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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	2
METHODS	2
ACKNOWLEDGEMENTS	7
REFERENCES	8
APPENDICES	10
CONTRIBUTIONS OF AUTHORS	14
DECLARATIONS OF INTEREST	14
NOTES	15

[Intervention Protocol]

Interventions for people with type 2 diabetes mellitus fasting during Ramadan

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of interventions for people with T2DM fasting during Ramadan.

BACKGROUND

The Muslim faith has approximately 1.5 billion followers and is one of the fastest growing faiths in the world (Hackett 2015). Annually, Muslims of pubertal age and older are obligated to observe the Ramadan fast. This involves abstaining from the consumption of food and fluids from dawn to dusk daily for about 30 days (Rashed 1992). The duration of daily fasting depends on the local daylight hours where the individual is residing. This can be up to 22 hours depending on the geographical location and the climatic season in which the month of Ramadan falls. Muslims who are travelling, menstruating, pregnant, or breastfeeding are exempt from fasting during Ramadan (Sakr 1975). Exemptions also exist for people who are ill, including those with chronic medical conditions such as diabetes.

Description of the condition

Diabetes is a global health issue that occurs in both low- and middle-income and high-income countries. Recent global estimates suggest that nearly 425 million people are living with diabetes, which represents a prevalence of approximately 8.8% (IDF 2017). Estimates in several large Muslim-majority countries suggest that the prevalence of diabetes in these countries is even higher and is expected to double in the next 25 years (IDF 2017). Many people with diabetes choose to fast during Ramadan. The lack of food and fluids during the fasting period increases the risk of dehydration and hypoglycaemia among people with diabetes. In addition, an individual's food habits tends to change during Ramadan in relation to the proportion of fat, protein, and carbohydrate eaten. There is also a general tendency to ingest food with high carbohydrate and sugar content during Ramadan and this heightens the risk of developing hyperglycaemia among people with diabetes (Salti 2004). As such, many interventions have been developed to ensure the optimal care of people with diabetes during Ramadan. These include Ramadan-focused education and

medication adjustment (Ibrahim 2015). However, Ramadan fasting by people with diabetes still represents a challenge for healthcare professionals as management guidelines are expert-based (IDF 2016).

The Epidemiology of Diabetes and Ramadan (EPIDIAR) study conducted in 2001 found that nearly 4 out of 5 people with type 2 diabetes mellitus (T2DM) fasted for at least 15 days during Ramadan (Salti 2004). Fasting during Ramadan heralds a sudden shift in meal times, meal quantity, meal quality, sleep pattern, and physical activity. Meal times are mainly nocturnal and this affects sleep quality and quantity. In people with diabetes, abstaining from food and fluid during fasting also leads to dehydration and increases the risk of hypoglycaemia. Indeed, in the EPIDIAR study, the risk of hypoglycaemia increased by 7.5 times in these individuals (Salti 2004). However, due to the long fasting hours, there is a tendency to consume meals high in carbohydrate during

fast breaking (Iftā r). In addition, as the general atmosphere of the Ramadan month is celebration, fasting during the day is often followed by a feast with a variety of food in the evening including those with high sugar content. This leads to increased risk of hyperglycaemia and diabetic ketoacidosis among people with diabetes (Salti 2004). As such, most trials have primarily focused on strategies that are intended to ensure that these individuals remain euglycaemic during this period, as well as reducing the risk of developing hypoglycaemia.

Description of the intervention

Over the past few years, several guidelines and diabetes management programmes have been developed to improve diabetes care, especially among those who wish to fast during Ramadan (Hassanein 2016; Ibrahim 2015). For example, several trials have examined the use of diabetes-focused education targeted at those who wished to fast during Ramadan. Bravis 2010 demonstrated in their trial that Ramadan-focused diabetes education was beneficial in reducing the risk of hypoglycaemia in those who fast. Other trials have focused on the role of switching pharmacotherapy to reduce the risk of hypoglycaemia (Lee 2016). There has been a wide range of interventions aimed at improving the provision of diabetes care and achieving euglycaemia for people who wish to fast during this period.

