PROTOCOL

SHORT TITLE: ATTITUDES TOWARD INSULIN: DEVELOPMENT, PILOT AND RCT

Development, Feasibility, and Efficacy of a Web-Based Intervention to Reduce Psychological Barriers to Insulin Therapy among Adults with Type 2 Diabetes

Protocol Number: SA-2017-11697

Version and date: V2.2b 6 June 2019

Stage 2: Pilot Study

Revision Chronology:

Version (day/month/year)	Change	Summary of changes
V1 (19/12/2017)	First protocol draft (stage 1 and 2), submitted to Funding body for approval.	
V2 (12/6/2018)	First full protocol draft, submitted to Funding body for approval.	Minor amendment to Stage 1 and 2, and addition of Stage 3 protocol details.
V2.1 (21/8/2018)	Minor refinements.	Minor refinements made in response to funder queries.
V2.2a (03/01/2019)	Stage 1 protocol (Intervention Development only) shown only. Minor refinements.	Stage-specific protocol. Minor refinements made to stage-specific protocol.
V2.2b (06/06/2019)	Stage 2 protocol (Pilot Study only) shown only. Minor refinements.	Stage-specific protocol. Minor refinements made to stage-specific protocol.

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CONFIDENTIAL

Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the ICH Guideline for Good Clinical Practice E6.

CONTENTS

PROTOCOL SYNOPSIS

The optimal management of type 2 diabetes (T2D) requires timely intensification of treatment to achieve and maintain target HbA1c, and prevent serious long-term complications (1, 2). Insulin therapy is the most efficacious diabetes treatment and T2D management guidelines recommended early consideration of insulin initiation (3, 4). However, international research suggests routine delay of clinically indicated insulin initiation among people with T2D (5, 6). Reasons for the perilous delay of treatment intensification are multifaceted, and include the experience of psychological insulin resistance (PIR) among people with T2D (7, 8). PIR is the reluctance to commence, use as recommended, or intensify insulin therapy (9). It is based upon the person's negative beliefs about insulin therapy, i.e. worries and inaccurate/unhelpful beliefs about the necessity for insulin, its side effects, its physical and social impact, and what insulin symbolises about their health and identity. Our research shows that one quarter of adults with T2D, for whom insulin is clinically indicated, are not at all willing to commence insulin if recommended by their health professional (10), and this 'willingness' is associated with actual insulin uptake (8).

Few evidence-based interventions exist to promote receptiveness to insulin therapy (11, 12), and none have been developed, evaluated, or are available, within Australia. Online interventions provide the ideal platform for wide reach (13), with minimal burden on limited healthcare resources. We have identified the need for a psycho-educational resource for people with T2D facing the decision to begin insulin therapy, which: a) is delivered online to enable wide reach with no additional burden on health service resources; b) recognises salient psychological barriers to insulin therapy among Australians with T2D (10, 14), c) utilises relevant, effective behaviour change techniques (15); d) is designed and refined with active involvement from end users, and; e) is rigorously evaluated to assess its impact on attitudes about insulin therapy. We will undertake a 24-month program of research to develop, pilot, and test the efficacy of a novel psycho-educational web-based resource to reduce negative attitudes towards insulin among adults with non-insulin using treated T2D. This stage-specific protocol describes the acceptability and feasibility testing of the intervention and the study design (pilot study).

1. ADMINISTRATIVE INFORMATION

1.1. Trial registration

The pilot study (Stage 2) will be registered on the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/) prior to commencement.

1.2. Sponsor

Study Sponsor	Deakin University
Contact name	Sally Brady
Address	Deakin Research Commercial, Geelong Campus 75 Pigdons Road, Waurn Ponds, Victoria 3216

1.3. Project co-ordination and oversight

This project will be co-ordinated from The Australian Centre for Behavioural Research in Diabetes (ACBRD), which is a partnership for better health between Diabetes Victoria and Deakin University, led by Dr Elizabeth Holmes-Truscott (Chief Investigator A) and Prof Jane Speight (Chief Investigator B). CIs Holmes-Truscott and Speight conceptualised the original study proposal, drafted the protocol and are responsible for the study.

A multidisciplinary Associate Investigator team has been formed to oversee the research project, including researchers and/or clinicians with expertise in health psychology, e-health, general practice, and diabetes nurse education. This includes Dr Edith Holloway (ACBRD), Prof Timothy Skinner (Copenhagen University), A/Prof John Furler and Prof David O'Neal (The University of Melbourne) and Dr Virginia Hagger (Deakin University).

