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A web-based intervention to reduce psychological barriers to insulin therapy among adults with non-insulin-treated type 2 diabetes: study protocol for a two-armed randomised controlled trial of 'Is Insulin Right for Me?'

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Abstract

Introduction Psychological barriers to insulin therapy are associated with the delay of clinically indicated treatment intensification for people with type 2 diabetes (T2D), yet few evidence-based interventions exist to address these barriers. We describe the protocol for a randomised controlled trial (RCT) examining the efficacy of a novel, theoretically-grounded, psycho-educational, web-based resource designed to reduce psychological barriers to insulin among adults with non-insulin treated T2D: *"Is insulin right for me?"*.

Methods and analysis Double-blind, parallel group RCT. A target sample of N=392 participants (n=196/arm) will be randomised (1:1) to *"Is insulin right for me?"* (intervention) or widely available online resources (control). Eligible participants include adults (18-75 years), residing in Australia, currently taking oral hypoglycaemic agents to manage T2D. They will be primarily recruited via invitations and reminders from the national diabetes registry (from a purposefully selected sample of N≥12,000). Exclusion criteria: experience of self-administered injectable; previously enrolled in pilot RCT; "very willing" to start insulin as baseline. Outcomes will be assessed via online survey at two weeks and six months. Primary outcome Between-group: difference in mean negative insulin treatment appraisal scores (ITAS Negative) at two-week and six-month follow-up. Secondary outcomes: Between-group differences in mean positive insulin appraisals (ITAS Positive) and percentage difference in intention to commence insulin at follow-up time-points. All data analyses will be conducted according to the intention-to-treat principle.

Ethics and dissemination Deakin University Human Research Ethics Committee (2020-073). Dissemination via peer-reviewed journals, conferences and a plain-language summary.

Trial registration Australian and New Zealand Clinical Trials Registry ACTRN12621000191897

Strengths and limitations of this study

- *'Is insulin right for me?'* is the first self-directed, theoretically-grounded web-based intervention targeting salient psychological barriers to insulin.
- This fully-powered randomised controlled trial will provide evidence of the impact and acceptability of *'Is insulin right for me?'*, to reduce negative insulin appraisals among adults with non-insulin-treated type 2 diabetes (T2D) and increase intention to initiate insulin.
- Limitations include the self-selected sample which may lead to an under-representation of those hardest to reach or most at need (i.e. those not at all willing to commence insulin).
- If effective at changing attitudes and intentions, then examination of the intervention's impact on actual timely insulin uptake and feasibility of implementation within clinical care will be warranted.

Introduction

Type 2 diabetes (T2D) is a progressive condition that requires timely adjustment of treatment to achieve and maintain optimal glucose outcomes (1-3), and prevent or delay the onset of micro and macrovascular complications (4, 5). A staged approach to pharmacological management of glucose in T2D is recommended (1-3), including early consideration and initiation of insulin where glycaemic outcomes are above target (typically HbA1c >7%,53 mmol/mol (2)) despite maximal dose of non-insulin medicines. However, vast literature suggests that treatment adjustment, including insulin initiation, is often delayed well beyond the point of clinical need (6, 7). For example, a large-scale (N=>80,000), retrospective study conducted in the UK, identified HbA1c at insulin initiation for people with T2D was ≥8.7% (72 mmol/mol) with a median time until insulin initiation of ≥6 years (8). Finally, a recent Australian primary care based prospective study identified that, among adults with T2D for whom insulin was clinically indicated (HbA1c ≥7.5%/58mmol/mol, with maximal oral therapy), receiving usual care, only 31% had initiated insulin within 24 months (9, 10).

Reasons for the delay of treatment intensification are multifaceted (7, 11, 12), and effective interventions targeting barriers to insulin use are required (13-15). At a systemic or health professional level, promising results have been shown using multi-disciplinary models of care (e.g. an enhanced practice nurse role within primary care setting (9)), effective consultation strategies (e.g. collaborative approach to care (16)), and insulin-specific structured education programs (17, 18). However, there is a parallel need for interventions which directly target the psychological barriers (negative beliefs and attitudes) to insulin held by the person with T2D. Our prior research demonstrated, independent of an optimised model of primary care ('stepping up'), attitudes toward insulin were associated with hypothetical willingness to initiate insulin, which, in turn predicted actual insulin use 12 months later (14, 19). Elsewhere, qualitative research with people with T2D attending an insulin-specific education program identified an unmet need for psychological barriers to insulin to be addressed appropriately (20). Furthermore, unaddressed negative insulin appraisals may have long-lasting impact on the optimal use of insulin and/or emotional wellbeing following insulin initiation (21-23). Such psychological barriers to insulin use include, for example, worries about performing injections, potential pain and side effects, as well as feelings of guilt and self-blame about the onset of the condition and/or the need for treatment progression (24).

Few evidence-based interventions targeting psychological barriers to insulin have been developed and fewer still are evaluated adequately, or implemented beyond research studies (17, 25, 26). Furthermore, preliminary data from relevant clinic-based and insulin starts group-education interventions suggest low intervention uptake among people with T2D (17, 26). In addition to common barriers to outpatient clinic and structured education program attendance discussed elsewhere (27, 28), this low uptake may be in part due to individuals concern that participation would lead to insulin acceptance (26). Furthermore, health professionals report limited time and resources to facilitate insulin starts (12), and express concerns about the added burden of intervention delivery on their already limited time (26). Effective interventions that complement clinical care (but are not reliant on a health professional for delivery) have the potential to be acceptable to both people with T2D and their health professionals.

Given the sheer size of the population with T2D, the potential for scalable implementation is also an important consideration. The internet may be an ideal platform to reach those with T2D with concerns about insulin, as it also allows for anonymity in information seeking. One third of Australian adults with T2D and suboptimal HbA1c report seeking online health information in a past 12 period (29). Further, online interventions for the management of T2D with clear theoretical groundings and

based on behaviour change techniques show favourable outcomes (30). While peak health bodies publish resources online about T2D treatments, these materials are not typically theoretically informed, do not use evidence-based behaviour change techniques (31, 32), and are rarely developed in consultation with, or evaluated among, people with T2D. Further, these resources are rarely targeted at addressing salient psychological barriers to treatment use.

In line with UK Medical Research Council (MRC) guidance for developing and evaluating complex intervention, we developed a theoretically-grounded, psycho-educational, web-based resource for people with non-insulin-treated T2D designed to reduce salient psychological barriers to insulin therapy: '*Is insulin right for me*?' (33). A pilot study demonstrated feasibility of a two-arm randomised controlled trial (RCT) design to test intervention efficacy, compared with widely available online informational resources, as well as acceptability of the intervention among adults with T2D (34).

This protocol describes the design of a double-blinded, parallel group, individually randomised controlled trial (two-arms, 1:1 ratio), comparing *'Is insulin right for me?'* (intervention) with widely available online text-based resources about insulin (control) among adults with non-insulin-treated T2D. We hypothesise an immediate (two weeks) and sustained (six months) positive effect of the intervention, compared to control, on negative insulin appraisals. We also expect the intervention to be acceptable to users and to be associated with immediate and sustained improvement in positive insulin appraisals and hypothetical willingness to begin insulin therapy.

Methods and analysis

Study setting

Participation in this Australian study, including provision of informed content, data collection and intervention exposure, is completely online, using personal computers/mobile devices.

Participants and recruitment

Potential participants will be enrolled in the study only if they meet all the inclusion criteria and none of the exclusion criteria. Inclusion criteria: aged 18 to 75 years; diagnosed with T2D; use of oral hypoglycaemic agents (OHAs); able to read/write in English and capable of providing informed consent; residing in Australia; access to an internet-enabled computer or tablet device for the duration of the study. Exclusion criteria: diagnoses of diabetes other than T2D; current or prior experience of self-administered injectable treatment for any illness or condition (including diabetes); unable to read/write in English; unable to use/access internet-enabled devices; enrolled as a participant in the pilot RCT (34); reports being "very willing" to initiate insulin therapy (measured using a single-item "hypothetical willingness" questionnaire), i.e. rendering it impossible to record improvement in this outcome measure.

The primary method of recruitment will be via invitation from the National Diabetes Services Scheme (NDSS). In total, ≥12,000 NDSS registrants (stratified by state) who have previously consented to being contacted about research opportunities will be invited to take part either via email (n=10,000) or postal mail (n=2,000) as per the registrants preferred method of contact. The NDSS is an Australian government initiative, administered by Diabetes Australia. The NDSS registry includes over 1.2 million Australians with T2D, and is considered to be one of the most comprehensive and up-to-date diabetes prevalence datasets in Australian (35). The research team will not have access to NDSS registrants' details unless they make contact/take part in the study, and the NDSS will not be notified of participating registrants. The total number of invited registrants was selected based on adoption of a conservative response rate of 8% (36), and an expected 46% translation from consent to enrolled participant (as seen in the pilot RCT; (34)). Invited NDSS registrants will receive an invitation reminder via e-mail or postal mail two weeks following first

contact. If our target sample size is not reached within four weeks of the initial invitation, a second NDSS e-mail/mailout will be sent until our target sample size is reached or the two-month recruitment period has concluded. The number of registrants contacted and method (e-mail vs. mail) for subsequent recruitment efforts will be informed by the success rate from the original invitation (i.e. percentage enrolled reporting hearing about the study via email or mail invitation). The study will also be advertised online via the researchers' affiliated professional websites and social media accounts, and a study flyer will be circulated to diabetes researcher and health professional networks.

Study procedure

The schedule of enrolment, intervention and assessment is detailed in Figure 1. Study recruitment will be open for a maximum of two months or until sample size (enrolled) is reached. Participation (from study entry to exit) will be for a duration of six months. Study advertisements will direct potential participants to the study website (hosted by Qualtrics™) to access the Plain Language Statement, provide informed consent, and complete screening questions online. Eligibility will be determined automatically based on responses. Eligible participants will be directed immediately to complete an online baseline survey, and, following submission, will be allocated at random to one of two study arms. Randomised participants will receive an email including details about how to access the relevant online resources for their study arm. For participants allocated to the intervention group, this will include a unique username and password enabling access to the resource (at their convenience) within the following two-week period. One week following allocation, participants will receive a reminder email to access/log into the resource. Participants will be sent an email with a link to the online follow-up survey at two weeks and six months following baseline. The two-week follow-up survey will be available for completion for two weeks, and the six-month follow-up survey will be available for completion for three weeks. Study end-point for all participants will be marked by either submission of the six-month follow-up survey (within 21 days of request), or non-submission at 22 days following the survey request.

Figure 1. Schedule of enrolment, interventions, and assessments.