Adverse effects of the intervention

While most interventions have focused on reducing the risk of hypoglycaemia during this period, at the same time there is an increased risk of developing hyperglycaemia, diabetic ketoacidosis, dehydration, and thrombosis in individuals who fast during Ramadan (Hassanein 2016; Ibrahim 2015).

How the intervention might work

Diabetes-focused education has been shown to improve an individual's knowledge and understanding of diabetes as well as their self-efficacy skills. In addition, a review suggests that organisational quality improvement strategies, such as case management or even team changes, can improve glycaemic control in people with T2DM (Tricco 2012). This has been shown to improve a wide variety of outcomes, including improved diet control, increased physical activities, and drug adherence (Allah 2018; Lee 2017). In addition, trials have shown that oral hypoglycaemic agents, especially sulphonylureas, increase the risk of hypoglycaemia among people with T2DM (Zammit 2005). This risk is heightened, especially during Ramadan, due to the need to fast for prolonged periods. As such, trials have also attempted to examine the role of non-sulphonylurea-based pharmacotherapies in reducing the risk of hypoglycaemia amongst these individuals (Lee 2016).

Why it is important to do this review

Over the past few years, the number of Muslim individuals who choose to fast during Ramadan has increased and is predicted to increase further in the coming decade (Pew Research 2017). Currently, most of the existing recommendations available from guidelines have largely been based upon expert opinion rather than evidence from existing clinical studies. While several systematic reviews have been recently published examining strategies to optimise health outcomes during Ramadan (Almansour 2017; Lee 2016), these reviews have not comprehensively examined all potential important outcomes, such as all-cause mortality, and socioeconomic outcomes, such as loss of workdays. In addition, since the publication of these reviews, several new trials have been published (Azar 2016; Wan Seman 2016). As such, there is a need to comprehensively synthesise these data to help guide the work of healthcare professionals.

OBJECTIVES

To assess the effects of interventions for people with T2DM fasting during Ramadan.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs).

Types of participants

All people with T2DM who fast during Ramadan.

Diagnostic criteria for T2DM

In order to be consistent with changes in the classification of and diagnostic criteria for diabetes mellitus, the diagnosis should be established using the standard criteria valid at the time the trial commenced (e.g. ADA 2003; ADA 2008; Alberti 1998). Ideally, the trial authors should describe the diagnostic criteria used in the trial. We will use the trial authors' definition of diabetes mellitus if necessary. Changes in diagnostic criteria may have produced significant variability in the clinical characteristics of the participants included and in the results obtained (which we will investigate through sensitivity analysis).

Types of interventions

We plan to investigate interventions aimed at improving the care of people with T2DM who fast during Ramadan, including organisational, pharmacological, or educational interventions.

Usual care is defined as standard care that individuals with T2DM should receive according to national guidelines.

We plan to investigate the following comparisons of intervention versus control/comparator.

Intervention

- Any organisational intervention/strategy implemented during Ramadan (such as changes to structure or organisation of the primary health care team including adding a team member or using a multidisciplinary team).
- Any changes to antidiabetic medications during Ramadan (such as switching from sulphonylurea to a dipeptidyl-peptidase-4 inhibitor (DPP4-I)).
- Any educational intervention (such as Ramadan-focused diabetes education) implemented before or during Ramadan.

Comparator

- Usual care or no intervention compared with any of the above mentioned interventions.

Concomitant interventions must be the same in both the intervention and comparator groups to establish fair comparisons. If a trial includes multiple arms, we will include any trial arm that meets the inclusion criteria.

Minimum duration of intervention

For interventions that involve changing of antidiabetic medications, the intervention would need to be at least 30 days duration or longer (i.e. started before Ramadan and continued until

the end of Ramadan). For educational interventions and organisational interventions, we will place no restriction on duration of intervention.