2. INTRODUCTION AND BACKGROUND

2.1. Background and rationale

Type 2 diabetes (T2D) is the fastest growing chronic condition in Australia (16), currently affecting 1.1 million Australians (17). T2D is a progressive condition that requires timely intensification of treatment to achieve and maintain optimal HbA1c (a measure of average blood glucose over 8-12

weeks), in order to prevent or delay the onset of devastating complications (e.g. kidney failure, blindness) (1, 2). A staged approach to pharmacological management of glucose levels in T2D is recommended (3, 18). First and second line therapies typically involve the introduction and intensification of oral hypoglycaemic agents (OHAs), while third line therapy and beyond may include the initiation of injectable treatments, including insulin therapy.

Insulin therapy is the most efficacious diabetes treatment available. It is the only diabetes management option that can maintain optimal blood glucose levels throughout the progression of beta cell failure (19). Complete beta cell failure generally occurs within 10 years of onset of T2D for most individuals (20). By preventing the development or progression of complications, insulin use indirectly contributes to maintaining both quantity and quality of life (21) and reduces the overall cost of diabetes, which are doubled in the presence of complications (22). Early consideration of insulin initiation is recommended internationally in T2D management guidelines (3, 4).

Despite proven efficacy, insulin is not used as widely as clinically indicated. In Australian primary care, ~50% of adults with T2D have an HbA1c above recommended target (>7%) (23, 24), suggesting many would benefit from optimised pharmacological treatment. However, only 20% of all Australians with T2D are using insulin (25), and research suggests insulin intensification is routinely delayed (6), typically occurring after several years of suboptimal Hba1c and maximum dose OHAS. For example, in the Australian 'Fremantle Diabetes Study', transition to insulin occurred at a median diabetes duration of 8 years and a median HbA1c of 9.4% (79mmol/mol) (26). This is corroborated by more recent data indicating that just 22% of adults with T2D for whom insulin was clinically indicated, receiving usual care in Victorian general practice, initiated insulin within the 12-month study period (27).

Reasons for the perilous delay of treatment intensification are multifaceted. Health professionals report personal barriers (e.g. lack of skills, experience, confidence) and systemic barriers (e.g. limited time and resources) to timely treatment intensification (7). Our research has demonstrated that insulin-specific health professional training programs and multi-disciplinary healthcare team support can facilitate timely insulin initiation (28). However, we have also demonstrated that willingness to commence insulin therapy among people with T2D is a predictor of actual insulin uptake independent of the model of care, or other clinical characteristics (8). One quarter of Australian adults with T2D, for whom insulin is clinically indicated, are 'not at all willing' to initiate insulin if recommended, and this group is significantly less likely to initiate insulin treatment (8). This suggests

that in addition to interventions to reduce health professional 'clinical inertia' (29), interventions are also needed that directly target people with T2D and address their psychological barriers to insulin use.

Psychological insulin resistance (PIR) is the reluctance to commence, use as recommended, or intensify insulin therapy experienced by a person with T2D (9). It is based upon the person's emotional and cognitive barriers to insulin use, e.g. worries about the necessity of insulin, its side effects, its physical and social impact, and feelings of guilt and self-blame about what insulin symbolises about health, self-care and identity. The latter includes the belief that insulin is an end-stage or 'last resort' treatment. Our research has previously identified that 80% of Australian adults with non-insulin-treated T2D believe that requiring insulin therapy means diabetes has become much more serious and 58% believe that insulin is a punishment or consequence of 'failing' to self-manage their diabetes previously (30). These negative beliefs and attitudes are significantly associated with low intention to initiate, and actual uptake of, insulin treatment (10, 31).

Negative attitudes toward, and reluctance to initiate, insulin treatment are malleable (8, 31, 32). However, despite the established relationship between belief/affects and treatment intensification, few interventions targeting negative attitudes toward insulin have been developed and none has been adequately evaluated, or implemented beyond trials (11, 12). Further, clinic-based interventions have been found to place additional burden on health professional resources (12). This suggests that an intervention to reduce negative attitudes towards insulin may be more accessible and acceptable if provided outside of, but complementary to, clinical care.

Online interventions provide the ideal platform for wide reach, with minimal burden on limited healthcare resources. Given the sheer size of the Australian population with T2D, the scalability of an intervention is an important consideration. The internet is a frequently used source of health information outside of, and between, medical appointments. In Australia, 86% of households have access to the internet (33), and one third of Australians with T2D and suboptimal HbA1c report seeking diabetes information online in the past 12 months (34). Internet-based interventions enable the cost-effective administration of highly accessible specialist behaviour change programs that can utilise content tailored to user characteristics, including interactive exercises (with immediate feedback), animations and audio/video resources. Compared to printed materials, internet-based interventions have been shown to be particularly beneficial for increasing engagement and comprehension among people with low health literacy, thus ensuring broad applicability (13).

