WOW: STATISTICAL ANALYSIS PLAN

Study Name: What Or When to eat to reduce the risk of type 2 diabetes (WOW)

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ABBREVIATIONS

AUC	Area under the curve
AUSDRISK	The Australian type 2 diabetes risk assessment tool
BMI	Body mass index
CGM	Continuous glucose monitoring
CP	Current best practice
DSMC	Data safety monitoring committee
HbA1c	Glycated haemoglobin
iAUC	Incremental area under the curve
M0, M4, M12	M0 = baseline; M4 = 4 month; and M12 = 12 month assessments
SAP	Statistical analysis plan
TRE	Time restricted eating
T2DM	Type II diabetes mellitus
WOW	Study: What Or When to eat to reduce the risk of type 2 diabetes

PREFACE

This statistical analysis plan (SAP) describes the planned analyses and reporting for the WOW study to compare the impact of time restricted eating (TRE) versus current best practice (CP) in adults at high risk of 2 diabetes. The purpose of this SAP is to outline the considerations and the pre-specified analyses for the WOW study.

The project is funded by the Medical Research Future Fund Preventative and Public Health Grant MRF1200555 awarded to Prof Heilbronn.

This study has been approved by the Central Adelaide Local Health Network Human Research Ethics Committee (#14023).

Study Objectives

Primary

To determine whether TRE is not inferior to current practice guidelines (CP) in dietetics to reduce HbA1c at 4 months, in individuals at high risk of developing T2DM.

Secondary

Secondary aim of this study is to assess the short (4 month) and long term (12 month) effect of TRE on HbA1c and glucose metabolism.

Exploratory

The exploratory aims of this study are to assess:

- Adherence of TRE vs CP over 4 and 12 months.
- The impact of TRE vs CP at 4 and 12 months on cardio-metabolic health.
- The impact of TRE vs CP at 4 months on 24-h profiles of glycaemia by CGM

Study Outcomes

Primary objective: 4 months

Primary efficacy outcome: Change in glycated haemoglobin (HbA1c)

Secondary efficacy outcomes

- Change in fasting glucose, insulin, and HOMA-IR
- Nocturnal glucose CGM AUC (midnight to 4 am)

Secondary objective: 12 months

Secondary efficacy outcomes

- Change in HbA1c
- Change in fasting glucose concentrations, insulin concentrations, HOMA-IR

Exploratory objective: Adherence

- Adherence: Self-reported (Assessed: Month 0.5, 1, 2, 3, 3.5, 4, 8, 11.5, 12)
- Diet records (energy, macronutrient intake) by diary (Assessed M0, M4, M12)
- Meal timing / eating window by self-reported meal timing, time stamped food photos (Assessed M0, M4, M12)

Exploratory objective: Cardiometabolic

- Cardiometabolic outcomes: C-reactive protein concentrations, blood lipid concentrations, blood pressure, heart rate (Assessed: M0, M4, M12)
- Liver health outcomes: Change in ALT, AST (Assessed: M0, M4, M12)
- Body mass and body composition by DXA, Waist and hip circumferences (Assessed: M0, M4, M12).
- Physical activity and sleep by inclinometer (ActivPAL), sleep assessed by questionnaire (Assessed: M0, M4, M12)
- Chronotype: by MEQ-SA (Assessed M0, M4, M12)