Minimum duration of follow-up

Minimal duration of follow-up will be at least 30 days (Ramadan fasting period). We will define any follow-up period that continues beyond the original timeframe for the primary outcome measure, as specified in the power calculation of the trial's protocol, as an extended follow-up period (also called open-label extension study) (Buch 2011; Megan 2012).

Types of outcome measures

We will include a trial even if it fails to report one or more of our primary or secondary outcome measures; however, if it reports none of our primary or secondary outcomes, we will exclude the trial but will provide some basic information in an additional table. We will investigate the following outcomes using the methods and time points specified below.

Primary outcomes

- Hypoglycaemic episodes.
- Health-related quality of life.
- Adverse events other than hypoglycaemia.

Secondary outcomes

- All-cause mortality.
- Glycosylated haemoglobin A1c (HbA1c).
- Blood pressure.
- Lipids.
- Body weight.
- Treatment satisfaction.
- Self-care behaviours.
- Socioeconomic effects.

Method of outcome measurement

- Hypoglycaemic episodes: classified as mild (self-managed), moderate (daily activities interrupted but self-managed), or severe (requiring assistance from others).
- Health-related quality of life: evaluated by a validated instrument, such as the diabetes-specific quality of life scale (DSQoLs) questionnaire.
- Adverse events other than hypoglycaemic episodes: such as anxiety and depression.
- All-cause mortality: death from any cause.
- HbA1c: measured in % or mmol/mol.
- Blood pressure: systolic and diastolic blood pressure measured in mmHg.

- Lipids: serum cholesterol (total cholesterol, high-density lipoprotein (HDL-) cholesterol and low-density lipoprotein (LDL-) cholesterol).
- Body weight: measured in kilograms (kg).
- Treatment satisfaction: evaluated by a validated instrument, such as the diabetes treatment satisfaction questionnaire (DTSQ).
- Self-care behaviours: evaluated with a validated instrument, such as summary of diabetes self-care activities (SDSCA).
- Socioeconomic effects: such as direct costs defined as admission/readmission rates, average length of stay, visits to general practitioner, accident/emergency visits; medication consumption; indirect costs defined as resources lost due to illness by the participant or their family member.

Timing of outcome measurement

- For hypoglycaemic episodes, adverse events other than hypoglycaemic episodes and all-cause mortality: any time after participants were randomised to the intervention/comparator groups.
- For health-related quality of life, HbA1c, blood pressure, lipids, body weight, treatment satisfaction, self-care behaviours, and socioeconomic effects: short-term (up to three months after Ramadan fasting) and mid-term (longer than three months after Ramadan fasting).

Search methods for identification of studies

Electronic searches

We will search the following sources from the inception of each database to the specified date and will place no restrictions on the language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO).
- MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE; from 1946 onwards).
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature).
 - PsycINFO Ovid.
 - ClinicalTrials.gov (www.clinicaltrials.gov).
 - World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/trialsearch/).

We will not include Embase in our search, as RCTs indexed in Embase are now prospectively added to CENTRAL via a highly sensitive screening process (Cochrane 2018).

We will continuously apply a MEDLINE (via Ovid SP) email alert service established by the Cochrane Metabolic and Endocrine

Disorders (CMED) Group to identify newly published trials using the same search strategy as described for MEDLINE (Appendix 1). After we submit the final review draft for editorial approval, the CMED Group will perform a complete search update on all databases available at the editorial office and will send the results to the review authors. Should we identify new trials for inclusion, we will evaluate these and incorporate the findings into our review draft (Beller 2013).

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, systematic reviews, meta-analyses, and health technology assessment reports. In addition we will contact authors of included trials to identify any additional information on the retrieved trials and establish whether we may have missed further trials.

We will not use abstracts or conference proceedings for data extraction unless full data are available from trial authors. This is because this information source does not fulfil the CONSORT requirements, which consist of “an evidence-based, minimum set of recommendations for reporting randomised trials” (CONSORT 2018; Scherer 2007). We will present information on abstracts or conference proceedings in the ‘Characteristics of studies awaiting classification’ table.