Online interventions for the management of T2D with clear theoretical groundings and based on proven behaviour change techniques show favourable outcomes (35). Peak bodies (e.g. Diabetes Australia) publish resources online about T2D treatments. However, these materials are not theoretically informed, do not use evidence-based behaviour change techniques (15, 36), and are rarely developed in consultation with, or evaluated by, people with T2D. Furthermore, these materials focus on providing information that is physiological (e.g. treatment types and mode of action) and practical (e.g. injection techniques), with little or no content addressing important psychological barriers to injectable treatments. Therefore, it is unknown whether these resources are relevant or acceptable to users, and it seems unlikely that they would reduce psychological barriers to insulin use.

We have identified the need for a psycho-educational resource for people with T2D facing the decision to begin insulin therapy, which: a) is delivered online to enable wide reach with no additional burden on health service resources; b) recognises salient psychological barriers to insulin therapy held by Australians with T2D (10, 14, 30), c) utilises relevant, effective behaviour change techniques (15, 36); d) is designed and refined with active involvement from end users (people with T2D) to ensure content is relevant and acceptable, and; e) is rigorously evaluated to assess its impact on attitudes to insulin therapy.

We will undertake a 24-month program of research to develop (1-6 months), pilot (7-12 months), and test the efficacy (13-24 months) of a novel psycho-educational web-based resource to reduce negative attitudes towards insulin among adults with non-insulin treated T2D. This protocol describes the second stage of a three-stage program of research: 1) the process of resource development, 2) a pilot study to assess the acceptability and feasibility of the intervention and the RCT protocol, and 3) a fully-powered parallel RCT to test the efficacy of the intervention.

2.2. Aim(s)

1) Intervention development: to develop a novel evidence-based psycho-educational web-based resource about insulin therapy for people with non-insulin T2D with iterative and active involvement of potential end users to ensure relevance and acceptability of the intervention. (See Section 3: Intervention Development)
2) Pilot Study: to conduct a pilot 2-armed RCT to examine the acceptability and the feasibility of study design and a novel web-based resource among adults with non-insulin-treated T2D. (See full protocol V2.1))

3) Randomised Controlled Trial: to conduct an individually randomised controlled trial to test the efficacy of a novel web-based resource (intervention), compared to widely available existing resources (control), to reduce negative attitudes toward insulin therapy, among adults with non-insulin-treated T2D (See full protocol V2.1)).

3. PILOT STUDY

To conduct a pilot 2-armed randomised controlled trial to examine the acceptability and the feasibility of the study design and the novel web-based resource among adults with non-insulin-treated T2D.

3.1. Study duration

The pilot study active recruitment, participation and data collection period will be conducted within a three-month period. Study recruitment will be open for a maximum of 2 months or until 40 consenting eligible participants have been randomised. Participation (from study entry to exit) will be for a minimum duration of 2 weeks and a maximum of 4 weeks.

3.2. Study objectives

3.2.1. Primary objective

The primary objective of the pilot study is to assess the feasibility (via recruitment and retention rates, and protocol compliance) of a two-armed randomised controlled trial (RCT) design using online enrolment, participation and data collection to evaluate the efficacy of a novel psycho-educational insulin therapy web-based resource.

3.2.2. Secondary objectives

The secondary objectives of this study are:

- to determine the acceptability of the intervention content and format for people with non-insulin-treated T2D via (1) website usage data, (2) detailed qualitative and quantitative survey feedback from participants about their experiences of intervention to inform future developments.

- to estimate the likely effect of the intervention, compared to the control, on change in negative insulin appraisals; knowledge about insulin; and willingness to commence insulin therapy at follow-up.

3.3. Study design

3.3.1. Type of study

The pilot study will use a double-blinded parallel group randomised controlled trial (two-arms, 1:1 ratio) design, comparing a novel psycho-educational insulin therapy web-based resource (intervention) with widely available online text-based information about insulin (control). This design will emulate the planned fully-powered RCT (Stage 3, Section 5). Outcomes will be assessed at baseline and 2-week follow-up.

3.3.2. Study setting

Participation will be completely online, using personal computers/mobile devices.

3.4. Participants and recruitment

3.4.1. Number of participants

40 eligible participants will be recruited, allowing for 50% attrition, for a minimum sample of 20 participants (40). See section 4.9.1 for details.

