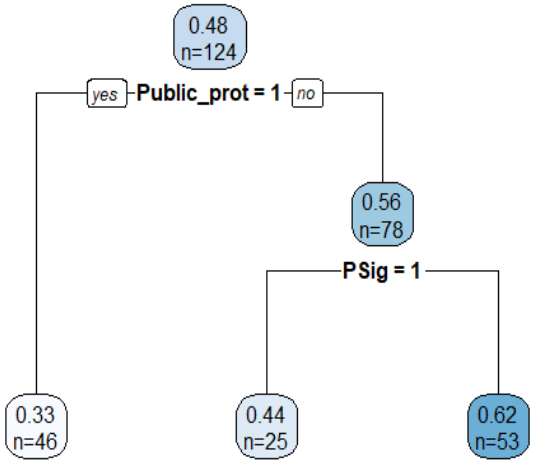
Trials with publicly available protocols (46) were less likely to have any changes than those without (78), 83% versus 95%, respectively. Of the 78 in the latter group, changes were also less likely for trials reporting statistically significant results on the primary analysis (25) compared to trials that did not (53), 88% versus 98%, respectively.

B. Change to primary outcome



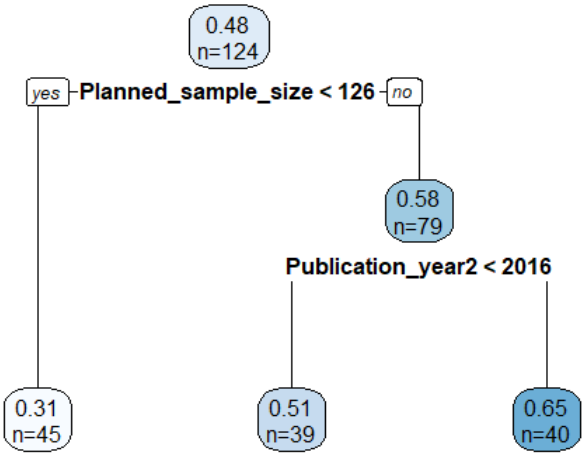
The best discriminator of *change to primary outcome* was whether the planned sample size was ≥ 245, followed by whether the publication year was before 2015 and whether the sample size was < 98. Trials with sample sizes ≥ 245 (64) were less likely to have changes to the primary outcome than those with smaller sample size (60), 33% versus 52%, respectively. Of the 64 trials in the former group, changes were less likely for trials published before 2015 (23) compared to trials that published later (41), 17% versus 41%, respectively. Of the 60 trials in the latter group, changes were less likely for trials with small sample sizes (29) compared to trials with slightly larger sample sizes in the range 98-244 (31), 41% versus 61%, respectively.

C. Change to eligibility criteria



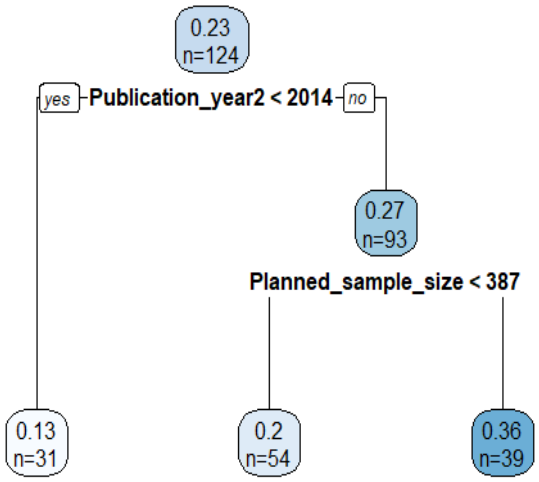
The best discriminator of *change to eligibility criteria* was whether protocols were publicly available. Trials with publicly available protocols (46) were less likely to have changes to eligibility criteria than those without (78), 33% versus 56%, respectively. Of the 78 in the latter group, changes were also less likely for trials reporting statistically significant results on the primary analysis (25) compared to trials that did not (53), 44% versus 62%, respectively.

D. Change to sample size



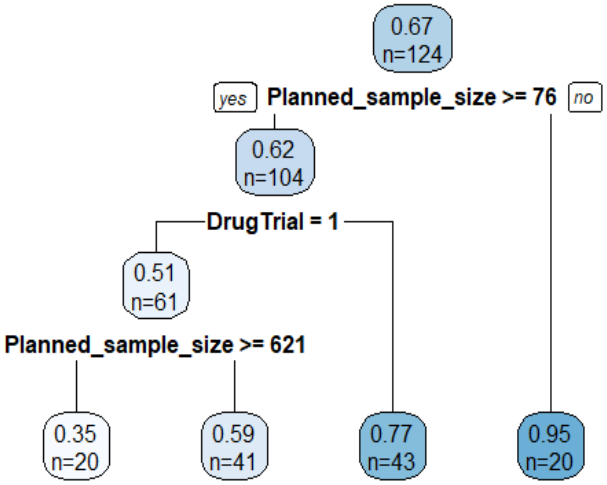
The best discriminator of *change to sample size* was whether planned sample size was < 126. Trials with smaller sample sizes (45) were less likely to have changes to sample size than those with larger sample sizes (79), 31% versus 58%, respectively. Of the 79 in the latter group, changes were also less likely for trials published before 2016 (39) compared to trials published more recently (40), 51% versus 65%, respectively.