		STUDY PERIOD			
		Enrolment		Post-allocation	
TIMEPOINT		***Screening***	**Baseline**	***Two weeks***	***Six months***
ENROLMENT:					
Informed consent		X			
Eligibility screen		X			
Randomisation			X		
INTERVENTIONS:					
Intervention: Is insulin right for me?			→	→	
Control			→	→	
ASSESSMENTS:					
Contact information	Name*, email address*	X		X	X
Pilot	Participation in the pilot study: yes/no*	X			
Recruitment	Referral method (e.g. NDSS invite)	X			
Demographics	Age*, gender*, country of residence*	X			
	Country of birth, primary language, relationship status, employment status, qualifications, postcode		X		
Diabetes	Diabetes type*, diabetes duration*, current diabetes management regimen*, prior use of self-administered injectable treatment*	X			
	Brand names of currently administered diabetes medications, most recent HbA1c (if known), frequency of self-monitoring of glucose (if any),		X		X
General health	Co-morbidities (kidney disease, retinopathy, neuropathy, heart disease, stroke, vascular disease, sexual dysfunction, other to be specified), weight and height		X		
Clinical discussion of insulin therapy	Recall of discussion/education about to insulin therapy in clinical setting; prior recommendation of insulin therapy by doctor		X		X

Previous information about insulin therapy	What information about insulin have you read		X		
Psychological insulin receptiveness	Hypothetical willingness to commence insulin (37)*	X		X	X
Attitudes towards insulin	Insulin Treatment Appraisal Scale: ITAS (38)		X	X	X
Knowledge	Diabetes-specific knowledge: Michigan Diabetes Research and Training Center's Revised Diabetes Knowledge Test: DKT-R (39)		X		
	Insulin-specific knowledge: Study specific items		X	X	X
Diabetes-specific distress	Problem Areas In Diabetes: PAID (40)		X	X	X
Illness perceptions	Brief Illness Perceptions Questionnaire: BIPQ (41)		X	X	X
Diabetes-specific self-efficacy	Confidence In (type 2) Diabetes Self-management scale: CIDS-2 (or insulin version at follow-up for participants commenced insulin (CIDS-1) (42)		X	X	X
Diabetes management satisfaction	Study specific item		X	X	X
Resource use and acceptability	Resource access (yes/no) If no: Reasons for not accessing If yes: User rating scale and feedback			X	
Further comments	Free-text box for participant to provide further feedback.			X	X

*compulsory questions for participation.

Randomisation and blinding

After baseline survey submission, participants will be stratified by gender and randomised to either the intervention or control arm using computer-generated, randomly permuted block sizes of four, six or eight. The randomisation sequence will be computer generated and the allocation will be fully concealed from both the investigators and participants. Upon randomisation, participants will receive an email from a researcher, independent of the study investigator team and who does not have access to the incoming survey data (except for participant ID, name, gender and email address), specifying access details to their allocated online resource. The statistician, participants, and investigator team will remained blinded to study arm allocation throughout data collection and analyses. The project manager (EEH), who will monitor incoming survey data, will be blinded from study arm allocation except where a participant self-identifies study arm allocation within the follow up surveys (e.g. in a free-text response box). Any breaches will be recorded and reported with the main findings.

Intervention

Intervention group participants will receive access to a novel psycho-educational web-based resource '*Is insulin right for me?*'. The intervention was developed using a systematic process grounded in behaviour change theory and has been described elsewhere (33). In brief, eight salient psychological barriers to insulin therapy were identified via literature search. Each barrier (i.e., determinant of behaviour) was mapped to relevant domains of the Theoretical Domains Framework (TDF) (43). Determinants were then mapped onto behaviour change techniques (BCTs) considered relevant to overcoming the modifiable barriers (32, 43). Content responding to each barrier was developed by the investigator team (experts in health psychology, primary care medicine and diabetes education) and refined following consumer feedback (cognitive debriefing interviews, n=6) and external expert peer review (n=5) to ensure relevance for people with T2D and clinical accuracy.

The eight barriers targeted in the '*Is insulin right for me'* resource are phrased as common questions, with one barriers/question per website page (See Table 1). The resource home page lists all eight barriers/questions as well as a preview (a key summary statement that responds to the question and content overview). For each barrier, each active intervention is presented on a separate webpage, (200-500 words; 5-minute read) to facilitate user engagement. In addition, the resource includes information about the key benefits of insulin therapy: (1) that it lowers blood glucose levels; (2) can lower your risk of long-term health complications; (3) can make you feel better; and (4) can make managing your diabetes more flexible. The lesser focus on benefits than barriers is due to the evidence that most people with T2D experience / report barriers to insulin therapy despite endorsing benefits (14, 19). Finally, the resource also provides links to other resources about T2D and insulin available from the NDSS, and study information.

Table 1. Description of the eight barriers targeted in the '*Is insulin right for me'* resource

Barrier (Question)	**Resource aim (using behaviour change theory)**	**Format of delivery**
Does insulin mean my diabetes is more serious?	• Challenge beliefs: Insulin therapy can be clinically recommended at any time • Shape knowledge: Provide information about the role of insulin • Motivate: Diabetes is always serious	Interactive quiz; video depicting progressive nature of T2D (imagery and text), imagery and personal quote

Do insulin injections cause complications?	• Shape knowledge: Provide information about diabetes complications risk factors • Motivate: Acknowledge where this belief comes from. Validate concerns	Text; imagery and personal quote
Is it my fault I need to inject insulin?	• Identification of self as role model: 'You are doing this for yourself, insulin is a good thing' • Restructuring the social environment: being prepared for how others may react • Encouragement and support: Sharing how you feel with others	Text; case study (with audio recording); statistic; and personal quote
Will I gain weight?	• Shaping knowledge: Many people gain a small amount of weight when they commence insulin therapy. There are things that you can do to prevent unhealthy weight gain • Motivate: Acknowledge and validate fear • Salience of side effect: for many, weight gain is small	Interactive quiz; text; imagery and personal quote
Will injecting hurt?	• Shaping beliefs: Dispel myths • Manage expectations: Information and strategies to alleviate and minimise discomfort • Demonstration: of a person injecting insulin • Encouragement: to discuss insulin therapy and any concerns with a health professional • Imagery: small/fine needles & site of the injection	Text; demonstration of injecting insulin; imagery and personal quote
What about hypos?	• Shape knowledge: Frequency/severity of hypos • Motivate: Acknowledge/validate fears 'having concerns about hypos is natural'. • Reduce emotional valence of the fear: Low risk of having a severe hypo. Support is available	Interactive quiz; text; imagery and personal quote
Will injecting insulin be a burden?	• Increase knowledge: You can take insulin with you wherever you go • Increase self-efficacy: The changes you need to make are minimal and you can handle them. • Weigh pros versus cons: Insulin can make management of diabetes easier	Text and personal quote
What will others think of me?	• Identification of self as role model: 'You are doing this for yourself, insulin is a good thing' • Restructuring the social environment: being prepared for how others may react	Case studies with examples (with audio recording); text; and personal quote

	• Encouragement and support: Start a 'safe' conversation to share how you feel with others	

Control group

Control arm participants will be directed to a static webpage including links to publicly available text-based NDSS factsheets, including: "Insulin" and "Medication for type 2 diabetes". The control group webpage also includes links to further information about the study and research team (consistent with intervention arm).

Outcomes

The co-primary outcome measure are the difference in mean negative insulin appraisals, as measured by the Insulin Treatment Appraisal Scale (ITAS) Negative subscale score (38), between the intervention and control arm at two-week and six-month follow-up, adjusted by baseline scores. We hypothesise that, at two weeks, a statistically significant difference in mean ITAS Negative scores of ≥4 points (approximately 0.5 standard deviations) will be observed between the intervention and control arm, favouring the intervention arm; and that this difference will be sustained at six months.

Our secondary outcome measures are immediate and sustained between-arm differences in: a) positive insulin appraisals, as measured by ITAS Positive subscale score (38); and b) hypothetical willingness to begin insulin therapy, as measured by a single item (37). We hypothesise that, at two weeks and six months, a statistically significant between-group difference will be observed in:

1. mean ITAS Positive scores, adjusted for baseline scores, favouring the intervention arm;
2. the percentage of participants who respond 'not at all willing' (hypothetical willingness item). The intervention arm will be less likely to be 'not at all willing' compared to controls.

The following survey data will be examined by study arm for process evaluation purposes:

1. Clinical discussion and recommendation of insulin therapy, change in medications, and satisfaction with diabetes management at six-month follow up
2. Change in secondary psychosocial outcome scores at two-week and six-month follow up: diabetes-specific distress (PAID) (40), illness perceptions (BIPQ) (41), diabetes-specific self-efficacy (CIDS) (42), study-specific insulin-related knowledge questionnaire.
3. Diabetes-specific knowledge at baseline (DKT-R) (39).
4. Study-specific resource use and acceptability (study specific items) as two-week follow up.

Figure 1 details the self-reported demographic, clinical, psychosocial, and study-specific data to be collected and the time-points at which they are to be collected. In addition, website analytics data will be collected to assess protocol fulfilment with the intervention resource (i.e. proportion of 'enrolled' participants who accessed the *'Is insulin right for me?* website at least once). Various analytics (e.g. average number of online resource visits; time (minutes) spent on online resource; most commonly (frequency, %) viewed pages) will be examined to explore any relationship(s) between type/duration of content accessed and the study outcomes. Finally, number of views and average time spent watching two videos embedded in the intervention resource will be captured via YouTube.

Sample size

A minimum sample size of N=250 (n=125 per arm) is required to detect a minimally important difference of half a standard deviation in ITAS Negative Scores (38) between study arms, at 85%

power and 0.05 significance level using a two-sided test. Assuming a 20% attrition rate at two weeks (34) and a further 20% attrition at six months, the targeted sample size inflates to approximately N=392 (n=196 per arm). Overall, a 40% attrition rate is incorporated into our estimated sample size and replacements will not be made for losses to follow-up.

Data collection, management and analysis

Participant-reported data will be collected online via Qualtrics™, hosted through the Deakin University secure network. Consent, eligibility screening and baseline survey data will be collected in a single sitting (directed via study advertisement link), and an email will provide enrolled participants with a link to online follow-up surveys. The intervention website will require participant log-in, allowing for automatic collection of website usage data for each intervention participant via Google Analytics.

To improve participant retention and protocol compliance, trial participants will receive reminder emails to access/view the allocated online resource (sent to all participants two weeks following allocation. In addition, reminder emails will be sent at one week (and two weeks for six-month time-point) to participants who have yet to commence their online follow-up surveys. To aid recruitment and retention, participants who complete all three surveys (the baseline, two-week *and* six-month follow-up) will be entered into a prize draw to win one of 20 $100 e-gift vouchers.

Participants who do not access their allocated resource(s) will still be followed up until the end of the trial unless they withdraw from the trial. Participants who do not complete the two-week follow up survey will have 'missing data' at two weeks, but remain eligible to complete the six-month follow up survey. Participants who do not complete the six-month follow up survey within three weeks of receipt will have 'missing data' at six months. Participants with missing data at both follow-up time-points will be deemed 'lost to follow-up'.

Study data collected from withdrawn participants will be deleted, with the exception of basic de-identified sample characteristics (gender, age, diabetes duration), trial arm allocation, timing of withdrawal, and reason for withdrawal, where applicable.

Data storage

At study conclusion, survey data and website usage data (for intervention participants only) will be downloaded from Qualtrics and Google Analytics, respectively, and linked according to participant ID. Identifiable information (email, name) will be separated from study data and stored along with participant ID number in a password-encrypted excel spreadsheet. All data will be stored in a secure electronic file accessible only by the research team. In accordance with clinical trial regulations, data will be kept for a minimum of 15 years after study completion and then disposed by erasing of electronic files.