3.4.2. Eligibility

Potentials participants will be enrolled in the study only if they meet all of the inclusion criteria and none of the exclusion criteria.

3.4.2.1. Inclusion criteria

Each participant must meet all of the following criteria, as self-reported, to be enrolled in this study:

- Aged 18 to 75 years at the time of randomisation
- Self-reported diagnosis of T2D
- Currently using oral hypoglycaemic agents for the treatment of T2D

- Able to read/write in English and capable of understanding the informed consent document and provide consent
- Residing in Australia at the time of randomisation and throughout the study period
- Access to an internet-enabled device (i.e. computer, tablet) for the duration of the study.

3.4.2.2. Exclusion criteria

Potential participants meeting any of the following criteria will be excluded from the study:

- Self-reported diagnosis of diabetes other than T2D (e.g. Type 1, gestational, LADA)
- Current use of an injectable diabetes medication (i.e. GLP-1 agonist, insulin) at the time of randomisation
- Prior experience of self-administered injectable treatment for any illness or condition
- Unable to read/write in English
- Unable to use/access internet-enabled devices (i.e. computer, tablet) during the study period
- 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.

3.4.3. Recruitment and identification of potential participants

Participants will be recruited using convenience sampling through websites, e-newsletters/blogs and social media (Twitter, Facebook) via the researchers' affiliated professional accounts (e.g. Deakin University, ACBRD). Australian diabetes charities, organisations and associations (e.g. Diabetes Australia, Diabetes Victoria) will be notified of, and encouraged to promote, the study through similar online means.

A participant prize draw will be used to incentivise participation and aid recruitment. All participants who complete the follow-up survey will be entered into a prize draw to win one double-pass gold class cinema voucher.

3.4.4. Consent

An online Plain Language Statement and Consent Form (PLSCF) will be developed, and will describe the purpose of the study to participants, the procedures to be followed, the risks and benefits of participation and contact details (email address and telephone number) for the research team in the event of any queries or questions. Prior to completing any study component (i.e. responding to screening questions to determine eligibility), potential participants will need to tick a box to confirm they have read and understood the PLSCF and consent to taking part. Consent will be voluntary and free from coercion. Participants will be encouraged to print a copy of the PLSCF for their records and a copy of the consent form will be accessible to all participants on the study website throughout their participation. The PLSCF and consent form will advise participants that they may be contacted via email and asked to respond to a small number of follow-up questions (via email reply or telephone) for safety reporting purposes (See Section 6.3.2). Participants will be advised that their non-response to these additional questions will not affect their eligibility or participation in this pilot study.

3.4.5. Participant withdrawal

Participants are free to withdraw from the study at any time upon their request, for any reason. Participants who *request* to be withdrawn from the study will be asked to nominate, but not required to provide, a reason for withdrawal. Withdrawing from the study will not affect their relationship with the researchers or study sponsors.

Participants will be withdrawn from the study if they do not submit a baseline survey, and therefore are not allocated to a trial arm. The investigator will also withdraw all participants from the study intervention if the study is terminated. Where applicable, basic de-identified sample characteristics (gender, age, diabetes duration), trial arm allocation, time of withdrawal (e.g. pre or post trial arm allocation) and reason for withdrawal, will be maintained for reporting purposes.

3.5. Trial allocation

3.5.1. Randomisation and blinding

After the baseline survey is submitted, participants will be allocated to one of two groups, on an equal allocation basis, stratified by gender. The randomisation sequence will be computer generated and the allocation fully concealed from the investigator, researcher team and participants.

Upon trial arm randomisation participants will receive an email specifying access details (including a unique log-in) to their allocated online resource about insulin therapy. Participants in both arms will be asked to explore their allocated resource within a 2-week period, and will receive one reminder email during this period encouraging them to access/log into the resource. Access to the online resource will conclude following the 2-week period, at which time participants will be requested (via email) to complete the follow-up survey.

3.5.2. Intervention group

Intervention group participants will receive access to the novel psycho-educational website. The development process (Stage 1) of intervention content and design is described in the Stage 1 Protocol. A description of the intervention to be assessed in the Pilot Study (Stage 2) will be added to the protocol as an appendix prior to study commencement.

3.5.3. Control group

Control arm participants will be directed to a static webpage including links to publications about insulin therapy which are currently available online to Australians with T2D. Specifically, the website will include text-based factsheets about insulin and other T2D medications published by the National Diabetes Services Scheme (NDSS): “Medication for type 2 diabetes”, “Insulin and type 2 diabetes”.

