A structured telephone-delivered intervention to reduce problem alcohol use (Ready2Change)

Australian New Zealand Clinical Trials Registry

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Statistical Analysis Plan (Addendum)

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Background

Current population surveys suggest around 20% of Australians meet diagnostic criteria for an alcohol use disorder. However, only a minority seek professional help due to individual and structural barriers, such as low health literacy, stigma, geography, service operating hours and wait lists. Telephone-delivered interventions are readily accessible and ideally placed to overcome these barriers. Ready2Change (R2C) is a randomised controlled trial (RCT) to examine the efficacy of a standalone, structured telephone-delivered intervention to reduce alcohol consumption problem severity and related psychological distress among individuals with problem alcohol use.

Study Design

R2C is a single site, parallel group, two-arm superiority RCT. We planned to recruit 344 participants from across Australia with problem alcohol use. After completing a baseline assessment, participants were randomly allocated to receive either the R2C intervention (n = 172, four to six sessions of structured, telephone-delivered intervention, R2C self-help resources, guidelines for alcohol consumption and stress management pamphlets) or the control condition (n = 172, four phone check-ins < 5 min, guidelines for alcohol consumption and stress management pamphlets).

Telephone follow-up assessments were planned to occur at 4–6 weeks, 3 months, 6 months and 12 months post-baseline. The primary outcome is the Alcohol Use Disorders Identification Test (AUDIT) score administered at 3 months post-baseline. Secondary outcomes include change in AUDIT score (6 and 12 months post-baseline), change in drinking patterns (i.e. number of drinking days; number of days where more than 2 standard drinks were consumed; number of days where more than 4 standard drinks were consumed [heavy drinking days]; total number of standard drinks in the past month), psychological distress, quality of life, adverse events, and cost effectiveness. Client experiences of the R2C telephone-delivered intervention were additionally explored.

Statistical Analysis Plan (SAP)

This plan, or SAP Addendum, provides additional detail to the statistical considerations that were documented in the statistical analysis plan pre-registered with ANZCTR.

As described in the pre-registered statistical analysis plan, data will be collated, cleaned and validated using programmed edit checks, in a database that will be locked prior to the unblinding of the study statistician. The primary analysis will take place after all subjects, not known to have withdrawn or not deemed lost to follow-up, have had their 12-month assessments, based on the intention to treat principle (i.e. subjects' data are analysed as randomised and as stratified).

A "per-protocol" sensitivity analysis will be restricted to those subjects with at least one post-baseline assessment, and, for subjects randomised to the R2C arm, participation in at

least one structured telephone counselling session. An additional sensitivity analysis will include a covariate for the number of structured telephone counselling sessions in which subjects, in the R2C arm, participated (1, 2, 3, 4, 5, 6; at least 4).

The repeated measurements of the outcome variables will be analysed by fitting linear mixed models, with fixed effects for treatment and time, and their interaction, and random effects for subjects and assessments within subjects, using restricted maximum likelihood (REML) – as well as accommodating missing values under the missing at random assumption, this method will allow the most suitable variance-covariance model for the repeated measures to be selected, using Akaike's Information Criterion, and, if appropriate, commonality of nonlinear trends over time to be explored via splines.

The F-test will be used to test for an overall group by time interaction and the primary comparison, between groups, of their changes from baseline to 3 months follow-up will be based on a t-test of the corresponding interaction contrast – this t-test will utilise the predicted means and their variance-covariance matrix; these are recovered from the fitted mixed model.

Diagnostic plots of residuals will be assessed and if deemed necessary, variance-stabilising transformations, such as the empirical logistic transformation, will be applied to the outcome variables and inferences will be based on the analyses conducted on the transformed scale.

In a series of exploratory analyses, mixed models with covariates for gender, illicit drug use, extent of exposure to the intervention, exposure to other treatments or programs, level of psychological distress and, as appropriate, level of alcohol use at baseline, will be fitted, including their interactions with treatment group, in order to identify moderating factors. Categorical, ordinal and binary outcomes will be analysed in a similar way using generalised linear mixed models (GLMMs).