Data collection and analysis

Selection of studies

Two review authors (SWHL and NML) will independently screen the abstract or title, or both, of every record we retrieve from the literature searches, to determine which trials we should assess further. We will obtain the full-text of all potentially relevant records. We will resolve any disagreements through consensus or by recourse to a third review author (RS). If we cannot resolve a disagreement, we will categorise the trial as a ‘study awaiting classification’ and will contact the trial authors for clarification. We will present an adapted PRISMA flow diagram to show the process of trial selection (Liberati 2009). We will list all articles excluded after full-text assessment in a ‘Characteristics of excluded studies’ table and will provide the reasons for exclusion.

Data extraction and management

For trials that fulfil our inclusion criteria, two review authors (SWHL and RS) will independently extract key participant and intervention characteristics. We will describe interventions by use of the ‘template for intervention description and replication’ (TI-DiER) checklist (Hoffmann 2014; Hoffmann 2017).

We will report data on efficacy outcomes and adverse events using standardised data extraction sheets from the CMED Group. We will resolve any disagreements by discussion or, if required, we will consult a third review author (NML).

We will provide information including trial identifier about potentially relevant ongoing trials in the 'Characteristics of ongoing trials' table and in a joint appendix 'Matrix of trial endpoint (publications and trial documents)'. We will try to find the protocol for each included trial and we will report primary, secondary, and other outcomes in comparison with data in publications in a joint appendix.

We will email all authors of included trials to enquire whether they would be willing to answer questions regarding their trials. We will present the results of this survey in an appendix. We will thereafter seek relevant missing information on the trial from the primary trial author(s), if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary trial, we will maximise the information yield by collating all available data. We will use the most complete data set aggregated across all known publications. We will list duplicate publications, companion documents, multiple reports of a primary trial, and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included trial. Furthermore, we will also list duplicate publications, companion documents, multiple reports of a trial, and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded trial.

Data from clinical trials registers

If data from included trials are available as study results in clinical trials registers, such as ClinicalTrials.gov or similar sources, we will make full use of this information and extract the data. If there is also a full publication of the trial, we will collate and critically appraise all available data. If an included trial is marked as a completed study in a clinical trial register but no additional information (study results, publication, or both) is available, we will add this trial to the 'Characteristics of studies awaiting classification' table.

Assessment of risk of bias in included studies

Two review authors (NML and RS) will independently assess the 'Risk of bias' of each included trial. We will resolve any disagreements by consensus or by consulting a third review author (SWHL). In the case of disagreement, we will consult the rest of the review author team and make a judgement based on consensus. If adequate information is unavailable from the publications, trial protocols, or other sources, we will contact the trial authors for more detail to request missing data on 'Risk of bias' items.

We will use the Cochrane 'Risk of bias' assessment tool ([Higgins 2017](#)), and will assign assessments of low, high, or unclear risk of bias (for details see [Appendix 2](#); [Appendix 3](#)). We will evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* according to the criteria and associated categorisations contained therein ([Higgins 2017](#)).

Summary assessment of risk of bias

We will present a 'Risk of bias' graph and a 'Risk of bias' summary figure.

We will distinguish between self-reported and investigator-assessed and adjudicated outcome measures.

We will consider the following self-reported outcomes.

- Hypoglycaemic episodes.
- Health-related quality of life.
- Adverse events other than hypoglycaemic episodes.
- Treatment satisfaction (including satisfaction with the intervention).
- Self-care behaviours.
- Blood pressure.
- Body weight.

We will consider the following outcomes to be investigator-assessed.

- Hypoglycaemic episodes.
- Adverse events other than hypoglycaemic episodes.
- All-cause mortality.
- HbA1c.
- Blood pressure.
- Lipids.
- Body weight.
- Socioeconomic effects.