3.6. Study procedure

Following provision of informed consent, participants will be asked to complete eligibility screening questions online. Eligibility will be automatically determined based on responses and ineligible participants will be thanked for their interest in the study. Eligible participants will be directed to complete an online baseline survey. Following submission of the survey, participants will be randomised to a study arm and receive relevant resource access details via an automated email.

Participants will be able to access the relevant resource at their leisure within a 2-week period. One week following allocation participants will receive an automatically generated reminder email to access/log into the resource. Following the 2-week period, participants will be sent an automated email with a link to the follow-up online survey. The follow-up survey will be available for completion for two weeks. Participants who have not completed the survey within one week of receipt will be sent reminder email. Participation (from eligibility screening to end-of study) will involve a minimum of two weeks and maximum of four weeks. Study endpoint for all participants will be marked by either submission of the follow-up survey (within 14 days of request), or non-submission at 15 days following survey request. The study procedure is detailed in Figure 1. A and the timeline for the entire study protocol is detailed in Section 7.

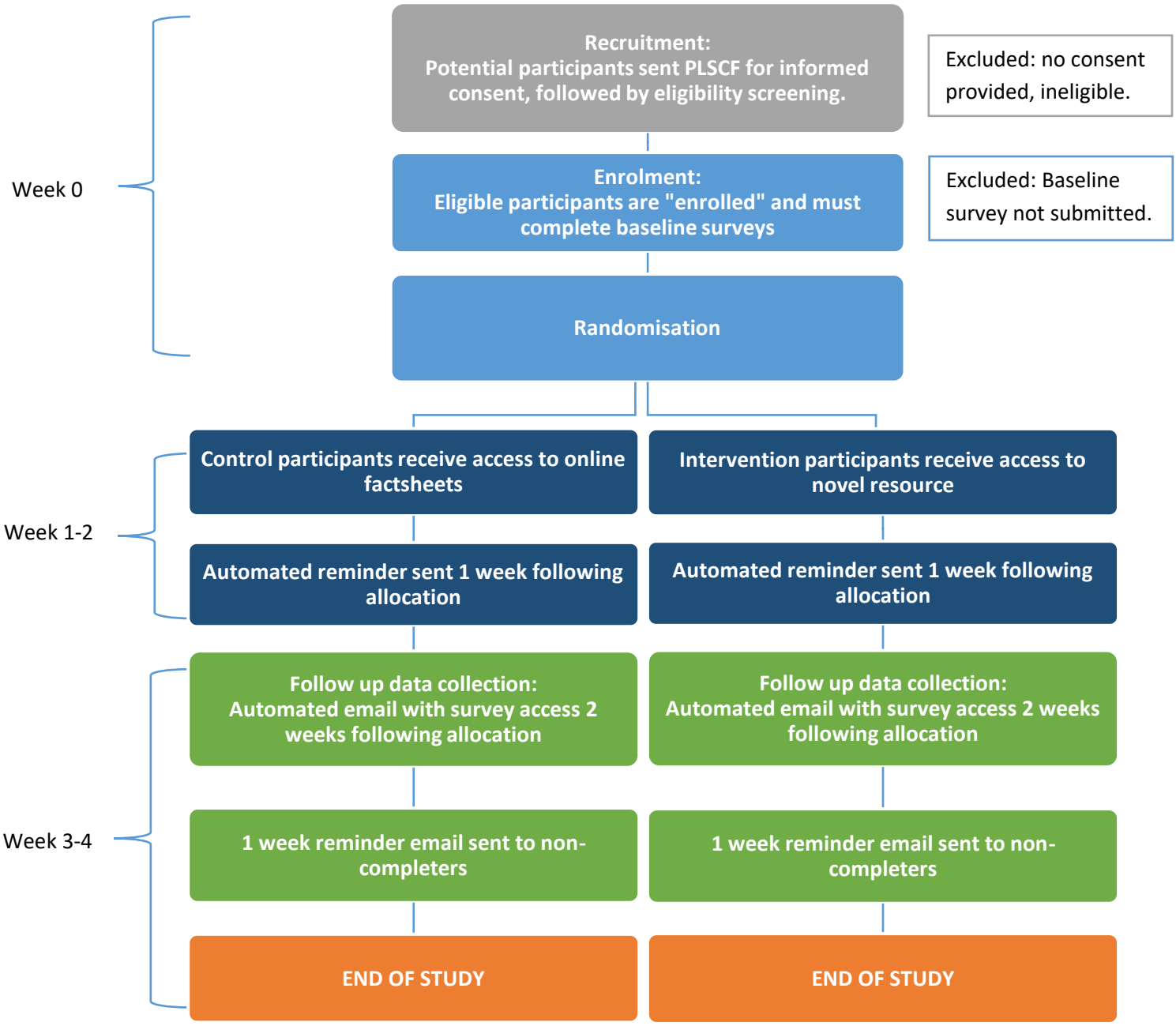

Figure 1. Flow chart of Stage 2: Pilot study procedure.