Analyses will be conducted using the most appropriate procedures in GenStat, R, SAS and STATA and additional analyses not specified in the published protocol or this addendum will be regarded as exploratory.

Statistical Analysis of the Primary and Key Secondary Outcome Variables

The primary outcome variable is alcohol problem severity at 3 months, assessed by the AUDIT. The time-frame has been adapted to cover the month prior to assessment (rather than the year) and thereby enable follow-up assessments at 6 and 12 months - the key secondary outcomes.

Primary Outcome Variable

The following guidance will be used for calculating the AUDIT scores:

> Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. AUDIT: The Alcohol Use Disorders Identification Test. Guidelines for Use in Primary Care. Second Edition. 2001, WHO/MSD/MSB/01.6a.

Missing values in the ten items that comprise the total AUDIT score and the three domain scores will be accommodated as follows:

(i) If the number of missing items in a domain, or the total, score is greater than 50% then no calculation will be done.

(ii) Else if the number of non-missing items in a domain, or the total, score is greater than or equal to 50% then a calculation will be done – the mean of the non-missing items will be divided by the range (namely 4) and multiplied by the maximum possible score for the domain or the total.

The Hazardous Alcohol Use domain score is the total of items 1, 2 and 3. The maximum possible score is 12.
The Dependence Symptoms domain score is the total of items 4, 5 and 6. The maximum possible score is 12.
The Harmful Alcohol Use domain score is the total of items 7, 8, 9 and 10. The maximum possible score is 16.
The AUDIT total score is the sum of all 10 items and the maximum possible score is 40.

Pseudo-code for the domain scores and the total score is as follows:

```
/* Hazardous Alcohol Use, 3 items, range = 0-4 */
NITEMS = 3;
XNUM = N(OF aud_howoft, aud_howmny, aud_bingfreq);
XMEAN = MEAN(OF aud_howoft, aud_howmny, aud_bingfreq);
IF XNUM GE NITEMS/2 THEN
HazardousAU = ((XMEAN)/4) * 12;

/* Dependence Symptoms, 3 items, range = 0-4 */
NITEMS = 3;
XNUM = N(OF aud_nostop, aud_failexp, aud_morn);
XMEAN = MEAN(OF aud_nostop, aud_failexp, aud_morn);
IF XNUM GE NITEMS/2 THEN
DependenceSymp = ((XMEAN)/4) * 12;

/* Harmful Alcohol Use, 4 items, range = 0-4 */
NITEMS = 4;
XNUM = N(OF aud_guilt, aud_mem, aud_inj, aud_concern);
XMEAN = MEAN(OF aud_guilt, aud_mem, aud_inj, aud_concern);
IF XNUM GE NITEMS/2 THEN
HarmfulAU = ((XMEAN)/4) * 16;

/* TotalScore, 10 items, range = 0-4 */
NITEMS = 10;
XNUM = N(OF aud_bingfreq, aud_concern, aud_failexp,
aud_guilt, aud_howmny, aud_howoft, aud_inj,
aud_mem, aud_morn, aud_nostop);
```

```
XMEAN = MEAN(OF aud_bingfreq, aud_concern, aud_failexp,
aud_guilt, aud_howmny, aud_howoft, aud_inj,
aud_mem, aud_morn, aud_nostop);
IF XNUM GE NITEMS/2 THEN
TotalScore = ((XMEAN)/4) * 40;
```

Inferences about the effect of R2C on the primary outcome will be based on the comparison, between treatment groups, of their changes from baseline to 3 months follow-up. This comparison will be based on a t-test of the corresponding interaction contrast – this t-test will utilise the predicted means and their variance-covariance matrix that are recovered from the fitted mixed model for all repeated assessments up to and including 12 months.