Exploratory objective: CGM measures

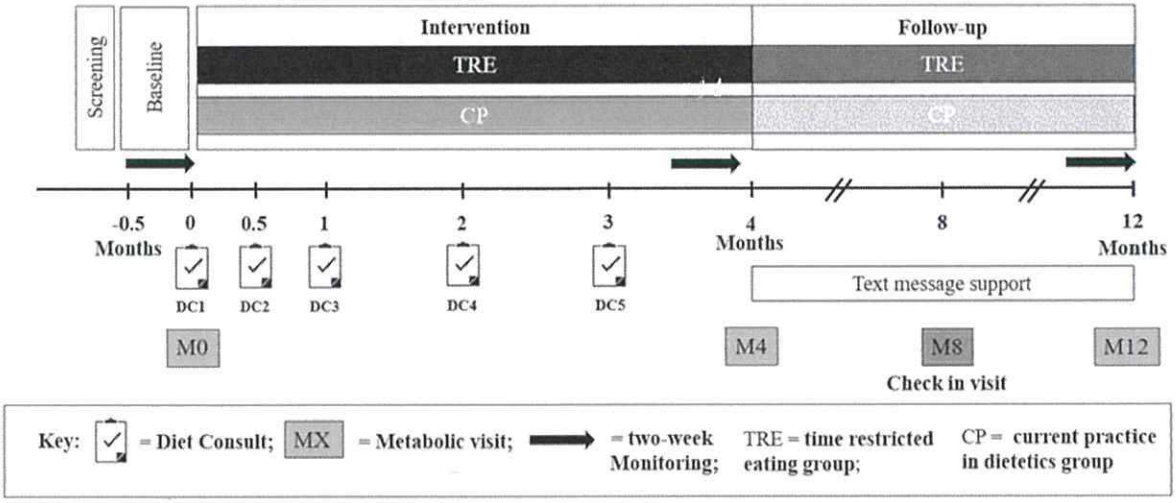
1) Change in 24-h profiles of glycaemia (i.e., iAUC, time-in range, glucose variability) by CGM (FreeStyle Libre Pro), (Assessed: M0, M4)

(Visit notation: M0 = baseline; M4 = 4 months; and M12 = 12 months.)

Study Details

Study Design: WOW is a parallel, single-blinded, multi-centre randomised controlled clinical trial.

Figure 1: Schedule of assessments



Study Population

Inclusion criteria

Study participants will be aged 35 to 70 years, overweight or obese (BMI: ≥25 but <45 kg/m^2) and will score ≥15 on the AUSDRISK assessment tool.

Exclusion criteria

- Type 1 or type 2 diabetes, or diabetes detected at screening HbA1c ≥6.5% (48 mmol/mol).
- The following medical conditions: Major psychiatric disorders (schizophrenia, major depressive disorder, bipolar disorder, eating disorders)
- Gastrointestinal disorders/disease (including malabsorption)
- Haematological disorders (i.e. thalassemia, iron-deficiency anaemia)
- Insomnia
- Currently receiving, or have received treatment/diagnosis of cancer in the past 3 years (excluding non-melanoma skin cancer)
- Significant liver or kidney disease requiring ongoing medical care
- Previous or planned gastro-intestinal surgery (including bariatric surgery)
- Congestive heart failure (NYHA stage 2 or above)
- Previous myocardial infarction or significant cardiac event ≤ 6 months prior to screening
- Previous cerebrovascular event ≤12 months prior to screening, and/or any other condition deemed unstable by the study physician.
- Any medication used, or known to lower blood glucose, or antidiabetic medications; diuretics or combination blood pressure medications containing a diuretic; beta-blockers; glucocorticoids; anti-epileptic medications; antipsychotic medications; Medications affecting weight, appetite or gut motility, opioid medications unless combined with paracetamol in a single formulation and used occasionally on a PRN basis
- Night shift work or individuals who work any shifts after 10 pm.
- Do not consume a regular breakfast (i.e. do not eat breakfast on an average of 5 or more days per week), and do not eat for more than 12 hours per day on an average of 5 or more days per week*
- Have an extreme or restricted pattern of eating (i.e. following an intermittent fasting diet) or already engaged in a TRE protocol
- Pregnant, planning a pregnancy or currently breastfeeding
- Those who have lost or gained >5% of body weight in the last 6 months
- Current smokers of cigarettes/marijuana/e-cigarettes/vaporisers
- Anyone unable to comprehend the study protocol or provide informed consent (i.e. due to English language or cognitive difficulties)

- Participants will not have seen a dietitian in the preceding 3 months.
- Kessler Psychological Distress Scale ≥30
- Eating Disorder Examination Questionnaire ≥2.8