3.6.1. Schedule of data collection

Table 1 details the self-reported demographic, clinical, psychosocial, and study-specific resource acceptability and experience data to be collected and the time-points at which they are to be collected.

Table 1. Details and timing of participant data collection

Concepts	Variables or Measures	Eligibility screening	Baseline survey	Follow-up survey
About you				
Contact information	First name*, email address*		X	
Demographics	Age*, gender*, country of residence*	X		
	Country of birth, primary language, relationship status, employment status, qualifications, postcode (indicator of socio-economic status)		X	
Clinical characteristics				
Diabetes	Type of diabetes*, 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), diabetes-related complications		X	
General health	Co-morbidities, 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	
Psychosocial characteristics				
Psychological insulin receptiveness	Hypothetical willingness to commence insulin (41)*	X		X
Attitudes towards insulin	Insulin Treatment Appraisal Scale: ITAS (39)		X	X
Diabetes-specific knowledge	Michigan Diabetes Research and Training Center's Revised Diabetes Knowledge Test: DKT-R (42)		X	X

Concepts	Variables or Measures	Eligibility screening	Baseline survey	Follow-up survey
Diabetes-specific distress	Problem Areas In Diabetes: PAID (43)		X	X
Illness perceptions	Brief Illness Perceptions Questionnaire: BIPQ (44)		X	X
Diabetes-specific self-efficacy	Confidence In (type 2) Diabetes Self-management scale: CIDS-2 (45)		X	X
Resource Acceptability^	Access to online resources during two-week period (yes/no) <u>If no:</u> Reasons for not accessing (pre-defined response options and/or free-response answers available) <u>If yes:</u> User rating of resource: ease of use; understanding and relevance of content; acceptability of design, length, and online format Preference for alternative information sources (e.g. hard copy leaflet, clinical education) Willingness to recommend the resource to others Likes/dislikes about the resource How the resource could be improved			X
Further comments	Free-text box for participant to provide any further feedback.			X

*Question completion required for participation. ^ study-specific items to be developed.

3.6.2. Protocol compliance and loss to follow-up

Accurate records will be kept regarding participant online resource access, if and when surveys are submitted and how complete they are. To improve participant retention and protocol compliance, trial participants will receive two reminder emails or text messages: 1) to access/view the allocated online resource, sent one week following allocation, and; 2) to complete the follow-up online survey, sent one week after survey completion is requested (only for participants who have not yet submitted the online survey). All participants will be asked to complete the follow-up survey, regardless of compliance with the protocol in the form of accessing the allocated online resource.

Participants who do not complete a follow-up survey within two-weeks of receipt will be declared 'lost to follow-up'. Data collected from participants declared lost to follow-up will be maintained for analysis.

3.6.2.1. Replacements

Recruitment will be ongoing until 40 consenting eligible participants are allocated to a trial arm. A 50% attrition rate is incorporated into our estimated sample size and replacements will not be made for losses to follow-up.

3.7. Outcomes

This pilot study is not designed or powered to test for statistically significant impact and therefore we do not specify a primary outcome, or set a level of statistical significance for interpreting analyses. The following outcomes reflect the defined primary and secondary study objectives.

1. Feasibility assessment outcomes:
    a) Recruitment ease: Time (days) taken to recruit and enrol (trial arm allocation) 40 consenting eligible participants; proportion (%) of eligible participants who submit a baseline survey (are enrolled/allocated);
    b) Protocol compliance: Proportion (%) of 'enrolled' participants who access the allocated resource ≥1 time(s).
    c) Loss to follow-up: Proportion (%) of enrolled participants who do not submit a follow-up survey
    d) Data completeness: proportion (%) of participants with complete baseline survey data; proportion (%) of participants with complete follow-up survey data
2. Acceptability assessment outcomes:
    a) Website analytics: average number of online resource visits; time (minutes) spent on online resource; most commonly (frequency, %) viewed pages (intervention only)
    b) Quantitative survey feedback: frequency (%) of participants who agree with positively worded study-specific items, comparing intervention/control online resources;
    c) Qualitative feedback: common themes identified for participants likes and dislikes about the resources and how they could be improved.
3. Likely effect of the intervention assessment outcome:

a) Mean change in Insulin Treatment Appraisal Scale (ITAS) Negative scores from baseline to follow-up survey, compared to the control arm.