The following sequence of mixed model analyses will be conducted:

(1) Analyse the raw (i.e. untransformed values) with an independence (i.e. equicorrelation) model for the repeated measurements
(2) Check residual variance assumptions using diagnostic residual plots and, if deemed necessary, explore the empirical logit transformation. Determine the measurement scale (raw or transformed).
(3) For the selected measurement scale, investigate three alternative error variance/covariance models (VCVMs) - Independence, First Order Autoregressive, i.e. AR(1) and Unstructured. Models will be compared using the Akaike Information Criterion (AIC) and the VCVM model with the smallest AIC will be selected unless a more parsimonious model has an AIC within 10 units of the minimum AIC in which case the more parsimonious VCVM model will be given preference.
(4) Declare the "definitive scale" (raw or transformed) and VCVM for the AUDIT Total Score and, if not contraindicated, use these also for the three domain scores.
(5) Report the definitive analyses.
(6) Conduct the PPS sensitivity analysis using the definitive approach identified in Step 5 and restrict this to the AUDIT Total Score.
(7) Explore adjustments for gender, illicit drug use, extent of exposure to the intervention, exposure to other treatments or programs, level of psychological distress and, if appropriate, level of alcohol use at baseline (and interactions with treatment group). A full list of covariates is in Appendix 1.
(8) Explore alternative representations of the AUDIT Total Score, in particular:
Ordered symptom categories defined as:
    1. Low-risk (AUDIT total score: 0-7 male, 0-6 female)
    2. Risky (AUDIT total score: 8-15 male, 7-15 female)
    3. Harmful/hazardous (AUDIT total score: 16-19)
    4. Probable dependence (AUDIT total score: 20-40)

Analysis of the above will use PROC GLIMMIX in SAS, the cumulative logit link function, and the multinomial distribution. A dichotomised (binary) representation with categories 1 and 2 combined and categories 3 and 4 combined will also be explored using a logit link function and the binomial distribution.

Secondary Outcomes

Alcohol Use Patterns

Past-month (30 days) alcohol consumption and heavy drinking days are assessed by the Alcohol Timeline Follow-back (TLFB). Heavy drinking days are measured as >40 grams of alcohol (>4 standard drinks). As well as assessments at baseline and 3, 6 and 12 months the repeated-measures analyses will also include an additional assessment that took place at 4 to 6 weeks post baseline. Four outcome variables will be analysed:

- TLFB: Drink Days
- TLFB: Drink Days with > 2 Standard Drinks
- TLFB: Drink Days with > 4 Standard Drinks
- TLFB: Standard Drinks in the Past Month

Statistical analyses will use the same approach, in particular Steps 1-5, as used for the primary outcome variable. Transformations other than the empirical logit (e.g. square root) will be explored if heterogeneous variation is evident in the diagnostic residual plots.

Kessler Psychological Distress Scale (K10)

In the absence of explicit published guidance, missing values in the ten items that comprise the Kessler Psychological Distress Scale (K10) will be accommodated as follows:

(i) If the number of missing items is greater than 50% then no calculation will be done.

(ii) Else if the number of non-missing items is greater than or equal to 50% then a calculation will be done – the mean of the non-missing items will be divided by the range (namely 5) and multiplied by the maximum possible score for the total (50).

The pseudo-code follows:

```
/* Total K10 Score, 10 items, range = 1-5 */
NITEMS = 10;
XNUM = N(OF
k10_tired,     k10_nerv,    k10_sonerv,   k10_hopeles,        k10_restles,
k10_sorestles, k10_depres,  k10_sodeprs,  k10_effort,        k10_worthles);
XMEAN = MEAN(OF
k10_tired,     k10_nerv,    k10_sonerv,   k10_hopeles,        k10_restles,
k10_sorestles, k10_depres,  k10_sodeprs,  k10_effort,        k10_worthles);
IF XNUM GE NITEMS / 2 THEN
Total_K10 = ((XMEAN)/5) * 50;
```

Statistical analyses will use the same approach, in particular Steps 1-5, as used for the primary outcome variable.

Quality of Life (QoL)

As above, all statistical analyses of QoL outcomes will use the same approach, in particular steps 1-5, as used for the primary outcome variable.

EUROHIS-QOL

The EUROHIS-QOL first-level item…

F1: How would you rate your quality of life?