Risk of bias for a trial across outcomes

Some risk of bias domains, such as selection bias (sequence generation and allocation sequence concealment), affect the risk of bias across all outcome measures in a trial. In case of high risk of selection bias, we will mark all endpoints investigated in the associated trial as being at high risk. Otherwise, we will not perform a summary assessment of the risk of bias across all outcomes for a trial.

Risk of bias for an outcome within a trial and across domains

We will assess the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both trial-level entries and outcome-specific entries). We consider low risk of bias to denote a low risk of bias for all key domains, unclear risk to denote an unclear risk of bias for one or more key domains, and high risk to denote a high risk of bias for one or more key domains.

Risk of bias for an outcome across trials and across domains

These are the main summary assessments that we will incorporate into our judgments about the quality of evidence in the 'Summary of findings' tables. We will define outcomes as at low risk of bias when most information comes from trials at low risk of bias, unclear risk when most information comes from trials at low or unclear risk of bias, and high risk when a sufficient proportion of information comes from trials at high risk of bias.

Measures of treatment effect

When at least two included trials are available for a comparison and a given outcome, we will try to express dichotomous data as a risk ratio (RR) or odds ratio (OR) with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale (e.g. weight loss in kg) we will estimate the intervention effect using the mean difference (MD) with 95% CIs. For continuous outcomes that measure the same underlying concept (e.g. health-related quality of life) but use different measurement scales, we will calculate the standardised mean difference (SMD). We will express time-to-event data as a hazard ratio (HR) with 95% CIs.

Unit of analysis issues

We will take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials, and multiple observations for the same outcome. If more than one comparison from the same trial is eligible for inclusion in the same meta-analysis, we will either combine groups to create a single pair-wise comparison or appropriately reduce the sample size so that the same participants do not contribute multiple times (splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjusting the precision of the comparison, it does not account for correlation arising from the same set of participants being in multiple comparisons (Higgins 2011).

We will attempt to re-analyse cluster-RCTs that have not appropriately adjusted for potential clustering of participants within clusters in their analyses. The variance of the intervention effects will be inflated by a design effect. Calculation of a design effect involves estimation of an intra-cluster correlation (ICC). We will obtain estimates of ICCs by contacting the trial authors, or will impute them using estimates from other included trials that report ICCs, or using external estimates from empirical research (e.g. Bell 2013). We plan to examine the impact of clustering using sensitivity analyses.

Dealing with missing data

If possible, we will obtain missing data from the authors of the included trials. We will carefully evaluate important numerical data such as screened, randomly assigned participants as well as

intention-to-treat, and as-treated and per-protocol populations. We will investigate attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we will critically appraise issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

In trials where the standard deviation (SD) of the outcome is not available at follow-up or we cannot recreate it, we will standardise by the mean of the pooled baseline SD from those trials that reported this information.

Where included trials do not report means and SDs for outcomes and we do not receive the necessary information from trial authors, we will impute these values by estimating the mean and variance from the median, range, and the size of the sample (Hozo 2005). We will investigate the impact of imputation on meta-analyses by performing sensitivity analyses, and we will report for every outcome which trials had imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we will not report trial results as the pooled effect estimate in a meta-analysis.

We will identify heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard χ^2 test with a significance level of $\alpha = 0.1$ (Deeks 2017). In view of the low power of this test, we will also consider the I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003).

When we find heterogeneity, we will attempt to determine the possible reasons for it by examining individual trial and subgroup characteristics.

Assessment of reporting biases

If we include 10 or more trials that investigate a particular outcome, we will use funnel plots to assess small-trial effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias (Sterne 2017). Therefore we will interpret the results carefully (Sterne 2011).

Data synthesis

We plan to undertake (or display) a meta-analysis only if we judge participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful. Unless good evidence shows homogeneous effects across trials, we will primarily summarise low risk of bias data using a random-effects model (Wood 2008). We will interpret random-effects meta-analyses with due consideration to the whole distribution of effects and present a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval needs at least three

trials to be calculated and specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events, such as event rates below 1%, we will use Peto's OR method provided that there is no substantial imbalance between intervention and comparator group sizes and intervention effects are not exceptionally large. In addition, we will also perform statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and we plan to carry out the following subgroup analyses including investigation of interactions (Altman 2003).