3.8. Data management

3.8.1. Data collection

All participant-reported data will be collected online via Qualtrics™, hosted through the Deakin University secure network. Once consent is provided, eligibility screening and baseline survey data will be collected in a single sitting. An email will be sent to the participant with a unique link to the follow-up survey following the trial.

The study website will require participant log-in, allowing for collection of website usage data for each participant, including hits, page views (frequency / duration), visit sessions (frequency / duration), click path.

3.8.2. Data storage

During the active study period, participant content and survey data will stored in Qualtrics™ via the Deakin University secure network. Only the research team will have access to this password-protected Qualtrics account. At the conclusion of the study all Qualtrics data and website usage data will be downloaded and linked according to participant ID. De-identified quantitative participant data will be saved as an IBM SPSS file and responses to free-text questions will be stored in an excel spreadsheet (which allows for a greater number of characters for string variables). Identifiable information (email, name) with linking participant ID will be separated from study data and stored in a password-encrypted excel spreadsheet. 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 clinical trial regulations, all original data will be kept for a minimum of 15 years following the publication of results and then disposed of by erasing of electronic files.

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, time of withdrawal (e.g. pre or post trial arm allocation) and reason for withdrawal, where applicable.

3.9. Statistical methods

3.9.1. Sample size estimation

No sample size calculation is required for a pilot study. However, a minimum sample size of at least 20 participants (10 per trial arm) is recommended (40). A sample size of 40 eligible consenting participants will be recruited and enrolled, allowing generously for up to 50% attrition. This inflated sample will ensure that a minimum sample size of N=20 is reached and provide opportunity to assess actual rates of loss to follow-up, protocol compliance and data completeness to inform the main RCT sample size calculation.

3.9.2. Analysis plan

This pilot study is not designed nor powered for testing the significance of change in negative insulin appraisals, strength of association between the intervention, compared to the control, or inferring causality between dependent and independent variables. Using quantitative data, descriptive statistics (frequencies, proportions, measures of central tendency) will be used to explore and describe the feasibility and acceptability of assessment outcomes. A crude estimate for the association between the intervention and ITAS negative scores will be examined using an unadjusted analysis of covariance (ANCOVA). The underlying assumptions of ANCOVA will be assessed where possible: scatter plots for linearity of relationship between baseline and post-intervention ITAS negative score, the Kolmogorov-Smirnov test and normal probability plots for normality of continuous variables and residuals, residual-vs-fitted plots for homoscedasticity of error variance and DFBETA plots for influential observations or outliers.

For the qualitative data, thematic analyses will be used to explore, and identify key themes, from free-text responses about participant's experiences of the resources to inform future developments.

4. ETHICS AND REPORTING

4.1. Assessment and mitigation of risk

There is no foreseeable risk of harm to participants undertaking any component of the research described in this stage-specific protocol. The pilot study baseline and follow-up assessments include

questions that may be interpreted as sensitive or personal in nature (e.g. feelings about living with diabetes, income and employment status). However, it is not expected that any items would cause distress. Further, participants are offered the opportunity to skip interview questions if preferred or withdraw at any time.

The PLSCF will include the contact details of the Deakin Human Research Ethics Manager and participants will be asked to report any concerns or complaints about the study to the Manager.

4.2. Research ethics approval

Ethics review and approval to conduct a pilot study (Stage 2) will be sought from Deakin University Human Research Ethics Committee (DUHREC). Letters of ethics approval will be obtained prior to the commencement of the study.

4.3. Reporting

Monthly study progress reports will be prepared, including, but not limited to: rates of recruitment, participation and attrition; study start and completion dates; data monitoring; adverse event reporting; and manuscript planning. Study reporting in month 12 will include a summary of the Pilot Study (Stage 2) preliminary analyses and a Stop/Go recommendation for the continuation or termination of the program of research.

4.3.1. Ethics reporting requirements

Reporting to the Deakin University Ethics group/committee will be at least annually, and at the completion of this stage-specific pilot study, including information on: progress to date; maintenance and security of records; compliance with the approved protocol; and compliance with any conditions of approval. In the event of any proposed changes to the protocol, any events which might affect the continuation of ethical acceptability of the project, serious or unexpected adverse effect of the participants, or study discontinuation, the Deakin University ethics committee/groups will be contacted by the Investigator immediately.