Sample size considerations

In a population of individuals with pre-diabetes, the difference of 0.2% in mean HbA1c was shown to be clinically relevant (Lindström 2003). As such we take the non-inferiority margin to be 0.1% and power our study for an additional benefit of 0.1% of TRE over control (i.e. powered for 0.2% mean difference). Literature suggests that the within group standard deviation to be 0.6% in this population of people with pre-diabetes (Parker 2014; Lindström 2003). Then with n=214 individuals with 4 months assessments (randomized 1:1 to each intervention), there is 80% power to conclude that TRE is non-inferior to CP with a margin of 0.1% in a baseline adjusted ANCOVA when the true difference is 0.1% in favour of TRE (2-sided alpha=0.05).

In planning the study we expected attrition at four months would be <20% requiring a sample size of 268. However due to slow accrual due to COVID and better than expected attrition (close to 10%) the target of n=214 was likely to be attained with n=247 randomized. Approval for this change has been obtained by the independent DSMC.

Randomization details

Stratified random length blocked randomisation by site (Adelaide or Melbourne) and baseline HbA1c (<5.7% vs ≥5.7 to 6.5%)

Estimand Considerations

Population

- Australian adults with obesity and at risk of diabetes (see inclusion/exclusion criteria above)

Variable

- Change from baseline in glycated haemoglobin (HbA1c) at 4 months.

Treatments

- Time restricted eating (TRE)
- Current best practice (CP)

Population Level Summary

Mean difference in HbA1c between treatment groups.

Intercurrent Events

- Discontinuation of diet for any reason (including: lifestyle, dislike of diet and non-related medical adverse events).
- Unable to attend four-month HbA1c assessment due to reasons unrelated to diet (including moving overseas or interstate).
- Drop-out of study with reason unspecified.

Intercurrent Event Strategies

- Due to the intervention being dietary modification it is assumed that efficacy outcomes are strongly tied to compliance, thereby intercurrent event strategies are defined as whether individuals were able to continue the diet or not.
- Treatment policy will be assumed for individuals with diet discontinuation by assuming zero compliance thereafter.
- Hypothetical policy will be assumed for individuals who left the study (without diet discontinuation) by imputing compliance as if they had continued with the study.
- For individuals with unspecified drop-out reason diet discontinuation (yes/no) will be imputed within treatment group, then compliance will be imputed accordingly (ie treatment or hypothetical policy).

Sensitivity Analysis: Worst case

- All individuals in the TRE group with drop-out reason unknown will be assumed that they had discontinued the diet.
- All individuals in the CP group with drop-out reason unknown will be imputed as if they had continued the diet.

Sensitivity Analysis: Complete case

- No imputation, the analysis will only include individuals with HbA1c assessed at 4 months. This analysis assumes the missing data are missing completely at random.

Statistical Considerations

Error control: For the primary outcome the difference between TRE and CP will be assessed for non-inferiority. If the non-inferiority null is rejected then superiority will be tested. Two-sided 95% confidence intervals will be reported (ie one-sided 2.5% type I error rate). No multiple test adjustments will be made for secondary and exploratory outcomes.

Analysis Sets: Analyses of efficacy outcomes at 4 and 12 months (HbA1c, fasting glucose, insulin, HOMA-IR) will include all randomized individuals via multiple imputation. This process also requires physical activity and compliance data, as such analyses of these outcomes will also include all randomized individuals. Analyses of all other (exploratory) outcomes will be complete case analyses.

Covariate adjustment: All comparisons of treatment effect will include adjustment for stratification factors (site and baseline HbA1c as a continuous variable) and for sex as it is known that men are higher risk for diabetes.

Descriptive Statistics: A CONSORT flow diagram will present the number of individuals who participated in online screening, and clinic visits 0-3 (Figure 1). Descriptive summary statistics will be reported for baseline characteristics of all individuals who were randomized.