- Gender: we expect men and women to respond differently to the management.
- Age: the risk of hypoglycaemia is higher among those who are older. As such, we will use 60 years as the cut-off age.
- Trial location: as Ramadan falls during the summer period, individuals fasting in countries located in the Northern hemisphere will be required to fast for up to 19 hours. This is expected to increase the risk of hypoglycaemia in these countries as opposed to trials conducted in tropics or Southern hemisphere.
- Treatment group: in individuals who use insulin, the risk of hypoglycaemia and weight gain can be higher compared to those who are on oral glucose-lowering agents.

Sensitivity analysis

We plan to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting analysis to the following.

- Published trials.
- Effect of risk of bias, as specified in the [Assessment of risk of bias in included studies](#) section.
- Very long or large trials to establish the extent to which they dominate the results.
- Using the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other), or country.

We will also test the robustness of results by repeating the analyses using different measures of effect size (RR, OR, etc.) and different statistical models (fixed-effect and random-effects models).

Certainty of the evidence

We will present the overall certainty of the evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related to internal validity (risk of bias,

inconsistency, imprecision, publication bias) and external validity, such as directness of results. Two review authors (NML and RS) will independently assess the certainty of the evidence for each outcome. We will resolve any differences in opinion by discussion or consulting a third review author (SWHL).

We will include an appendix entitled 'Checklist to aid consistency and reproducibility of GRADE assessments', to help with standardisation of the 'Summary of findings' tables (Meader 2014). Alternatively, we will use the GRADEpro Guideline Development Tool (GDT) software and will present evidence profile tables as an appendix (GRADEproGDT 2015). We will present results for the outcomes as described in the [Types of outcome measures](#) section. If meta-analysis is not possible, we will present the results in a narrative format in the 'Summary of findings' table. We will justify all decisions to downgrade the quality of trials using footnotes, and we will make comments to aid the reader's understanding of the Cochrane Review where necessary.

'Summary of findings' table

We will present a summary of the evidence in a 'Summary of findings' table. This will provide key information about the best estimate of the magnitude of the effect, in relative terms and as absolute differences, for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. We will create the 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017), and will use Review Manager 5 table editor (RevMan 2014). We will report the following outcomes, listed according to priority.

- Hypoglycaemic episodes
- Health-related quality of life
- Adverse events other than hypoglycaemic episodes
- All-cause mortality
- Treatment satisfaction (including satisfaction with the intervention)
- HbA1c
- Socioeconomic effects.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Search strategies

MEDLINE (Ovid SP)

1. (ramadan* or ramadhan*).tw.
 2. (religio* adj3 (fast or fasting)).tw.
 3. or/1-2
 4. exp Diabetes Mellitus, Type 2/
 5. (MODY or NIDDM or T2DM or T2D).tw.
 6. diabet*.tw.
 7. or/4-6
 8. 3 and 7
 - [9-19: *Cochrane Handbook 2008 RCT filter - sensitivity max. version*]
 9. randomized controlled trial.pt.
 10. controlled clinical trial.pt.
 11. randomi?ed.ab.
 12. placebo.ab.
 13. drug therapy.fs.
 14. randomly.ab.
 15. trial.ab.
 16. groups.ab.
 17. or/9-16
 18. exp animals/ not humans/
 19. 17 not 18
 20. 8 and 19
 - [21: *Wong 2006- systematic reviews filter - Spec version*]
 21. cochrane database of systematic reviews.jn. or search*.tw. or meta analysis.pt. or medline.tw. or systematic review.tw
 22. 8 and 21
 23. 20 or 22
-

Appendix 2. 'Risk of bias' assessment

'Risk of bias' domains

Random sequence generation (selection bias due to inadequate generation of a randomised sequence)