Statistical methods

Quantitative data analyses will be performed using Stata/SE 16.0 and/or IBM SPSS 26. Descriptive statistics will be used to describe participant baseline characteristics and psychological outcomes at each time point. Participant characteristics at baseline will be visually assessed by allocation for imbalance. The overall characteristics of the study cohort will be compared to those lost to follow-up.

An intention-to-treat (ITT) approach will be adopted whereby participants will be analysed according to the arm they were allocated to, and all participants will be included in the analysis. A linear mixed effects model will be used to estimate the difference in mean ITAS Negative scores between arms at

two weeks and six months using restricted maximum likelihood estimation. Treatment arm and all three time-points (baseline, two weeks and six months) will be included as fixed effects in the model. Random effects will be used to account for repeated participant measures. The outcome measure will be adjusted by the stratification factor (gender), as well as age, diabetes duration and education should these be imbalanced between the arms at baseline.

ITAS Positive Scores (secondary outcome), and continuous psychosocial process evaluation outcomes (e.g. PAID, BIPQ, CIDS) will be analysed using the same modelling approached described above. An ordinal logistic mixed effects model will be used to quantify between-arm differences in the willingness to begin insulin therapy (secondary outcome) at the various time points.

Generalised linear mixed effects models assume any missing data are missing at random. This assumption will be tested in a sensitivity analyses whereby a pattern mixture model will be used to determine whether study conclusions would change should the missing data not be missing at random.

Descriptive data will be used to explore trends in protocol fulfilment, website analytics and acceptability data, as well as medication changes and clinical discussion of insulin therapy at six months separately for each study arm.

Monitoring

Co-authors EHT and JS are the responsible investigators and will oversee the research project. During recruitment and data collection, the number of potential participants consenting, eligible and enrolled as well as dates of all participant encounters (i.e. enrolment; intervention access & reminder emails; survey access, reminder and closure) and survey completion will be monitored by EEH and communicated to investigator team. The primary funding body will be allowed access to all de-identified data from the study for audit purposes, if requested.

This research protocol does not include administration or manipulation of, or investigation of the effects of, any pharmacological or therapeutic goods. However, in line with the pharmacovigilance reporting requirements of the funding body, all survey data collected will be screened for adverse events that may be associated with the funding body's products and, in the event of the research team becoming aware of a potential adverse event, participants will be contacted (via email) and invited to respond to additional questions about this event (e.g. medication brand name, dose and timing, healthcare utilisation symptoms, other consequences). Non-response will not affect participation in the study proper. De-identified information obtained about the event will be submitted to the funder and, if relevant, the Australian Therapeutic Goods Administration.

Patient and public involvement

People with T2D were involved in the review and iterative refinement of the intervention content and design. This involved cognitive debriefing interviews with six adults with T2D to review draft content during intervention development, for which the findings and consequential refinements are detailed elsewhere (33, 34). In addition, user ratings and qualitative feedback were provided by 13 pilot RCT participants who were allocated to the intervention (34). Refinements made to the intervention following piloting included, for example, improving website navigation between barrier webpages and the addition of 'print-friendly' downloadable PDF content (34). People with T2D were not involved in the development of the study design, nor will they be involved in conduct of the study or dissemination of the study findings.

Ethics and dissemination

This trial received ethical approval Deakin University Human Research Ethics Committee (Ref: 2020-073). This study will be conducted in compliance with this protocol (version**:** SA-2017-11697; V2.2e 16 June 2020), which is registered with the Australian New Zealand Clinical Trials Registry (ACTRN: 12621000191897, registered Feb 23 2021). Note, this protocol was submitted for registration prior to recruitment of the first participant (Dec 10, 2020), though approved retrospectively following enrolment of the first participant (Jan 11 2021) and prior to last participant enrolment. Any changes to the protocol will be communicated to the human research ethics committee, funder, and trial register. Protocol registration will be updated with any approved amendments to the protocol, and protocol departures will be documented in any reports or manuscripts resulting from this study.

Potential participants view the study plain language form online (Appendix 1) and must indicate consent (by ticking a box) prior to participating. Participants are free to withdraw from the study at any time, and for any reason, prior to completion of data collection.

The findings will be prepared for academic presentation at scientific meetings and in peer-reviewed journals. A lay summary of findings will be published on the research team's website and disseminated via e-newsletter. Study findings will also be reported to the funding body.

De-identified data may be made available, upon request, to the funding body.

Discussion

This randomised controlled trial will provide high quality evidence regarding the efficacy and acceptability of a novel, web-based resource: *'Is insulin right for me?'*. Using best-practice intervention development principles and evaluation guidance (33, 34), the intervention was designed to reduce salient psychological barriers to insulin, which are extremely common among people with T2D and associated with deleterious delay of insulin uptake (14, 44). To our knowledge, this study will be the first fully-powered randomised controlled trial conducted to test the impact of any intervention specifically designed to address salient psychological barriers to insulin among adults with T2D reporting some level of psychological insulin resistance.

The described study will provide evidence of the acceptability of this web-based resource among Australians with T2D who report some level of psychological insulin resistance, which may inform real-world implementation strategies and further refinements as required. A potential limitation of this trial is the self-selection bias of the sample recruited via an invitation from the NDSS, which may not be representative of those most in need (i.e. those with a high HbA1c yet not at all willing to commence insulin) as well as linguistically diverse communities. If the intervention is shown to be efficacious, further research will be warranted to investigate its impact on timely insulin uptake (and consequently on HbA1c), as well as the feasibility of implementation in primary care settings among adults with T2D for whom treatment intensification is clinically indicated.

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Author contributions

EHT and JS conceived of the intervention and the described program of research. EHT and JS developed the study protocol, with input from all authors. EH, JS, TS and EHT led the development of the intervention, with contributions from JF, and VH. EHT was responsible for drafting the manuscript. All authors contributed to and approved the final manuscript.

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Competing interests statement

EHT has undertaken research funded by an unrestricted educational grant from Abbott Diabetes Care, AstraZeneca, and Sanofi; received speaker fees from Novo Nordisk and Roche to Australian Centre for Behavioural Research in Diabetes (ACBRD); and served on an advisory board for AstraZeneca. EEH has no conflicts of interest to disclose. JF has received unrestricted educational grants for research support from Roche, Sanofi, and Medtronic. TS serves on advisory boards for Novo Nordisk and Liva Health Care, and is currently on a EIT Health research grant held jointly with Roche Diagnostics. JS has served on advisory boards for Janssen, Medtronic, Roche Diabetes Care, and Sanofi Diabetes; her research group (Australian Centre for Behavioural Research in Diabetes [ACBRD]) has received honoraria for this advisory board participation and has also received unrestricted educational grants and in-kind support from Abbott Diabetes Care, AstraZeneca, Medtronic, Roche Diabetes Care, and Sanofi Diabetes. JS has also received sponsorship to attend educational meetings from Medtronic, Roche Diabetes Care, and Sanofi Diabetes, and consultancy income or speaker fees from Abbott Diabetes Care, AstraZeneca, Medtronic, Novo Nordisk, Roche Diabetes Care, and Sanofi Diabetes. All other authors have no conflicts of interest to declare.

Appendix 1. Plain Language Statement and Consent Form

Attitudes towards insulin therapy for people with type 2 diabetes

Plain Language Statement and Consent Form

Date: May 2020

Full Project Title: Development, Feasibility, and Efficacy of a Web-Based Intervention to Reduce Psychological Barriers to Insulin Therapy among Adults with Type 2 Diabetes (Stage 3: Full RCT)

Principal Investigators: Dr Elizabeth Holmes-Truscott and Professor Jane Speight, The Australian Centre for Behavioural Research in Diabetes (ACBRD), Deakin University

Associate Investigators: Dr Edith Holloway, ACBRD, Deakin University; Professor Timothy Skinner, Department of Rural Health, La Trobe University; Associate Professor John Furler, Department of General Practice, The University of Melbourne; Professor David O'Neal, St Vincent's Hospital, The University of Melbourne; and Dr Virginia Hagger, School of Nursing and Midwifery, Deakin University.

Dear participant,

You are invited to take part in this research project because you have type 2 diabetes, are aged between 18 and 75 years of age and take oral medication to manage your diabetes. In this study, we are investigating people's attitudes towards injecting insulin. We are also testing online resources about medications for type 2 diabetes. We want to know which resource(s) is the most useful for people with type 2 diabetes, who have questions or concerns about injecting insulin. Taking part involves exploring the web-based resource(s) and completing three online surveys over 6 months.

Below you can read further information about the study, so that you can decide if you would like to take part. Please take the time to read this information carefully. You can also print a copy of the PDF *(hyperlink to ethics approved version of the PLS inserted here)* or ask the

study team for a hard copy to be sent to you. Ask the study team questions about anything you don't understand or want to know more about.

If you consent to taking part in this study, please click the box at the end of this webpage.

What is the purpose of this research?

Insulin is very effective for lowering blood glucose levels. Your doctor may recommend injecting insulin if other medications are unable to keep your blood glucose within your target range. However, people with type 2 diabetes may have concerns or questions about starting insulin. The purpose of this study is to test whether web-based resource(s) are useful for people with type 2 diabetes who have questions or concerns about starting insulin injections. The findings of this research may be used to inform what online resources about medications are available for people with type 2 diabetes in the future. We expect a total of 392 adults with type 2 diabetes will take part in this study.

Who can take part?

You can take part in this study if you:

- have type 2 diabetes and are currently taking oral medication to manage your diabetes. If you are currently, or have in the past, used self-administered injectable treatment for any illness or condition (for example insulin) you are NOT eligible to take part in the study.
- are between 18 and 75 years of age
- are able to read and speak English
- currently live in Australia
- have access to the internet and a computer (desktop, laptop) or tablet

You are not eligible to take part if you participated in the associated Pilot Study (between October and December 2019): Development, Feasibility, and Efficacy of a Web-Based Intervention to Reduce Psychological Barriers to Insulin Therapy among Adults with Type 2 Diabetes (Stage 2: Pilot Study).

What does taking part involve?

Taking part in this study will involve:

- Accessing and viewing a web-based resource(s) about medications for type 2 diabetes. You will be asked to do this at least once (and as many times you like) over a 2-week period.
- Completing three online surveys. The first survey will be upon entry to the study, the second survey will be emailed to you two weeks later and the third survey will be emailed to you at 6-months.
- Each survey will take 20 minutes to complete.
- The survey will include questions about you (age, gender, education), your diabetes, attitudes and knowledge about insulin, your understanding about diabetes and some questions about how diabetes makes you feel.
- You will also be asked to provide your name and email address. This is so we can link each of your surveys together and look at any changes in your responses over time. Any information you share with us will remain confidential.

After you have completed the first online survey on entry into the study, you will be allocated to one of two groups. You will receive a link to one of two web-based resources on insulin and type 2 diabetes. You have a 50% chance of being assigned to each group (like tossing a coin). You will have two weeks to explore the resource(s) allocated to you. We will send you an e-mail reminder during the two-week period to look at the resources. You will then be sent follow-up surveys at 2 weeks and 6 months.