Statistical Methods

Primary Outcome

The primary analysis of the primary outcome is a covariate adjusted linear regression of differences in HbA1c at 4 months, adjusting treatment group (TRE vs CP), baseline HbA1c (continuous), site (Adelaide vs Melbourne) and sex (male vs female).

Non-inferiority will be concluded if upper 95% confidence interval of the effect estimate of the difference between groups (TRE – CP) is less than 0.1%. If non-inferiority is concluded then superiority may also be concluded if the upper 95% confidence interval excludes a between group difference of 0%.

This analysis will be performed in all randomized individuals with individuals using multiple imputation using chained equations within treatment groups and combined using Rubin's rules. The variables used in the multiple imputation are HbA1c (M0, M4 & M12), age, sex, site, fasting glucose (M0, M4 & M12) and insulin (M0, M4 & M12) concentrations, steps per day (M0, M4 & M12), nocturnal glucose CGM AUC (M0, M4), reason for dropout (related/unrelated to diet) and average compliance (first 4 months, and 4 to 12 months). Compliance will be imputed as per the intercurrent event strategies and the average compliance calculated over each period. Imputation will use multiple chained equations (*mice* R package), details of which are presented in the Appendix.

Secondary & Exploratory Outcomes

Treatment effect for the change in HbA1c at 12 months and other outcomes required for the multiple imputation of the primary outcome (assessed at 4 and/or 12 months) will be assessed using the same methodology as for the primary outcome, i.e. generalized linear regressions with multiple imputation for missing data.

Other outcomes will be analysed using generalized linear regressions adjusting for the same covariates, however these analyses will be complete case analyses.

Safety Outcomes

Summaries, for all adverse events and for those events believed to be related to the intervention, will be reported. In both cases, if an individual has experienced the adverse event on multiple occasions, only the event with the maximum grade will be reported.

When there are at least four individuals who experience a particular adverse event, a Fisher exact test will be conducted comparing the rates of occurrence (irrespective of grade) between the two intervention groups. No adjustments for multiple testing will be performed.

REFERENCES

Parker AR, Byham-Gray L, Denmark R, Winkle PJ (2014) The Effect of Medical Nutrition Therapy by a Registered Dietitian Nutritionist in Patients with Prediabetes Participating in a Randomized Controlled Clinical Research Trial. Journal of the Academy of Nutrition and Dietetics 114: 1739-1748

Lindström J, Louheranta A, Mannelin M, et al. (2003) The Finnish Diabetes Prevention Study (DPS). Lifestyle intervention and 3-year results on diet and physical activity 26: 3230-3236

Appendix

Data pre-processing

CGM baseline glucose algorithm estimated using the algorithm provided below. Nocturnal CGM iAUC calculated as the area under the curve of CGM glucose minus baseline between 12 midnight and 4am.

Total number of steps is set to missing if the number of assessment days is less than 5.

Imputation Overview

Missing data is imputed within allocated treatment group.

HbA1c, fasting glucose concentration, fasting insulin concentration and steps-per-day are imputed on log scale and back transformed for analyses on the original scale.

Log of the total steps-per-day is analysed with an offset of log of number of days assessed.

Baseline variables are used for imputing all variables.

All variables within an assessment period are used per assessment period, diet-discontinue (no vs yes), average compliance (per period) and repeated measures of each variable are also included.

For example imputing 4 month (log) HbA1c uses all baseline variables, all 4 month variables, the binary diet-discontinue variable, the four month average compliance and the 12 month (log) HbA1c variable.

All variables are imputed with predictive mean matching except the compliance and diet-discontinue variables for which ordinal and logistic regressions are used respectively.