E. Change to primary analysis set



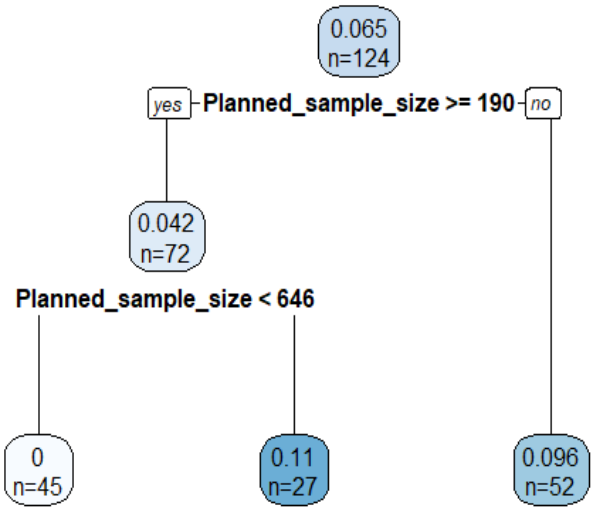
The best discriminator of *change to primary analysis set* was whether the publication year was before 2014. Trials published before 2014 (31) were less likely to have changes to analysis set than those published from 2014 (93), 13% versus 27%, respectively. Of the 93 in the latter group, changes were less likely for trials with smaller sample sizes (<387) (54) compared to trials with larger sample sizes (39), 20% versus 36%, respectively.

F. Change to primary analysis method



The best discriminator of *change to primary analysis method* was whether the planned sample size was ≥ 76, followed by whether the interventions investigated were drugs and whether the sample size was large ≥ 621. Trials with sample sizes ≥ 76 (104) were less likely to have changes to the primary analysis method than those with very small sample sizes (20), 62% versus 95%, respectively. Of the 104 trials in the former group, changes were less likely for trials investigating drug interventions (61) compared to trials that investigated other interventions (43), 51% versus 77%, respectively. Of the 61 drug trials, changes were less likely for trials with large sample sizes (20) compared to trials with smaller sample sizes in the range 76-620 (41), 35% versus 59%, respectively.

G. Change to primary comparison

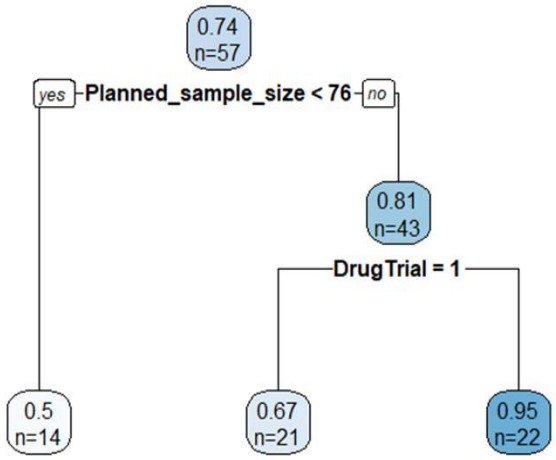


The best discriminator of *change to primary comparison* was whether the planned sample size was ≥ 190. Trials with larger sample sizes (72) were less likely to have changes to the primary comparison than small trials (52), 4% versus 10%, respectively. Of the 72 in the former group, changes were unlikely for trials with smaller sample sizes in the range 190-645 (45) compared to trials with larger sample sizes (27), 0% versus 11%, respectively.

Table 2. Changes to 57 trials without available protocols: univariate and logistic regression analyses (any change only)

Variable	Univariate analysis: odds ratio (95% CI)	Relaxed LASSO odds ratio	Logistic regression: odds ratio (95% CI)
Statistical significance declared	2.27 (0.62–8.30)	NA	2.63 (0.66–10.5)
Drug trial (*v* other trial type)	0.41 (0.12–1.42)	NA	0.41 (0.12–1.47)
Planned sample size (per participant)	1.00 (1.00–1.00)	NA	1 (1.00–1.00)
Publication year (per year)	1.06 (0.86–1.32)	NA	1.08 (0.85–1.37)

Figure 2. Recursive partitioning for 57 trials without available protocols (any change only)



The best discriminator of *any change* was whether the planned sample size was < 76. Trials with very small sample sizes (14) were less likely to have any changes than larger trials (43), 50% versus 81%, respectively. Of the 43 in the latter group, changes were less likely for drug trials (21) compared to trials investigating other interventions (22), 67% versus 95%, respectively.