Taking part in this study does not involve any change to your diabetes management or changes to the medications you take.

Who is conducting this study?

Deakin University is conducting this study with funding from Sanofi-aventis Australia Pty Ltd (Sanofi). The study is coordinated by researchers (Principal Investigators) at The Australian Centre for Behavioural Research in Diabetes (ACBRD), a partnership for better health between Diabetes Victoria and Deakin University. The Principal Investigators take responsibility for the study. Participants will only be contacted by the research team including the principal investigators, the study project manager or research assistant.

Are there any benefits for me personally?

People take part in studies like this for many reasons. For example:

- Taking part offers an opportunity to learn about and inform new diabetes research;

- Taking part offers an opportunity to think about your diabetes and reflect on your experiences;
- Taking part in research will help us to help other people with diabetes (either now or in the future).

In addition, participants who complete the study (i.e., access the web-based resource(s) and complete all three surveys) will be entered into a prize draw to win one of 20 $100 department store gift cards that can be used at over 20 major retail stores in Australia.

Are there any risks to me?

No, we do not believe that this study will cause you any harm or put you at risk of harm. The study surveys include questions that may be sensitive or personal in nature (e.g. feelings about living with diabetes, income and employment status). However, we do not expect any question to cause you any distress. If you should become upset during the survey, you may stop completing the questions at any time. We encourage you to contact the researchers to discuss this. The researchers will be understanding and supportive. You have the right to refuse to answer any question that makes you uncomfortable.

If, as a result of participation, you do become distressed, you may wish to seek further information and support from beyondblue: Beyondblue – National Information Line Ph: [redacted] or visit: http://www.beyondblue.org.au/

If you have any questions about your diabetes following the survey, we encourage you to contact your health professional or to call the National Diabetes Services Scheme Helpline: [redacted].

Can I withdraw at any time?

Yes. You are free to withdraw from this study at any time. If you decide not to take part while completing an online survey, you can stop the survey and notify a member of the research team. Deciding not to take part (or to withdraw) will not affect your relationship with the ACBRD, Deakin University, Diabetes Victoria, or the study funder (Sanofi). If you withdraw from the study before, during, or immediately after you have completed the online surveys, we can remove any information you have shared from our analysis. However, once the study is closed your data will be de-identified and merged with other people's data. This means that you will not be able to withdraw the information you shared because we will not know which data are yours.

What will happen to my information?

Any information you share with us will remain strictly confidential. The survey data will be stored in a database via the Deakin University secure network. Only the research team will have access to the password protected data. Once we have collected all of the data and are ready to analyse the results, the survey responses will downloaded and de-identified. These files will not include any identifying information about you. Identifiable information (for example your email, name) will be stored in a password-encrypted excel spreadsheet. Any personal details you share about yourself (e.g. surname, contact details) for the purposes of enrolling you into the study will be destroyed (electronic files to be deleted) after you have completed the final survey. Safety follow-up interview data will be stored electronically (i.e. audio files). All data will be stored in a secure Deakin University computer file accessible only by the ACBRD research team. In accordance with government requirements, your data will be stored for at least fifteen (15) years following the publication of the results and then destroyed by erasing electronic files and shredding paper copies.

The overall results of the study may be published or presented in academic journals, at conferences, and in diabetes magazines and newsletters. Participants will be able to access any publications or reports resulting from the study on the ACBRD website (www.acbrd.org.au). No-one will be able to identify you from any of the information we publish or present. The study funder may request access to the de-identified data. These data will not include any information that could be used to identify you. We will take great care to protect your identity. Your privacy is very important to us.

Who is funding this project?

This project forms part of an Investigator Sponsored Study (SA-2017-11697) which is supported by Sanofi-aventis Australia Pty Ltd (Sanofi). Sanofi has no involvement in the study design, data analysis or interpretation and will not have any access to personally identifying information collected (e.g. contact details). De-identified study data may be shared with Sanofi, including survey results. Your personal and contact details will not be shared with Sanofi.

If you share with us (via the study surveys, e-mail or phone) any adverse events (safety issues) associated with therapeutic goods (e.g. medications) during your involvement with

this study, we are required to report these to Sanofi. This could include any adverse events associated with the funder's products. Therefore, all the data that we collect from you will be screened for adverse events that may be associated with medications you take now or have taken in the past. In the event that you report an adverse event, we will contact you and ask a small number of additional questions (e.g. medication brand, dose, symptoms etc). If you decide not to answer the questions, this will not affect your participation in the study.

In addition, the researchers will notify the Deakin University Human Research Ethics Committee (DUHREC) of any adverse incidents, events, reactions that have a possible causal relationship with this research.

Has this study been approved by an Ethics committee?

Yes. This study has been reviewed and approved by Deakin University's Human Research Ethics Committee (DUHREC), reference number 2020-073.

Who can I contact about this study?

If you would like further information or have any questions about the study, please contact:
Dr Elizabeth Holmes-Truscott (e: [redacted] t: [redacted]),

Professor Jane Speight (e: [redacted] t: [redacted]), or

Dr Edith Holloway (e: [redacted] t: [redacted]), at the ACBRD.
To find out more about the work of the ABCRD, you may like to visit the website: www.acbrd.org.au.

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:
The Human Research Ethics Office, Deakin University, 221 Burwood Highway, Burwood Victoria 3125, Telephone: [redacted], email: [redacted]. Please quote project number 2020-073.

Consent Form

Please tick the box at the bottom of the page to indicate your agreement with each statement.

- I have read and I understand the Plain Language Statement.
- I freely agree to participate in this project according to the conditions in the Plain Language Statement.
- I have access to a copy of the Plain Language Statement and Consent form to print and keep.
- I understand and consent to completing three online surveys: at entry into the study, two-weeks and 6-months later. I will also be invited to explore web-based resources about type 2 diabetes and injecting insulin.
- I understand that if I report any adverse events (safety issues) associated with therapeutic goods (e.g. medications) I will be contacted and asked a small number of additional questions. If I decide not to answer the questions, this will not affect my participation in the study.
- I understand that the research team will not reveal my identity or personal details to anyone outside the research team, including where information is published or presented in any public form about this research study.
- I understand that the research team or the study funders may use the information I share in a closely related project, or an extension of the current research project, and that this information will be de-identified.

☐ **I have read and understood the information above and agree to take part in this study.**

I am ready to start completing the Attitudes Towards Insulin Study

Withdrawal Form

To be used for participants who wish to withdraw from the project

Date: May 2020

Full Project Title: Development, Feasibility, and Efficacy of a Web-Based Intervention to Reduce Psychological Barriers to Insulin Therapy among Adults with Type 2 Diabetes (Stage 3: Full RCT)

Reference Number: 2020-073

**********IMPORTANT***********

Complete this form and return it to us only if you decide to WITHDRAW from the above-named study.

I wish to withdraw from participating in the study entitled 'Development, Feasibility, and Efficacy of a Web-Based Intervention to Reduce Psychological Barriers to Insulin Therapy among Adults with Type 2 Diabetes (Stage 3: Full RCT)'. I do not want to take part in any additional study activities ***and*** I do not want the information I have already provided to be included in any analysis or study publications. I understand that withdrawing the information I have already provided will not be possible after completion of the second survey. I understand that withdrawing from the study will not adversely affect my relationship with any of the organisations conducting this study. I understand that withdrawing from the study will not affect the care or treatment I receive from any health professionals.

Participant's name (please print)

.....

Participant's signature.....

Date.....

Dr Elizabeth Holmes-Truscott

The Australian Centre of Behavioural Research in Diabetes

570 Elizabeth St, Melbourne, VIC 3000

T: [redacted]

E: [redacted]

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Author response
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title: A web-based intervention to reduce psychological barriers to insulin therapy among adults with non-insulin-treated type 2 diabetes: study protocol for a two-armed randomised controlled trial of '*Is Insulin Right for Me?*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	ACTRN12621000091897
	2b	All items from the World Health Organization Trial Registration Data Set	See trial registration details.
Protocol version	3	Date and version identifier	**Protocol number, version, date:** SA-2017-11697; V2.2e 16 June 2020 (See title page & main text: '*Ethics and dissemination'*
Funding	4	Sources and types of financial, material, and other support	See *Funding statement.*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	See *Authorship contribution statement*
	5b	Name and contact information for the trial sponsor	See *Funding statement*

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See *Funding statement*
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	See *Funding statement*; *Authorship contribution statement*, and; main text (*Monitoring*)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	See *Introduction,* from paragraph 3
	6b	Explanation for choice of comparators	See *Introduction,* paragraph 4, and final paragraph.
Objectives	7	Specific objectives or hypotheses	See *Introduction,* final paragraph.
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	See *Introduction,* final paragraph.
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	See *Methods and analysis, Study setting*
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	See *Methods and analysis, Participants and recruitment*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	See *Methods and analysis, Intervention* See *Methods and analysis, Control group*
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	See *Methods and analysis, Data collection, management and analysis,* second paragraph. See *Methods and analysis, Outcomes,* final paragraph.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	See *Methods and analysis, Outcomes*
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See *Methods and analysis, Study procedure, Figure 1.*
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	See *Methods and analysis, Sample size*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	See *Methods and analysis, participants and recruitment*
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	See *Methods and analysis, Randomisation and blinding*

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	See *Methods and analysis, Randomisation and blinding*
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	See *Methods and analysis, Randomisation and blinding*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	See *Methods and analysis, Randomisation and blinding*
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	See *Methods and analysis, Randomisation and blinding*
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	See *Methods and analysis, Outcomes* See *Methods and analysis, Study procedure, Figure 1.*
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	See *Methods and analysis, Data collection, management and analysis,* second paragraph.

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	See *Methods and analysis, Data collection, management and analysis, Data storage.*.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	See *Methods and analysis, Data collection, management and analysis, Statistical methods*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	See *Methods and analysis, Data collection, management and analysis, Statistical methods*
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	See *Methods and analysis, Data collection, management and analysis, Statistical methods*
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	See *Methods and analysis, Data collection, management and analysis, Monitoring.*
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	See *Methods and analysis, Monitoring.*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A The primary funding body will be allowed access to all de-identified data from the study for audit purposes, if requested.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	See *Ethics and dissemination: This* trial received ethical approval Deakin University Human Research Ethics Committee (Ref: 2020-073).
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	See *Ethics and dissemination.*
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	See *Ethics and dissemination.*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	See *Methods and analysis, Data collection, management and analysis*
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	See *Competing interests statement*
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	See *Methods and analysis, Data collection, management and analysis, Data Storage.* *See Ethics and dissemination:* De-identified data may be made available, upon request, to the funding body.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	See *Ethics and dissemination.*
	31b	Authorship eligibility guidelines and any intended use of professional writers	See *Authorship contribution statement.*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A web-based intervention to reduce psychological barriers to insulin therapy among adults with non-insulin-treated type 2 diabetes: study protocol for a two-armed randomised controlled trial of 'Is Insulin Right for Me?'