Imputation Code

```
####################
## Multiple Imputation
####################

set.seed(1234)

MNAR.type <- 0
## MNAR.type <- 0 => Primary estimand strategy
## MNAR.type <- 1 => Worst-case sensitivity analysis

## Imputation variables
{
  m0.list <- c(
    'state', 'age', 'sex'
    , "hba1c.log.v1", "glu.log.v1", "insulin.log.v1"
    , 'total.num.steps.log.v1', "cgm.iauc.v1"
  )
  m0.list <- m0.list[order(colSums(is.na(full.data[,m0.list])))]
  m2.list <- c('ice.grp', paste('m', c(0.5, 1, 2, 3, 3.5, 4), sep=''), "m4.compliance")
  m4.list <- c(
    "hba1c.log.v2", "glu.log.v2", "insulin.log.v2"
    , "total.num.steps.log.v2", "cgm.iauc.v2"
  )
  m4.list <- m4.list[order(colSums(is.na(full.data[,m4.list])))]
  m8.list <- c(paste('m', c(8, 12), sep=''), "m12.compliance")
  m12.list <- c("hba1c.log.v3", "glu.log.v3", "insulin.log.v3", "total.num.steps.log.v3")
  m12.list <- m12.list[order(colSums(is.na(full.data[,m12.list])))]
  aux.list <- c("id", "group", "drop.out.time", "num.valid.days.log.v1", "num.valid.days.log.v2", "num.valid.days.log.v3")
  table(table(c(m0.list, m2.list, m4.list, aux.list))) # all 1s

  var.list <- c(m0.list, m2.list, m4.list, m8.list, m12.list)
  #c(var.list, aux.list)[!c(var.list, aux.list) %in% names(full.data)]
  imp.data <- full.data[, c(var.list, aux.list)]
  colSums(is.na(imp.data))
}

## Sensitivity Analysis: Worse case
{
  if (MNAR.type == 1) {
    imp.data$ice.grp[imp.data$group. == 0 & is.na(imp.data$ice.grp)] <- 'Completer'
    imp.data$ice.grp[imp.data$group. == 1 & is.na(imp.data$ice.grp)] <- 'Discontinue diet'
  }
}


## Imputation formula per variable
{
  fm.list <- NULL
  for (var. in m0.list) {
    # var. <- m0.list[4]
    fm. <- paste(var., "~", paste('m0.list[!m0.list %in% c(var., "total.num.steps.log.v1")]', collapse=' + '))
    if (grepl('total.num.steps.log', var.)) fm. <- paste(fm., ' + I(total.num.steps.log.v1 - num.valid.days.log.v1)')
    if (grepl('total.num.steps.log', var.)) fm. <- paste(fm., ' + offset(num.valid.days.log.v1) + I(total.num.steps.log.v2 - num.valid.days.log.v2) + I(total.num.steps.log.v3 - num.valid.days.log.v3)')
    if (var. %in% c("hba1c.log.v1", "glu.log.v1", "insulin.log.v1")) fm. <- paste(c(fm., sub("v1", "v2", var.)), collapse=' + ')
    if (var. %in% c("cgm.iauc.v1")) {
      fm. <- paste(c(fm., sub("v1", "v2", var.)), collapse=' + ')
    }; fm.list <- c(fm.list, as.formula(fm.)); rm(fm.)
  }; rm(var.)
  for (var. in m2.list) {
    # var. <- m2.list[1]
    fm. <- paste(var., "~ (", paste(c(
      m0.list[!m0.list %in% c('total.num.steps.log.v1')], c('ice.grp', 'm4.compliance')[! c('ice.grp', 'm4.compliance') %in% var.]
      , m4.list[!m4.list %in% c('total.num.steps.log.v2')]
    ), collapse=' + '), ')')
    fm. <- paste(fm., ' + I(total.num.steps.log.v1 - num.valid.days.log.v1) + I(total.num.steps.log.v2 - num.valid.days.log.v2)')
    fm.list <- c(fm.list, as.formula(fm.)); rm(fm.)
  }; rm(var.)
  for (var. in m4.list) {
    fm. <- paste(var., "~ (", paste(c(
      m0.list[!m0.list %in% c('total.num.steps.log.v1')]
      , c('m4.compliance')
      , m4.list[!m4.list %in% c(var., 'total.num.steps.log.v2')]
    ), collapse=' + '), ')')
    fm. <- paste(fm., ' + I(total.num.steps.log.v1 - num.valid.days.log.v1)')