… has a 5-point response format on a Likert scale, ranging from 'very poor' to 'very good'.

If considered necessary, a generalized linear mixed model, as in Step 8 for the primary outcome, will be fitted using PROC GLIMMIX in SAS, with the cumulative logit link function, and the multinomial distribution.

AQoL-6D Quality of Life

The domain (dimension) scores will be the standardised sums of the relevant items as described in Richardson et al (2012). The formula for standardisation is…

$$100*(1 - ((x - \min)/(\max - \min)))$$

… where "x" is the relevant sum, and "min" and "max" are respectively the minimum and maximum possible sums. For example, for the "coping" domain or dimension, which is the sum of scores on three 5-point Likert scales, min=3 and max=15.

A domain score will be treated as missing if one or more of the component items are missing.

For the computation of the total score, missing values in the 20 items that comprise the total AQoL-6D will be accommodated as follows:

(i) If the number of missing items is greater than 50% then no calculation will be done.

(ii) Else if the number of non-missing items is greater than or equal to 50% then a calculation will be done – the mean of the non-missing items will be divided by the range (namely 5) and multiplied by the maximum possible score for the total (100).

APPENDIX 1.

List of covariates for exploratory analyses of the primary outcome variable:

- gender | gndr

- age (as a continuous covariate and also as quartile groups)

- relationship status | rlshp_stat

- remoteness | geog *(if some categories too small, report on geographic area, where major city = metropolitan; inner regional + outer regional + remote = non-metropolitan)*

- education | edu *(collapse categories to: < Year 12 or equivalent | Year 12 or equivalent | Vocational training, apprenticeship, Certificate I, II, III, IV | Diploma, advanced diploma, associate degree | Bachelor's degree | Postgraduate degree (e.g. Master's or Doctoral degree)*

- previous AOD treatment | prev_aodtrt

- current additional treatment | trt_current

- age of first alcohol consumption | alc_agefirst

- age commenced regular alcohol consumption | alc_agereg

- attempted change in alcohol consumption in the month prior to trial | sc_alc_change *(binary: change attempted or not)*

- perceived harm of current alcohol consumption | sc_alc_ownuse *(indicator of alcohol literacy? Could collapse some categories, currently: 1, very harmful | 2, somewhat harmful | 3, neither harmful or beneficial | 4, somewhat beneficial | 5, very beneficial | 6, don't know)*

- psychological distress | k10_score

- quality of life (EUROHIS-QOL single item) | eurohis_qol

- quality of life (AQoL-6D) | total scores (simple, unweighted sum)

- employment | cd_employ

- past-month number of drinking days (TLFB) | tlf_drinkdays_fix

- past-month days where >2 standard drinks consumed (TLFB) | tlf_days_2stand_fix

- past-month days where >4 standard drink consumed (TLFB) | tlf_days_4stand_fix

- total number of standard drinks in the past month (TLFB) | tlf_totalmonth_fix

- Socio-Economic Indexes for Areas (SEIFA) scored from postcode data

- past-month use of other commonly-used substances:

- tobacco (45.6% of the sample) | su_tob_yn_fix
- cannabis (21.2%) | su_cnb_yn_fix
- amphetamine-type stimulants (8.1%) | su_amp_yn_fix
- prescribed sedatives (8.1%) | su_sedp_yn_fix
- cocaine (7.3%) | su_co_yn_fix
- prescribed opioids (5.5%) | su_opdp_yn_fix

Additional exploratory analyses involving the primary outcome:

The ordered symptom categories of the AUDIT total score, defined as…

1. Low-risk (AUDIT total score: 0-7 male, 0-6 female)
2. Risky (AUDIT total score: 8-15 male, 7-15 female)
3. Harmful/hazardous (AUDIT total score: 16-19)
4. Probable dependence (AUDIT total score: 20-40)

… will also be used as a potential covariate, together with treatment group and their two-way interaction, in exploratory analyses of some binomial endpoints such as current additional treatment (trt_current) and future additional treatment (trt_future).