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Abstract

Introduction: Psychological barriers to insulin therapy are associated with the delay of clinically indicated treatment intensification for people with type 2 diabetes (T2D), yet few evidence-based interventions exist to address these barriers. We describe the protocol for a randomised controlled trial (RCT) examining the efficacy of a novel, theoretically-grounded, psycho-educational, web-based resource designed to reduce psychological barriers to insulin among adults with non-insulin treated T2D: *"Is insulin right for me?"*.

Methods and analysis: Double-blind, parallel group RCT. A target sample of N=392 participants (n=196/arm) will be randomised (1:1) to *"Is insulin right for me?"* (intervention) or widely available online resources (control). Eligible participants include adults (18-75 years), residing in Australia, currently taking oral hypoglycaemic agents to manage T2D. They will be primarily recruited via invitations and reminders from the national diabetes registry (from a purposefully selected sample of N≥12,000). Exclusion criteria: experience of self-administered injectable; previously enrolled in pilot RCT; "very willing" to start insulin as baseline. Outcomes will be assessed via online survey at two weeks and six months. Primary outcome Between-group: difference in mean negative insulin treatment appraisal scores (ITAS Negative) at two-week and six-month follow-up. Secondary outcomes: Between-group differences in mean positive insulin appraisals (ITAS Positive) and percentage difference in intention to commence insulin at follow-up time-points. All data analyses will be conducted according to the intention-to-treat principle.

Ethics and dissemination: Deakin University Human Research Ethics Committee (2020-073). Dissemination via peer-reviewed journals, conferences and a plain-language summary.

Trial registration: Australian and New Zealand Clinical Trials Registry ACTRN12621000191897

Strengths and limitations of this study

- *'Is insulin right for me?'* is the first self-directed, theoretically-grounded web-based intervention targeting salient psychological barriers to insulin.
- This fully-powered randomised controlled trial will provide evidence of the impact of *'Is insulin right for me?'* to reduce negative insulin appraisals and increase intention to initiate insulin among adults with non-insulin-treated type 2 diabetes (T2D) recruited via a national diabetes registry.
- Comprehensive data collection, including demographic and clinical characteristics, psychosocial outcomes, and website analytics, will enable process evaluation analyses.
- Limitations include the self-selected sample, which may lead to an under-representation of those hardest to reach or most at need (i.e. those not at all willing to commence insulin).
- Further, this study is not designed to identify the intervention's impact on actual timely insulin uptake nor feasibility of implementation within clinical care.

Introduction

Type 2 diabetes (T2D) is a progressive condition that requires timely adjustment of treatment to achieve and maintain optimal glucose outcomes (1-3), and prevent or delay the onset of micro and macrovascular complications (4, 5). A staged approach to pharmacological management of glucose in T2D is recommended (1-3), including early consideration and initiation of insulin where glycaemic outcomes are above target (typically HbA1c >7%,53 mmol/mol (2)) despite maximal dose of non-insulin medicines. However, vast literature suggests that treatment adjustment, including insulin initiation, is often delayed well beyond the point of clinical need (6, 7). For example, a large-scale (N=>80,000), retrospective study conducted in the UK, identified HbA1c at insulin initiation for people with T2D was ≥8.7% (72 mmol/mol) with a median time until insulin initiation of ≥6 years (8). Finally, a recent Australian primary care based prospective study identified that, among adults with T2D for whom insulin was clinically indicated (HbA1c ≥7.5%/58mmol/mol, with maximal oral therapy), receiving usual care, only 31% had initiated insulin within 24 months (9, 10).

Reasons for the delay of treatment intensification are multifaceted (7, 11, 12), and effective interventions targeting barriers to insulin use are required (13-15). At a systemic or health professional level, promising results have been shown using multi-disciplinary models of care (e.g. an enhanced practice nurse role within primary care setting (9)), effective consultation strategies (e.g. collaborative approach to care (16)), and insulin-specific structured education programs (17, 18). However, there is a parallel need for interventions which directly target the psychological barriers (negative beliefs and attitudes) to insulin held by the person with T2D. Our prior research demonstrated, independent of an optimised model of primary care ('stepping up'), attitudes toward insulin were associated with hypothetical willingness to initiate insulin, which, in turn predicted actual insulin use 12 months later (14, 19). Elsewhere, qualitative research with people with T2D attending an insulin-specific education program identified an unmet need for psychological barriers to insulin to be addressed appropriately (20). Furthermore, unaddressed negative insulin appraisals may have long-lasting impact on the optimal use of insulin and/or emotional wellbeing following insulin initiation (21-23). Such psychological barriers to insulin use include, for example, worries about performing injections, potential pain and side effects, as well as feelings of guilt and self-blame about the onset of the condition and/or the need for treatment progression (24).

Few evidence-based interventions targeting psychological barriers to insulin have been developed and fewer still are evaluated adequately, or implemented beyond research studies (17, 25, 26). Furthermore, preliminary data from relevant clinic-based and insulin starts group-education interventions suggest low intervention uptake among people with T2D (17, 26). In addition to common barriers to outpatient clinic and structured education program attendance discussed elsewhere (27, 28), this low uptake may be in part due to individuals concern that participation would lead to insulin acceptance (26). Furthermore, health professionals report limited time and resources to facilitate insulin starts (12), and express concerns about the added burden of intervention delivery on their already limited time (26). Effective interventions that complement clinical care (but are not reliant on a health professional for delivery) have the potential to be acceptable to both people with T2D and their health professionals.

Given the sheer size of the population with T2D, the potential for scalable implementation is also an important consideration. The internet may be an ideal platform to reach those with T2D with concerns about insulin, as it also allows for anonymity in information seeking. One third of Australian adults with T2D and suboptimal HbA1c report seeking online health information in a past 12 period (29). Further, online interventions for the management of T2D with clear theoretical groundings and

based on behaviour change techniques show favourable outcomes (30). While peak health bodies publish resources online about T2D treatments, these materials are not typically theoretically informed, do not use evidence-based behaviour change techniques (31, 32), and are rarely developed in consultation with, or evaluated among, people with T2D. Further, these resources are rarely targeted at addressing salient psychological barriers to treatment use.

In line with UK Medical Research Council (MRC) guidance for developing and evaluating complex intervention, we developed a theoretically-grounded, psycho-educational, web-based resource for people with non-insulin-treated T2D designed to reduce salient psychological barriers to insulin therapy: '*Is insulin right for me*?' (33). A pilot study demonstrated feasibility of a two-arm randomised controlled trial (RCT) design to test intervention efficacy, compared with widely available online informational resources, as well as acceptability of the intervention among adults with T2D (34).

This protocol describes the design of a double-blinded, parallel group, individually randomised controlled trial (two-arms, 1:1 ratio), comparing *'Is insulin right for me?'* (intervention) with widely available online text-based resources about insulin (control) among adults with non-insulin-treated T2D. We hypothesise an immediate (two weeks) and sustained (six months) positive effect of the intervention, compared to control, on negative insulin appraisals. We also expect the intervention to be acceptable to users and to be associated with immediate and sustained improvement in positive insulin appraisals and hypothetical willingness to begin insulin therapy.

Methods and analysis

Study setting

Participation in this Australian study, including provision of informed content, data collection and intervention exposure, is completely online, using personal computers/mobile devices.

Participants and recruitment

Potential participants will be enrolled in the study only if they meet all the inclusion criteria and none of the exclusion criteria. Inclusion criteria: aged 18 to 75 years; diagnosed with T2D; use of oral hypoglycaemic agents (OHAs); able to read/write in English and capable of providing informed consent; residing in Australia; access to an internet-enabled computer or tablet device for the duration of the study. Exclusion criteria: diagnoses of diabetes other than T2D; current or prior experience of self-administered injectable treatment for any illness or condition (including diabetes); unable to read/write in English; unable to use/access internet-enabled devices; enrolled as a participant in the pilot RCT (34); reports being "very willing" to initiate insulin therapy (measured using a single-item "hypothetical willingness" questionnaire (35)), i.e. rendering it impossible to record improvement in this outcome measure.

The primary method of recruitment will be via invitation from the National Diabetes Services Scheme (NDSS). A random sample of ≥12,000 NDSS registrants, aged 18-75 years with non-insulin-treated T2D, who have previously consented to being contacted about research opportunities will be invited to take part either via email (n=10,000) or postal mail (n=2,000) as per the registrants preferred method of contact. The NDSS is an Australian government initiative, administered by Diabetes Australia. The NDSS registry includes over 1.2 million Australians with T2D, and is considered to be one of the most comprehensive and up-to-date diabetes prevalence datasets in Australian (36). The random sample will be stratified by state and territory to facilitate representation across Australia, ideally in line with population distribution across the eight states and territories. The research team will not have access to NDSS registrants' details unless they make contact/take part in the study, and the NDSS will not be notified of participating registrants. The total number of invited registrants was selected based on adoption of a conservative response rate

of 8% (37), and an expected 46% translation from consent to enrolled participant (as seen in the pilot RCT; (34)). Invited NDSS registrants will receive an invitation reminder via e-mail or postal mail two weeks following first contact. If our target sample size is not reached within four weeks of the initial invitation, a second NDSS e-mail/mailout will be sent until our target sample size is reached or the two-month recruitment period has concluded. The number of registrants contacted and method (e-mail vs. mail) for subsequent recruitment efforts will be informed by the success rate from the original invitation (i.e. percentage enrolled reporting hearing about the study via email or mail invitation). The study will also be advertised online via the researchers' affiliated professional websites and social media accounts, and a study flyer will be circulated to diabetes researcher and health professional networks.

Study procedure

The schedule of enrolment, intervention and assessment is detailed in Figure 1. Study recruitment will be open for a maximum of two months or until sample size (enrolled) is reached. Participation (from study entry to exit) will be for a duration of six months. Study advertisements will direct potential participants to the study website (hosted by Qualtrics™) to access the Plain Language Statement, provide informed consent, and complete screening questions online. Eligibility will be determined automatically based on responses. Eligible participants will be directed immediately to complete an online baseline survey, and, following submission, will be allocated at random to one of two study arms. Randomised participants will receive an email including details about how to access the relevant online resources for their study arm. For participants allocated to the intervention group, this will include a unique username and password enabling access. All participants will be asked to access their allocated resource(s) at their convenience within the following two-week period, with no further instruction provided regarding the number of resource visits, or length of time viewing the resources(s). One week following allocation, participants will receive a reminder email to access/log into the resource. Participants will be sent an email with a link to the online follow-up survey at two weeks and six months following baseline. The two-week follow-up survey will be available for completion for two weeks, and the six-month follow-up survey will be available for completion for three weeks. Study end-point for all participants will be marked by either submission of the six-month follow-up survey (within 21 days of request), or non-submission at 22 days following the survey request.

Randomisation and blinding

After baseline survey submission, participants will be stratified by gender (due to prior gender imbalance observed among participants recruited to related studies (9, 21)) and randomised to either the intervention or control arm using computer-generated, randomly permuted block sizes of four, six or eight. The randomisation sequence will be computer generated and the allocation will be fully concealed from both the investigators and participants. Upon randomisation, participants will receive an email from a researcher, independent of the study investigator team and who does not have access to the incoming survey data (except for participant ID, name, gender and email address), specifying access details to their allocated online resource. The statistician, participants, and investigator team will remained blinded to study arm allocation throughout data collection and analyses. The project manager (EEH), who will monitor incoming survey data, will be blinded from study arm allocation except where a participant self-identifies study arm allocation within the follow up surveys (e.g. in a free-text response box). Any breaches will be recorded and reported with the main findings.