    if (grepl('total.num.steps.log.v2', var.)) fm. <- paste(fm., ' + offset(num.valid.days.log.v2) + I(total.num.steps.log.v1 - num.valid.days.log.v1) + I(total.num.steps.log.v3 - num.valid.days.log.v3)')
    if (!grepl('total.num.steps.log.v2', var.)) fm. <- paste(fm., ' + I(total.num.steps.log.v1 - num.valid.days.log.v1) + I(total.num.steps.log.v2 - num.valid.days.log.v2)')
    if (var. %in% c('hba1c.log.v2', 'glu.log.v2', 'insulin.log.v2')) fm. <- paste(c(fm., sub('v2', 'v3', var.)), collapse=' + ')
    fm.list <- c(fm.list, as.formula(fm.)); rm(fm.)
  }; rm(var.)
  for (var. in m8.list) {
    # var. <- m2.list[1]
    fm. <- paste(var., "~ (", paste(c(
      m0.list[!m0.list %in% c('total.num.steps.log.v1')], c('m4.compliance')
      , m4.list[!m4.list %in% c('total.num.steps.log.v2')]
      , 'm12.compliance'[!'m12.compliance' %in% var.]
    ), collapse=' + '), ')')
    fm. <- paste(fm., ' + I(total.num.steps.log.v1 - num.valid.days.log.v1) + I(total.num.steps.log.v2 - num.valid.days.log.v2)')
    fm.list <- c(fm.list, as.formula(fm.)); rm(fm.)
  }; rm(var.)
  for (var. in m12.list) {
    fm. <- paste(var., "~ (", paste(c(
      m0.list[!m0.list %in% c('total.num.steps.log.v1')]
      , c('m4.compliance', 'm12.compliance')
      , m12.list[!m12.list %in% c(var., 'total.num.steps.log.v3')]
    ), collapse=' + '), ')')
    fm. <- paste(fm., ')')
    if (grepl('total.num.steps.log.v3', var.)) fm. <- paste(fm., ' + offset(num.valid.days.log.v3) + I(total.num.steps.log.v1 - num.valid.days.log.v1) + I(total.num.steps.log.v2 - num.valid.days.log.v2)')
    if (!grepl('total.num.steps.log.v3', var.)) fm. <- paste(fm., ' + I(total.num.steps.log.v1 - num.valid.days.log.v1) + I(total.num.steps.log.v3 - num.valid.days.log.v3)')
    if (var. %in% c("hba1c.log.v3", "glu.log.v3", "insulin.log.v3")) fm. <- paste(c(fm., sub('v3', 'v2', var.)), collapse=' + ')
    fm.list <- c(fm.list, as.formula(fm.)); rm(fm.)
  }; rm(var.)
  fm.list <- as.list(fm.list)
  names(fm.list) <- c(m0.list, m2.list, m4.list, m8.list, m12.list)
  fm.list$m4.compliance <- as.formula('m4.compliance ~ 1')
  fm.list$m12.compliance <- as.formula('m12.compliance ~ 1')
  rm(aux.list, m0.list, m2.list, m4.list, m8.list, m12.list)
}
```

```
## Imputation methods
{
  library(mice)
  mice.fit <- mice(
    data=imp.data
    , m=1, maxit=0
    , blocks=var.list
    , visitSequent=var.list
    , formulas=fm.list
  )
  # mice.fit$loggedEvents
  method. <- mice.fit$method
  method.[names(method.) == 'm4.compliance'] <- (
    "~ I((
        0.5*as.numeric(as.character(m0.5))*((ice.grp == 'Completer') + (ice.grp == 'Discontinue diet')*(drop.out.time >= 0.5))
        + 0.5*as.numeric(as.character(m1))*((ice.grp == 'Completer') + (ice.grp == 'Discontinue diet')*(drop.out.time >= 1))
        + 1*as.numeric(as.character(m2))*((ice.grp == 'Completer') + (ice.grp == 'Discontinue diet')*(drop.out.time >= 2))
        + 1*as.numeric(as.character(m3))*((ice.grp == 'Completer') + (ice.grp == 'Discontinue diet')*(drop.out.time >= 3))
        + 0.5*as.numeric(as.character(m3.5))*((ice.grp == 'Completer') + (ice.grp == 'Discontinue diet')*(drop.out.time >= 3.5))
        + 0.5*as.numeric(as.character(m4))*((ice.grp == 'Completer') + (ice.grp == 'Discontinue diet')*(drop.out.time >= 4))
      )/14/4)"
  )
  method.[names(method.) == 'm12.compliance'] <- (
    "~ I((