4.3.2 Pharmacovigilance monitoring and funding body reporting requirements

This research protocol does not include administration or manipulation of, or investigation of the effects of, any pharmacological or therapeutic goods. In line with the pharmacovigilance reporting requirements of the funding body (Section 6.4), all data collected will be screened for adverse events that may be associated with the funding body's products. In the event of the research team becoming aware of a potential adverse event regarding the possible administration of a Sanofi product, and a serious adverse event relating to any therapeutic goods, participants will be contacted via telephone and invited to respond (in a brief, structured interview) to a small number of additional questions about this event (e.g. medication brand name, dose and timing, healthcare utilisation (e.g. ambulance or hospitalisation), symptoms, other consequences). Non-response will not affect participation in the study proper. Participants will be advised via the PLSCFCF that they may be contacted for further information regarding safety events, as per requirements from the study funder. All Adverse Drug Reactions, whether potential or confirmed, related to any Sanofi product will be reported to the funding body within 24 hours of study staff becoming aware of the possible event. Additional information obtained about the event via follow-up questions will be submitted to the funder within 24 hours of the study staff becoming aware of this additional information. In the event of the research team becoming aware of a serious adverse event associated with any therapeutic goods, this will be reported to the Australian Therapeutic Goods Administration. All study staff with access to participant data will be trained to identify potential adverse events.

4.4. Financial disclosure and conflicts of interest

This Investigator Sponsored Study is largely funded by Sanofi-aventis Australia Pty Ltd (Sanofi). Sanofi funding will support project manager salary and direct research costs. Costs associated with participation incentives will be funded by the ACBRD. In-kind support including project oversight will be provided by the Investigator team. Sanofi will have no involvement in the study design, data analysis or interpretation, or dissemination of findings. Sanofi will be allowed access to all de-identified data from the study for research and audit purposes, if requested. The investigators have no conflicts to declare.

5. TIMELINE

The planned timeline for this 24-month program of research is shown in Table 3, with details of the stage-specific deliverables only. For a complete study timeline see the full protocol (Version 2.1).

Estimated Year	2019									2020												
Estimated Month	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Month number for study duration (1-24)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Stage 1: Website development																						
Stage 2: Pilot Study																						
Prepare study docs & ethics application																						
Submit ethics & receive approval																						
Protocol registration																						
Recruitment, enrolment, randomisation																						
Follow up data collection (2-weeks)																						
Database lock																						
Preliminary analyses for reporting purposes																						
Annual report (Stop/go)																						
In-depth analyses, interpretation & write up																						
Stage 3: Full RCT																						

6. DISSEMINATION PLAN

Chief Investigators Holmes-Truscott and Speight hold the primary responsibility for publication of the study results.

In is anticipated that this program of research will result in a minimum of two peer-reviewed journal publications: 1) development and pilot testing of the intervention; planned submission mid 2020 (target journal: *Implementation Science* or *BMJ Open Diabetes Research and Care*); 2) full RCT main outcomes; planned submission early 2021 (target journal: *Diabetes Care* or *Diabetic Medicine*). Additional academic dissemination may include publication of secondary data analyses (research questions to be determined). In addition, it is expected that the Pilot and RCT findings will be submitted for presentation at (inter)national scientific conferences including, for example, the Australasian Diabetes Congress (ADS & ADEA Annual Scientific Meeting) and the American Diabetes Association Scientific Meeting.

Following peer-reviewed academic publication (i.e. conference abstract, journal article), study findings will be written up as plain language blog posts and published on the ACBRD website. The blog posts will be promoted via the ACBRD social media accounts, and e-newsletter, and pilot study participants (who provided prior consent to be contacted for this purpose) will receive a copy via email. Results may also be summarised for inclusion in a consumer magazine (e.g. Diabetes Australia's *Circle* magazine) and one or more professional magazines (e.g. *Australian Diabetes Educator*, *Diabetes and Primary Care Australia*, *Diabetes Management*).

7. TRANSLATION OF FINDINGS

It is anticipated that this program of research will provide evidence of the impact of a novel web-based intervention among Australian adults with T2D, including reduced negative insulin appraisals, and improved willingness to initiate insulin therapy. If the intervention is found to be successful, national and/or state-based Australian diabetes member organisation will be contacted to discuss making the web-based resource freely available online to all Australians. In addition, funding will be sought to conduct a clinic-based trial to explore the impact of the intervention on actual insulin uptake (and consequently on HbA1c) among adults with type 2 diabetes for whom treatment intensification is clinically indicated.

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