Intervention

Intervention group participants will receive access to a novel psycho-educational web-based resource, '*Is insulin right for me?*'. The intervention was developed using a systematic process grounded in behaviour change theory and has been described elsewhere (33). In brief, eight salient psychological barriers to insulin therapy were identified via literature search. Each barrier (i.e., determinant of behaviour) was mapped to relevant domains of the Theoretical Domains Framework (TDF) (38). Determinants were then mapped onto behaviour change techniques (BCTs) considered relevant to overcoming the modifiable barriers (32, 38). Content responding to each barrier was developed by the investigator team (experts in health psychology, primary care medicine and diabetes education) and refined following consumer feedback (cognitive debriefing interviews, n=6) and external expert peer review (n=5) to ensure relevance for people with T2D and clinical accuracy.

The eight barriers targeted in the '*Is insulin right for me'* resource are phrased as common questions, with one barriers/question per website page (See Table 1). The resource home page lists all eight barriers/questions as well as a preview (a key summary statement that responds to the question and content overview). The intervention is purposefully brief and self-directed, with the home page text asking which of eight questions about insulin are concerns for participants. For each selected barrier, an active intervention is presented on a separate webpage (200-500 words; 5-minute read) to facilitate user engagement. In addition, the resource includes information about the key benefits of insulin therapy: (1) that it lowers blood glucose levels; (2) can lower your risk of long-term health complications; (3) can make you feel better; and (4) can make managing your diabetes more flexible. The lesser focus on benefits than barriers is due to the evidence that most people with T2D experience / report barriers to insulin therapy despite endorsing benefits (14, 19). Finally, the resource also provides links to other resources about T2D and insulin available from the NDSS, and study information.

Table 1. Description of the eight barriers targeted in the '*Is insulin right for me'* resource

Barrier (Question)	Resource aim (using behaviour change theory)	Format of delivery
Does insulin mean my diabetes is more serious?	• Challenge beliefs: Insulin therapy can be clinically recommended at any time • Shape knowledge: Provide information about the role of insulin • Motivate: Diabetes is always serious	Interactive quiz; video depicting progressive nature of T2D (imagery and text), imagery and personal quote
Do insulin injections cause complications?	• Shape knowledge: Provide information about diabetes complications risk factors • Motivate: Acknowledge where this belief comes from. Validate concerns	Text; imagery and personal quote
Is it my fault I need to inject insulin?	• Identification of self as role model: 'You are doing this for yourself, insulin is a good thing' • Restructuring the social environment: being prepared for how others may react • Encouragement and support: Sharing how you feel with others	Text; case study (with audio recording); statistic; and personal quote

Will I gain weight?	• Shaping knowledge: Many people gain a small amount of weight when they commence insulin therapy. There are things that you can do to prevent unhealthy weight gain • Motivate: Acknowledge and validate fear • Salience of side effect: for many, weight gain is small	Interactive quiz; text; imagery and personal quote
Will injecting hurt?	• Shaping beliefs: Dispel myths • Manage expectations: Information and strategies to alleviate and minimise discomfort • Demonstration: of a person injecting insulin • Encouragement: to discuss insulin therapy and any concerns with a health professional • Imagery: small/fine needles & site of the injection	Text; demonstration of injecting insulin; imagery and personal quote
What about hypos?	• Shape knowledge: Frequency/severity of hypos • Motivate: Acknowledge/validate fears 'having concerns about hypos is natural'. • Reduce emotional valence of the fear: Low risk of having a severe hypo. Support is available	Interactive quiz; text; imagery and personal quote
Will injecting insulin be a burden?	• Increase knowledge: You can take insulin with you wherever you go • Increase self-efficacy: The changes you need to make are minimal and you can handle them. • Weigh pros versus cons: Insulin can make management of diabetes easier	Text and personal quote
What will others think of me?	• Identification of self as role model: 'You are doing this for yourself, insulin is a good thing' • Restructuring the social environment: being prepared for how others may react • Encouragement and support: Start a 'safe' conversation to share how you feel with others	Case studies with examples (with audio recording); text; and personal quote

Control group

Control arm participants will be directed to a static webpage including links to publicly available text-based NDSS factsheets, including: "Insulin" and "Medication for type 2 diabetes". The control group webpage also includes links to further information about the study and research team (consistent with intervention arm).

Outcomes

The co-primary outcome measures are the difference in mean negative insulin appraisals, as measured by the Insulin Treatment Appraisal Scale (ITAS) Negative subscale score (39), between the intervention and control arm at two-week and six-month follow-up, adjusted by baseline scores. We hypothesise that, at two weeks, a statistically significant difference in mean ITAS Negative scores of ≥4 points (approximately 0.5 standard deviations) will be observed between the intervention and control arm, favouring the intervention arm; and that this difference will be sustained at six months.

Our secondary outcome measures are immediate and sustained between-arm differences in: a) positive insulin appraisals, as measured by ITAS Positive subscale score (39); and b) hypothetical willingness to begin insulin therapy, as measured by a single item (35). We hypothesise that, at two weeks and six months, a statistically significant between-group difference will be observed in:

1. mean ITAS Positive scores, adjusted for baseline scores, favouring the intervention arm;
2. the percentage of participants who respond 'not at all willing' (hypothetical willingness item). The intervention arm will be less likely to be 'not at all willing' compared to controls.

The following survey data will be examined by study arm for process evaluation purposes:

1. Clinical discussion and recommendation of insulin therapy, change in medications, and satisfaction with diabetes management at six-month follow up
2. Change in secondary psychosocial outcome scores at two-week and six-month follow up: diabetes-specific distress (PAID) (40), illness perceptions (BIPQ) (41), diabetes-specific self-efficacy (CIDS) (42), study-specific insulin-related knowledge questionnaire.
3. Diabetes-specific knowledge at baseline (DKT) (43).
4. Study-specific resource use and acceptability (study specific items) as two-week follow up.

Figure 1 details the self-reported demographic, clinical, psychosocial, and study-specific data to be collected and the time-points at which they are to be collected. In addition, website analytics data will be collected to assess protocol fulfilment with the intervention resource (i.e. proportion of 'enrolled' participants who accessed the *'Is insulin right for me?* website at least once). Various analytics (e.g. average number of online resource visits; time (minutes) spent on online resource; most commonly (frequency, %) viewed pages) will be examined to explore any relationship(s) between type/duration of content accessed and the study outcomes. Finally, number of views and average time spent watching two videos embedded in the intervention resource will be captured via YouTube.

Sample size

Using a power analysis for repeated measures analysis of variance, a minimum sample size of N=250 (n=125 per arm) is required to detect a minimally important difference of half a standard deviation (SD=9) in ITAS Negative Scores (39) between study arms with a correlation of 0.65 between repeated measures, at 85% power and 0.05 significance level using a two-sided test. Assuming a 20% attrition rate at two weeks (34) and a further 20% attrition at six months, the targeted sample size inflates to approximately N=392 (n=196 per arm). Overall, a 40% attrition rate is incorporated into our estimated sample size and replacements will not be made for losses to follow-up.

Data collection, management and analysis

Participant-reported data will be collected online via Qualtrics™, hosted through the Deakin University secure network. Consent, eligibility screening and baseline survey data will be collected in a single sitting (directed via study advertisement link), and an email will provide enrolled participants with a link to online follow-up surveys. The intervention website will require participant log-in,

allowing for automatic collection of website usage data for each intervention participant via Google Analytics.

To improve participant retention and protocol compliance, trial participants will receive reminder emails to access/view the allocated online resource (sent to all participants two weeks following allocation. In addition, reminder emails will be sent at one week (and two weeks for six-month time-point) to participants who have yet to commence their online follow-up surveys. To aid recruitment and retention, participants who complete all three surveys (the baseline, two-week *and* six-month follow-up) will be entered into a prize draw to win one of 20 $100 e-gift vouchers.

Participants who do not access their allocated resource(s) will still be followed up until the end of the trial unless they withdraw from the trial. Participants who do not complete the two-week follow up survey will have 'missing data' at two weeks, but remain eligible to complete the six-month follow up survey. Participants who do not complete the six-month follow up survey within three weeks of receipt will have 'missing data' at six months. Participants with missing data at both follow-up time-points will be deemed 'lost to follow-up'.

Study data collected from withdrawn participants will be deleted, with the exception of basic de-identified sample characteristics (gender, age, diabetes duration), trial arm allocation, timing of withdrawal, and reason for withdrawal, where applicable.

Data storage

At study conclusion, survey data and website usage data (for intervention participants only) will be downloaded from Qualtrics and Google Analytics, respectively, and linked according to participant ID. Identifiable information (email, name) will be separated from study data and stored along with participant ID number in a password-encrypted excel spreadsheet. All data will be stored in a secure electronic file accessible only by the research team. In accordance with clinical trial regulations, data will be kept for a minimum of 15 years after study completion and then disposed by erasing of electronic files.

Statistical methods

Quantitative data analyses will be performed using Stata/SE 16.0 and/or IBM SPSS 26. Descriptive statistics will be used to describe participant baseline characteristics and psychological outcomes at each time point. Participant characteristics at baseline will be visually assessed by allocation for imbalance. The overall characteristics of the study cohort will be compared to those lost to follow-up.

An intention-to-treat (ITT) approach will be adopted whereby participants will be analysed according to the arm they were allocated to, and all participants will be included in the analysis. A linear mixed effects model will be used to estimate the difference in mean ITAS Negative scores between arms at two weeks and six months using restricted maximum likelihood estimation. Treatment arm, all three time-points (baseline, two weeks and six months), and the interaction between treatment arm and time-points will be included as fixed effects in the model. Random effects will be used to account for repeated participant measures. The outcome measure will be adjusted by age, diabetes duration and education should these be imbalanced between the arms at baseline. As a sensitivity analysis, pattern mixture models will be used to determine whether study conclusions from the analyses described above would change should data be missing not at random.

ITAS Positive Scores (secondary outcome), and continuous psychosocial process evaluation outcomes (e.g. PAID, BIPQ, CIDS) will be analysed using the same modelling approached described

above. An ordinal logistic mixed effects model will be used to quantify between-arm differences in the willingness to begin insulin therapy (secondary outcome) at the various time points.

Descriptive data will be used to explore trends in protocol fulfilment, website analytics and acceptability data, as well as medication changes and clinical discussion of insulin therapy at six months separately for each study arm.

Monitoring

Co-authors EHT and JS are the responsible investigators and will oversee the research project. During recruitment and data collection, the number of potential participants consenting, eligible and enrolled as well as dates of all participant encounters (i.e. enrolment; intervention access & reminder emails; survey access, reminder and closure) and survey completion will be monitored by EEH and communicated to investigator team. The primary funding body will be allowed access to all de-identified data from the study for audit purposes, if requested.