          4*as.numeric(as.character(m8))*((ice.grp == 'Completer') + (ice.grp == 'Discontinue diet')*(drop.out.time >= 8))
          + 4*as.numeric(as.character(m12))*((ice.grp == 'Completer') + (ice.grp == 'Discontinue diet')*(drop.out.time >= 12))
        )/14/8)"
  )
  method.

  rm(mice.fit)
}
ls()

## Imputation per treatment group
M. <- 100; N.iter <- 100
for (group. in 0:1) {

  library(mice)
  mice.fit <- mice(
    data=imp.data[imp.data$group == group.,]
    , m=M., maxit=N.iter
    , blocks=var.list
    , visitSequent=var.list
    , formulas=fm.list
    , method=method.
    , print=T
  )
  mice.fit$loggedEvents
  # plot(mice.fit)

  if (group. == 0) mice.fit.g0 <- mice.fit
  if (group. == 1) mice.fit.g1 <- mice.fit
  rm(mice.fit)

); rm(group., M., N.iter)
rm(var.list, method., fm.list, imp.data)
ls()



####################
## Primary Analysis
####################

## HbA1c at 4 months
library(mice)
fm. <- "lm(exp(hba1c.log.v2) - exp(hba1c.log.v1) ~ group + sex + state + exp(hba1c.log.v1))"
output <- summary(pool(with(
  data = rbind(mice.fit.g0, mice.fit.g1)
  , expr = eval(parse(text=fm.))
))); output
grp.est <- output$estimate[2]
grp.est.se <- output$std.error[2]
grp.est.df <- output$df[2]
grp.est.p <- output$p.value[2]
if (grp.est.p < 0.001) grp.est.p <- '<0.001'
if (grp.est.p >= 0.01) grp.est.p <- format(round(grp.est.p, 2), nsmall=2)
if (grp.est.p < 0.01 & grp.est.p >= 0.001) grp.est.p <- format(round(grp.est.p, 3), nsmall=3)
paste(
  'iTRE - CP: '
  , format(round(grp.est, 2), nsmall=2), ' ['
  , format(round(grp.est - qt(1-0.05/2, df=grp.est.df)*grp.est.se, 2), nsmall=2), ', '
  , format(round(grp.est + qt(1-0.05/2, df=grp.est.df)*grp.est.se, 2), nsmall=2), ']; p='
  , grp.est.p, sep=''
); rm(grp.est, grp.est.se, grp.est.df, grp.est.p, output, fm.)
```

```
####################
## Secondary outcome example analyses
####################

## HbA1c at 12 months
library(mice)
fm. <- "lm(exp(hba1c.log.v3) - exp(hba1c.log.v1) ~ group + sex + state + exp(hba1c.log.v1))"
output <- summary(pool(with(
  data = rbind(mice.fit.g0, mice.fit.g1)
  , expr = eval(parse(text=fm.))
))); output
grp.est <- output$estimate[2]
grp.est.se <- output$std.error[2]
grp.est.df <- output$df[2]
paste(
  'iTRE - CP: '
  , format(round(grp.est, 2), nsmall=2), ' ['
  , format(round(grp.est - qt(1-0.05/2, df=grp.est.df)*grp.est.se, 2), nsmall=2), ', '
  , format(round(grp.est + qt(1-0.05/2, df=grp.est.df)*grp.est.se, 2), nsmall=2), ']'
  , sep=''
), rm(grp.est, grp.est.se, grp.est.df, output, fm.)


## Other Secondary outcomes will also adjust for their baseline and HbA1c at baseline
## Glucose at 4 months
library(mice)
fm. <- "lm(exp(glu.log.v2) - exp(glu.log.v1) ~ group + sex + state + exp(glu.log.v1) + exp(hba1c.log.v1))"
output <- summary(pool(with(
  data = rbind(mice.fit.g0, mice.fit.g1)
  , expr = eval(parse(text=fm.))
))); output
grp.est <- output$estimate[2]
grp.est.se <- output$std.error[2]
grp.est.df <- output$df[2]
paste(
  'iTRE - CP: '
  , format(round(grp.est, 2), nsmall=2), ' ['
  , format(round(grp.est - qt(1-0.05/2, df=grp.est.df)*grp.est.se, 2), nsmall=2), ', '
  , format(round(grp.est + qt(1-0.05/2, df=grp.est.df)*grp.est.se, 2), nsmall=2), ']'
  , sep=''
); rm(grp.est, grp.est.se, grp.est.df, output, fm.)

rm(mice.fit.g0, mice.fit.g1, MNAR.type)
ls()
########################## EOF ##############################
```