For each included trial, we will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups

- Low risk of bias: the trial authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person performed this who was not otherwise involved in the trial. We will consider the use of the minimisation technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process.
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on

(Continued)

hospital or clinic record number; allocation by judgment of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment)

We will describe for each included trial the method used to conceal allocation to interventions prior to assignment and we will assess whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, internet-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We will also evaluate trial baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgment for selection bias (Corbett 2014). Chance imbalances may also affect judgments on the risk of attrition bias. In the case of unadjusted analyses, we will distinguish between trials that we rate as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and trials that we judge as being at low risk of bias on the basis of baseline similarity alone (Corbett 2014). We will reclassify judgements of unclear, low or high risk of selection bias as specified in Appendix 3.

Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the trial)

We will evaluate the risk of detection bias separately for each outcome (Hróbjartsson 2013). We will note whether endpoints were self-reported, investigator-assessed or adjudicated outcome measures (see below)

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judge that the outcome is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the trial does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of trial participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment)

We will evaluate the risk of detection bias separately for each outcome (Hróbjartsson 2013). We will note whether endpoints were self-reported, investigator-assessed or adjudicated outcome measures (see below)

- Low risk of bias: blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judge that the outcome measurement is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias due to amount, nature or handling of incomplete outcome data)

For each included trial or each outcome, or both, we will describe the completeness of data, including attrition and exclusions from the analyses. We will state whether the trial reported attrition and exclusions, and report the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We will also note if the trial reported the reasons for attrition or exclusion and whether missing data were balanced across groups or were related to outcomes. We will consider the implications of missing outcome data per outcome such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between trial arms)

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.

(Continued)

- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias; the trial did not address this outcome.
- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes enough to induce clinically-relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting)

We will assess outcome reporting bias by integrating the results of the appendix 'Matrix of trial endpoints (publications and trial documents)' (Boutron 2014; Jones 2015; Mathieu 2009), with those of the appendix 'High risk of outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) classification' (Kirkham 2010). This analysis will form the basis for the judgement of selective reporting

- Low risk of bias: the trial protocol was available and all the trial's prespecified (primary and secondary) outcomes that were of interest to this review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all the trial's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review were reported incompletely so that we cannot enter them in a meta-analysis; the trial report failed to include results for a key outcome that we would expect to have been reported for such a trial (ORBIT classification).

Other bias

- Low risk of bias: the trial appears to be free from other sources of bias.
- Unclear risk of bias: there was insufficient information to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the trial had a potential source of bias related to the specific trial design used; the trial was claimed to be fraudulent; or the trial had some other serious problem.

Appendix 3. Selection bias decisions

Selection bias decisions for trials that reported unadjusted analyses: comparison of results obtained using method details alone versus results obtained using method details and trial baseline information^a

Reported randomisation and allocation concealment methods	Risk of bias judgement using methods reporting	Information gained from study characteristics data	Risk of bias using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable (s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk

(Continued)

		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable (s)	Unclear risk^b
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables ^c	Low risk
		No baseline details	Unclear risk
Sequence is not truly randomised or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable (s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables ^c	Unclear risk
		No baseline details	High risk
<p>^aTaken from Corbett 2014; judgements highlighted in bold indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias compared with using methods reporting alone.</p> <p>^bImbalance was identified that appears likely to be due to chance.</p> <p>^cDetails for the remaining important prognostic variables are not reported</p>			

CONTRIBUTIONS OF AUTHORS

All review authors contributed to, read and approved the final protocol draft.

DECLARATIONS OF INTEREST

Shaun Wen Huey Lee (SWHL): no known conflicts of interest.

Nai Ming Lai (NML): no known conflicts of interest.

Won Sun Chen (WSC): no known conflicts of interest.

Renukha Sellappans (RS): no known conflicts of interest.

NOTES

We have based parts of the [Methods](#), as well as [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#) of this Cochrane Protocol on a standard template established by the CMED Group.