This research protocol does not include administration or manipulation of, or investigation of the effects of, any pharmacological or therapeutic goods. However, in line with the pharmacovigilance reporting requirements of the funding body, all survey data collected will be screened for adverse events that may be associated with the funding body's products and, in the event of the research team becoming aware of a potential adverse event, participants will be contacted (via email) and invited to respond to additional questions about this event (e.g. medication brand name, dose and timing, healthcare utilisation symptoms, other consequences). Non-response will not affect participation in the study proper. De-identified information obtained about the event will be submitted to the funder and, if relevant, the Australian Therapeutic Goods Administration.

Patient and public involvement

People with T2D were involved in the review and iterative refinement of the intervention content and design. This involved cognitive debriefing interviews with six adults with T2D to review draft content during intervention development, for which the findings and consequential refinements are detailed elsewhere (33, 34). In addition, user ratings and qualitative feedback were provided by 13 pilot RCT participants who were allocated to the intervention (34). Refinements made to the intervention following piloting included, for example, improving website navigation between barrier webpages and the addition of 'print-friendly' downloadable PDF content (34). People with T2D were not involved in the development of the study design, nor will they be involved in conduct of the study or dissemination of the study findings.

Ethics and dissemination

This trial received ethical approval Deakin University Human Research Ethics Committee (Ref: 2020-073). This study will be conducted in compliance with this protocol (version: SA-2017-11697; V2.2e 16 June 2020), which is registered with the Australian New Zealand Clinical Trials Registry (ACTRN: 12621000191897, registered Feb 23 2021). Note, this protocol was submitted for registration on 10 December 2020, prior to recruitment commencement (11 Jan 2021), though approved retrospectively following enrolment of the first participant and prior to last participant enrolment. Any changes to the protocol will be communicated to the human research ethics committee, funder, and trial register. Protocol registration will be updated with any approved amendments to the protocol, and protocol departures will be documented in any reports or manuscripts resulting from this study.

Potential participants view the study plain language form online (Supplementary File 1) and must indicate consent (by ticking a box) prior to participating. Participants are free to withdraw from the study at any time, and for any reason, prior to completion of data collection.

The findings will be prepared for academic presentation at scientific meetings and in peer-reviewed journals. A lay summary of findings will be published on the research team's website and disseminated via e-newsletter. Study findings will also be reported to the funding body.

De-identified data may be made available, upon request, to the funding body.

Discussion

This randomised controlled trial will provide high quality evidence regarding the efficacy and acceptability of a novel, web-based resource: *'Is insulin right for me?'*. Using best-practice intervention development principles and evaluation guidance (33, 34), the intervention was designed to reduce salient psychological barriers to insulin, which are extremely common among people with T2D and associated with deleterious delay of insulin uptake (14, 44). To our knowledge, this study will be the first fully-powered randomised controlled trial conducted to test the impact of any intervention specifically designed to address salient psychological barriers to insulin among adults with T2D reporting some level of psychological insulin resistance.

The described study will provide evidence of the acceptability of this web-based resource among Australians with T2D who report some level of psychological insulin resistance, which may inform real-world implementation strategies and further refinements as required. A potential limitation of this trial is the expected low response rate and self-selection bias of the sample recruited via an invitation from the NDSS, which may not be representative of those most in need (i.e. those with a high HbA1c yet not at all willing to commence insulin) as well as linguistically diverse communities. Participants' demographic characteristics (e.g. gender, state/territory, language, country of birth) will be compared to the general Australian population of adults with T2D to examine the representativeness of the sample. If the intervention is shown to be efficacious, further research will be warranted to investigate its impact on timely insulin uptake (and consequently on HbA1c), as well as the feasibility of implementation in primary care settings among adults with T2D for whom treatment intensification is clinically indicated.

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Author contributions

EHT and JS conceived of the intervention and the described program of research. EHT and JS developed the study protocol, with input from EEH, HMH, JF, VH and TS. EEH, JS, TS and EHT led the development of the intervention, with contributions from JF, and VH. HMH calculated the sample size and developed the statistical analysis plan. EHT was responsible for drafting the manuscript, which EEH, HMH, JF, VH, TS and JS reviewed and contributed to. All authors approved the final manuscript.

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This work was supported by an instigator-sponsored-study grant from Sanofi-Aventis Australia Pty Ltd (Sanofi). Sanofi was not involved in the study design, and will not be involved in the collection, analysis or interpretation of the study data, but was given the opportunity to view the manuscript prior to submission. The decision to submit for publication was made independently by the authors. Sanofi will be allowed access to all de-identified data from the study for research and audit purposes, if requested. Costs associated with participation incentives, website development and data management were funded (in full, or partially) by the Australian Centre for Behavioural Research in Diabetes (ACBRD). In-kind support including project oversight was provided by the Investigator team. JS is supported by the core funding to the ACBRD provided by the collaboration between Diabetes Victoria and Deakin University. EHT was supported by the same plus a Deakin University Deans Research Postdoctoral Fellowship (2018-2020).

Competing interests statement

EHT has undertaken research funded by an unrestricted educational grant from Abbott Diabetes Care, AstraZeneca, and Sanofi; received speaker fees from Novo Nordisk and Roche to Australian Centre for Behavioural Research in Diabetes (ACBRD); and served on an advisory board for AstraZeneca. EEH has no conflicts of interest to disclose. JF has received unrestricted educational grants for research support from Roche, Sanofi, and Medtronic. TS serves on advisory boards for Novo Nordisk and Liva Health Care, and is currently on a EIT Health research grant held jointly with Roche Diagnostics. JS has served on advisory boards for Janssen, Medtronic, Roche Diabetes Care, and Sanofi Diabetes; her research group (Australian Centre for Behavioural Research in Diabetes [ACBRD]) has received honoraria for this advisory board participation and has also received unrestricted educational grants and in-kind support from Abbott Diabetes Care, AstraZeneca, Medtronic, Roche Diabetes Care, and Sanofi Diabetes. JS has also received sponsorship to attend educational meetings from Medtronic, Roche Diabetes Care, and Sanofi Diabetes, and consultancy income or speaker fees from Abbott Diabetes Care, AstraZeneca, Medtronic, Novo Nordisk, Roche Diabetes Care, and Sanofi Diabetes. All other authors have no conflicts of interest to declare.

		STUDY PERIOD			
		Enrolment		Post-allocation	
TIMEPOINT		*Screening*	Baseline	*Two weeks*	*Six months*
ENROLMENT:					
Informed consent		X			
Eligibility screen		X			
Randomisation			X		
INTERVENTIONS:					
Intervention: Is insulin right for me?			→	→	
Control			→	→	
ASSESSMENTS:					
Contact information	Name[a], email address[a]	X		X	X
Pilot	Participation in the pilot study: yes/no[a]	X			
Recruitment	Referral method (e.g. NDSS invite)	X			
Demographics	Age[a], gender[a], country of residence[a]	X			
	Birth country, language, relationship status, employment, qualifications, postcode		X		
Diabetes	Diabetes type[a], duration[a], and management regimen[a], prior use of injections[a]	X			
	Diabetes medications, most recent HbA1c, glucose monitoring behaviour		X		X
General health	Diabetes-related co-morbidities[b], weight, height		X		
Clinical discussion of insulin therapy	Recall of prior clinical discussion and recommendation of insulin		X		X
Previous information about insulin therapy	What information about insulin have you read		X		
Psychological insulin receptiveness	Hypothetical willingness to commence insulin (35)[a]	X		X	X
Attitudes towards insulin	Insulin Treatment Appraisal Scale: ITAS (39)		X	X	X
Knowledge	Diabetes-specific: Diabetes Knowledge Test-True/False Version: DKT (43)		X		
	Insulin-specific knowledge: Study specific items		X	X	X
Diabetes-specific distress	Problem Areas In Diabetes: PAID (40)		X	X	X
Illness perceptions	Brief Illness Perceptions Questionnaire: BIPQ (41)		X	X	X
Diabetes-specific self-efficacy	Confidence In (type 2) Diabetes Self-management scale: CIDS-2 (or insulin version at follow-up for participants commenced insulin (CIDS-1) (42)		X	X	X
Diabetes management satisfaction	Study specific item		X	X	X
Resource use and acceptability	Resource access (yes/no). Reasons for not accessing; OR user rating scale (were questions answered?), free-text feedback (questions, likes/dislikes, improvements)			X	
Further comments	Free-text box for participant to provide further feedback.			X	X

Figure 1. Schedule of enrolment, interventions, and assessments.[a] compulsory questions for participation. [b] Co-morbidities included: kidney disease, retinopathy, neuropathy, heart disease, stroke, vascular disease, sexual dysfunction, other (to be specified).

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Supplementary File 1. Plain Language Statement and Consent Form

Attitudes towards insulin therapy for people with type 2 diabetes

Plain Language Statement and Consent Form

Date: May 2020

Full Project Title: Development, Feasibility, and Efficacy of a Web-Based Intervention to Reduce Psychological Barriers to Insulin Therapy among Adults with Type 2 Diabetes (Stage 3: Full RCT)

Principal Investigators: Dr Elizabeth Holmes-Truscott and Professor Jane Speight, The Australian Centre for Behavioural Research in Diabetes (ACBRD), Deakin University

Associate Investigators: Dr Edith Holloway, ACBRD, Deakin University; Professor Timothy Skinner, Department of Rural Health, La Trobe University; Associate Professor John Furler, Department of General Practice, The University of Melbourne; Professor David O'Neal, St Vincent's Hospital, The University of Melbourne; and Dr Virginia Hagger, School of Nursing and Midwifery, Deakin University.

Dear participant,

You are invited to take part in this research project because you have type 2 diabetes, are aged between 18 and 75 years of age and take oral medication to manage your diabetes. In this study, we are investigating people's attitudes towards injecting insulin. We are also testing online resources about medications for type 2 diabetes. We want to know which resource(s) is the most useful for people with type 2 diabetes, who have questions or concerns about injecting insulin. Taking part involves exploring the web-based resource(s) and completing three online surveys over 6 months.

Below you can read further information about the study, so that you can decide if you would like to take part. Please take the time to read this information carefully. You can also print a copy of the PDF *(hyperlink to ethics approved version of the PLS inserted here)* or ask the study team for a hard copy to be sent to you. Ask the study team questions about anything you don't understand or want to know more about.

If you consent to taking part in this study, please click the box at the end of this webpage.

What is the purpose of this research?

Insulin is very effective for lowering blood glucose levels. Your doctor may recommend injecting insulin if other medications are unable to keep your blood glucose within your target range. However, people with type 2 diabetes may have concerns or questions about starting insulin. The purpose of this study is to test whether web-based resource(s) are useful for people with type 2 diabetes who have questions or concerns about starting insulin injections. The findings of this research may be used to inform what online resources about medications are available for people with type 2 diabetes in the future. We expect a total of 392 adults with type 2 diabetes will take part in this study.

Who can take part?

You can take part in this study if you:

- have type 2 diabetes and are currently taking oral medication to manage your diabetes. If you are currently, or have in the past, used self-administered injectable treatment for any illness or condition (for example insulin) you are NOT eligible to take part in the study.
- are between 18 and 75 years of age
- are able to read and speak English
- currently live in Australia
- have access to the internet and a computer (desktop, laptop) or tablet

You are not eligible to take part if you participated in the associated Pilot Study (between October and December 2019): Development, Feasibility, and Efficacy of a Web-Based Intervention to Reduce Psychological Barriers to Insulin Therapy among Adults with Type 2 Diabetes (Stage 2: Pilot Study).