CGM code

```
CGM.baseline.fn <- function(y, t, threshold=1, smooth.range=4*2*3 + 1, iter=8) {
  # y = time series observations
  # t = time of observations
  # smooth.range = #obs/hr * both directions * duration (hr) + 1 (median)
  # threshold = deviations from local mean (Note that threshold can be defined as residual SD
  #, but not needed here.)
  # iter = number of iterations for

  ## Ensure y is correctly ordered
  y <- y[order(t)]

  ## Ensure no two consecutive readings with the same value the same
  cond. <- c(F, y[-1] == y[-length(y)])
  y[cond.] <- y[cond.] + 1/100/sum(cond.)
  rm(cond.)

  ## Generate baseline smooth y without large deviations (large defined as > threshold)
  smoothed.y <- y
  signals <- rep(0,length(y))
  for (it. in 1:iter) {
    # it. <- 1
    library(zoo)
    smoothed.y[signals != 0] <- NA
    smoothed.y <- rollapply(
      data=smoothed.y
      , width=smooth.range
      , partial=T
      , by.column = FALSE
      , FUN=function(x) { return(mean(x, na.rm=T))})
    smoothed.y <- na.fill(smoothed.y, "extend")

    ## When smoothed.y too high due to NA imputing reduce by threshold
    smoothed.y[y < smoothed.y - threshold] <- smoothed.y[y < smoothed.y - threshold] - threshold
    smoothed.y <- rollmean(smoothed.y, k=ceiling((smooth.range - 1)/2), fill='extend')

    # Asymmetric signal detection.
    signals <- rep(0,length(y))
    signals[y > smoothed.y + threshold*it./iter] <- 1

  }; rm(it.)

  ## Find peaks in signals, separated by dips
  neg.change <- c(y[-length(y)] < y[-1], F) & c(F, y[-1] < y[-length(y)])
  # ## exclude dips that consist of a single time point.
  pos.change <- c(y[-length(y)] > y[-1], F) & c(F, y[-1] > y[-length(y)])
  neg.change[neg.change & c(pos.change[-1], F) & c(F, pos.change[-length(y)])] <- F
  ## Set resulting dips to 0
  signals[neg.change & signals == 1] <- 0

  ## Peak = max of consecutive signals.
  signal.grp <- c(1, cumsum(signals[-length(y)] != signals[-1]) + 1)
  peaks <- y == tapply(y, signal.grp, max)[tapply(y, signal.grp,)] & signals == 1

  return(list("signals"=signals, "peaks"=peaks, "avgFilter"=smoothed.y))
  rm(y, t, threshold, iter, smooth.range, smoothed.y, neg.change, pos.change, signal.grp, signals)
}
```