What does taking part involve?

Taking part in this study will involve:

- Accessing and viewing a web-based resource(s) about medications for type 2 diabetes. You will be asked to do this at least once (and as many times you like) over a 2-week period.
- Completing three online surveys. The first survey will be upon entry to the study, the second survey will be emailed to you two weeks later and the third survey will be emailed to you at 6-months.
- Each survey will take 20 minutes to complete.
- The survey will include questions about you (age, gender, education), your diabetes, attitudes and knowledge about insulin, your understanding about diabetes and some questions about how diabetes makes you feel.
- You will also be asked to provide your name and email address. This is so we can link each of your surveys together and look at any changes in your responses over time. Any information you share with us will remain confidential.

After you have completed the first online survey on entry into the study, you will be allocated to one of two groups. You will receive a link to one of two web-based resources on insulin and type 2 diabetes. You have a 50% chance of being assigned to each group (like tossing a coin). You will have two weeks to explore the resource(s) allocated to you. We will send you an e-mail reminder during the two-week period to look at the resources. You will then be sent follow-up surveys at 2 weeks and 6 months.

Taking part in this study does not involve any change to your diabetes management or changes to the medications you take.

Who is conducting this study?

Deakin University is conducting this study with funding from Sanofi-aventis Australia Pty Ltd (Sanofi). The study is coordinated by researchers (Principal Investigators) at The Australian Centre for Behavioural Research in Diabetes (ACBRD), a partnership for better health between Diabetes Victoria and Deakin University. The Principal Investigators take responsibility for the study. Participants will only be contacted by the research team including the principal investigators, the study project manager or research assistant.

Are there any benefits for me personally?

People take part in studies like this for many reasons. For example:

- Taking part offers an opportunity to learn about and inform new diabetes research;
- Taking part offers an opportunity to think about your diabetes and reflect on your experiences;
- Taking part in research will help us to help other people with diabetes (either now or in the future).

In addition, participants who complete the study (i.e., access the web-based resource(s) and complete all three surveys) will be entered into a prize draw to win one of 20 $100 department store gift cards that can be used at over 20 major retail stores in Australia.

Are there any risks to me?

No, we do not believe that this study will cause you any harm or put you at risk of harm. **The study surveys include questions that may be sensitive or personal in nature (e.g. feelings about living with diabetes, income and employment status). However, we do not expect any question to cause you any distress.** If you should become upset during the survey, you may stop completing the questions at any time. We encourage you to contact the researchers to discuss this. The researchers will be understanding and supportive. You have the right to refuse to answer any question that makes you uncomfortable.

If, as a result of participation, you do become distressed, you may wish to seek further information and support from beyondblue: Beyondblue – National Information Line Ph: [redacted] or visit: http://www.beyondblue.org.au/

If you have any questions about your diabetes following the survey, we encourage you to contact your health professional or to call the National Diabetes Services Scheme Helpline: [redacted].

Can I withdraw at any time?

Yes. **You are free to withdraw from this study at any time**. If you decide not to take part while completing an online survey, you can stop the survey and notify a member of the research team. Deciding not to take part (or to withdraw) will not affect your relationship with the ACBRD, Deakin University, Diabetes Victoria, or the study funder (Sanofi). If you withdraw from the study before, during, or immediately after you have completed the online surveys, we can remove any information you have shared from our analysis. However, once the study is closed your data will be de-identified and merged with other people's data. This means that you will not be able to withdraw the information you shared because we will not know which data are yours.

What will happen to my information?

Any information you share with us will remain strictly confidential. The survey data will be stored in a database via the Deakin University secure network. Only the research team will have access to the password protected data. Once we have collected all of the data and are ready to analyse the results, the survey responses will downloaded and de-identified. These files will not include any identifying information about you. Identifiable information (for example your email, name) will be stored in a password-encrypted excel spreadsheet. Any personal details you share about yourself (e.g. surname, contact details) for the purposes of enrolling you into the study will be destroyed (electronic files to be deleted) after you have completed the final survey. Safety follow-up interview data will be stored electronically (i.e. audio files). All data will be stored in a secure Deakin University computer file accessible only by the ACBRD research team. In accordance with government requirements, your data will be stored for at least fifteen (15) years following the publication of the results and then destroyed by erasing electronic files and shredding paper copies.

The overall results of the study may be published or presented in academic journals, at conferences, and in diabetes magazines and newsletters. Participants will be able to access any publications or reports resulting from the study on the ACBRD website (www.acbrd.org.au). No-one will be able to identify you from any of the information we publish or present. The study funder may request access to the de-identified data. These data will not include any information that could be used to identify you. We will take great care to protect your identity. Your privacy is very important to us.

Who is funding this project?

This project forms part of an Investigator Sponsored Study (SA-2017-11697) which is supported by Sanofi-aventis Australia Pty Ltd (Sanofi). Sanofi has no involvement in the study design, data analysis or interpretation and will not have any access to personally identifying information collected (e.g. contact details). De-identified study data may be shared with Sanofi, including survey results. Your personal and contact details will not be shared with Sanofi.

If you share with us (via the study surveys, e-mail or phone) any adverse events (safety issues) associated with therapeutic goods (e.g. medications) during your involvement with this study, we are required to report these to Sanofi. This could include any adverse events associated with the funder's products. Therefore, all the data that we collect from you will be screened for adverse events that may be associated with medications you take now or have taken in the past. In the event that you report an adverse event, we will contact you and ask a small number of additional questions (e.g. medication brand, dose, symptoms etc). If you decide not to answer the questions, this **will not affect your participation in the study.**

In addition, the researchers will notify the Deakin University Human Research Ethics Committee (DUHREC) of any adverse incidents, events, reactions that have a possible causal relationship with this research.

Has this study been approved by an Ethics committee?

Yes. **This study has been reviewed and approved by Deakin University's Human Research Ethics Committee (DUHREC), reference number 2020-073.**

Who can I contact about this study?

If you would like further information or have any questions about the study, please contact:
Dr Elizabeth Holmes-Truscott (e: [redacted] t: [redacted]),

Professor Jane Speight (e: [redacted] t: [redacted]), or

Dr Edith Holloway (e: [redacted] t: [redacted]), at the ACBRD.
To find out more about the work of the ABCRD, you may like to visit the website: www.acbrd.org.au.

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:
The Human Research Ethics Office, Deakin University, 221 Burwood Highway, Burwood Victoria 3125, Telephone: [redacted], email: [redacted]. Please quote project number 2020-073.

Consent Form

Please tick the box at the bottom of the page to indicate your agreement with each statement.

- I have read and I understand the Plain Language Statement.
- I freely agree to participate in this project according to the conditions in the Plain Language Statement.
- I have access to a copy of the Plain Language Statement and Consent form to print and keep.
- I understand and consent to completing three online surveys: at entry into the study, two-weeks and 6-months later. I will also be invited to explore web-based resources about type 2 diabetes and injecting insulin.
- I understand that if I report any adverse events (safety issues) associated with therapeutic goods (e.g. medications) I will be contacted and asked a small number of additional questions. If I decide not to answer the questions, this **will not affect my participation in the study.**
- I understand that the research team will not reveal my identity or personal details to anyone outside the research team, including where information is published or presented in any public form about this research study.
- I understand that the research team or the study funders may use the information I share in a closely related project, or an extension of the current research project, and that this information will be de-identified.

☐ **I have read and understood the information above and agree to take part in this study.**

I am ready to start completing the Attitudes Towards Insulin Study

Withdrawal Form

To be used for participants who wish to withdraw from the project

Date: May 2020

Full Project Title: Development, Feasibility, and Efficacy of a Web-Based Intervention to Reduce Psychological Barriers to Insulin Therapy among Adults with Type 2 Diabetes (Stage 3: Full RCT)

Reference Number: 2020-073

*********IMPORTANT*********

Complete this form and return it to us only if you decide to WITHDRAW from the above-named study.

I wish to withdraw from participating in the study entitled 'Development, Feasibility, and Efficacy of a Web-Based Intervention to Reduce Psychological Barriers to Insulin Therapy among Adults with Type 2 Diabetes (Stage 3: Full RCT)'. I do not want to take part in any additional study activities ***and*** I do not want the information I have already provided to be included in any analysis or study publications. I understand that withdrawing the information I have already provided will not be possible after completion of the second survey. I understand that withdrawing from the study will not adversely affect my relationship with any of the organisations conducting this study. I understand that withdrawing from the study will not affect the care or treatment I receive from any health professionals.

Participant's name (please print) .....

Participant's signature..... Date.....

Dr Elizabeth Holmes-Truscott

The Australian Centre of Behavioural Research in Diabetes

570 Elizabeth St, Melbourne, VIC 3000

T: [redacted]

E: [redacted]

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Author response
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Pg 2, line 7
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	ACTRN12621000191897 Pg 3, line 33
	2b	All items from the World Health Organization Trial Registration Data Set	See trial registration details. Pg 3, line 33
Protocol version	3	Date and version identifier	Title page (pg 2, line 13) & main text (pg 14, line 50)
Funding	4	Sources and types of financial, material, and other support	See Funding statement (pg 16, line 23)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page (pg 2, line 20) & Authorship contribution statement (pg 16, line 12)
	5b	Name and contact information for the trial sponsor	Investigator sponsored study; Corresponding author (pg 2, line 2)

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See Funding statement (pg 16, line 23)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Authorship contribution statement (pg 16, line 12); main text: Randomisation (pg 6, line 41) & Monitoring (pg 11, line 11)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pg 4-5
	6b	Explanation for choice of comparators	Pg 4, line 55 to pg 5, line 8
Objectives	7	Specific objectives or hypotheses	Pg 5, line 21-25
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Pg 5, line 18-21
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Pg 5, line 30-3

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Pg 5 – 6, starting line 34
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pg 7, line 4 to pg 8, line 57
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Pg 10, line 6-12 Pg 9, line 32-41
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pg 9, line 3-41
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 (pg 18)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Pg 9, line 44-52

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Pg 5, line 48 to pg 6, line 13. Pg 10, line 10-12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Pg 6, line 41-48
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Pg 6, line 48-56
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Pg 6, line 46-56
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pg 6, 48-56
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Pg 6, 53-56
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pg 9, lines 5-42; pg 9, line 55 – pg 10, line 5; Figure 1 (pg 18)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Pg 10, lines 6-25
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Pg 10, lines 27-35
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pg 10/11, lines 38-9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pg 11, line 6-9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Pg 10, line 46-57
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P. 11, line 11-30
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P. 11, line 21-30
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P. 11, line 13-30
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P. 11, line 49-50
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P. 11, line 56-60
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P. 12, line 3-6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Pg 9, line 56- pg 10, line 5; Pg 10, line 28-35
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Pg 16, lines 40-58
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Pg 10, line 32-36; Pg 12, line 12.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Pg 12, line 8-11
	31b	Authorship eligibility guidelines and any intended use of professional writers	Pg 16, 12-21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1. (pg 19)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.